DRUGDEX® Evaluations

OXCARBAZEPINE

0.0 Overview

1) Class

a) This drug is a member of the following class(es):

Anticonvulsant

Dibenzazepine Carboxamide

2) Dosing Information

a) Adult

1) Partial seizure, monotherapy

a) initiation of monotherapy, 300 mg ORALLY twice a day, then increas by 300 mg/day every third day to 1200 mg/day OR 2400 mg/day in patie from other antiepileptic drug therapy to oxcarbazepine monotherapy (Pr TRILEPTAL(R) oral tablets, oral suspension, 2005)

b) conversion to monotherapy, initial, 300 mg ORALLY twice a day; ma dosage by up to 600 mg/day at weekly intervals to 2400 mg/day reache weeks while simultaneously reduce the dose of concomitant antiepilepti 3-6 weeks (Prod Info TRILEPTAL(R) oral tablets, oral suspension, 2005

2) Partial seizure; Adjunct

a) initial, 300 mg ORALLY twice a day; may increase dosage by up to 6 weekly intervals to 1200 mg/day (Prod Info TRILEPTAL(R) oral tablets, suspension, 2005)

b) Pediatric

1) with adjunctive therapy, children 2 to less than 4 years of age may require the oxcarbazepine dose per body weight compared to adults; and children 4 equal to 12 years of age may require a 50% higher oxcarbazepine dose per compared to adults (Prod Info TRILEPTAL(R) oral tablets, oral suspension, 2

a) Partial seizure, monotherapy

1) 4 to 16 year old, initiation of monotherapy, 8-10 mg/kg/day ORA divided doses; may increase dose by 5 mg/kg/day every 3 days to t recommended maintenance dose (Prod Info TRILEPTAL(R) oral tab suspension, 2005)

2) 4 to 16 year old, conversion to monotherapy, initial, 8-10 mg/kg/ in 2 divided doses; may increase doses by up to 10 mg/kg/day at w to the recommended maintenance dose; simultaneously reduce the concomitant antiepileptic drugs over 3-6 weeks (Prod Info TRILEPT tablets, oral suspension, 2005)

3) 4 to 16 year old, maintenance, 600 to 900 mg/day for 20 kg chil 1200 mg/day for 25 to 30 kg; 900 to 1500 mg/day for 35 to 40 kg ch 1500 mg/day for 45 kg children; 1200 to 1800 mg/day for 50 to 55 k 1200 to 2100 mg/day for 60 to 70 kg children (Prod Info TRILEPTA tablets, oral suspension, 2005)

b) Partial seizure; Adjunct

1) 4 to 16 years old, initial, 8-10 mg/kg/day ORALLY in 2 divided d 600 mg/day(Prod Info TRILEPTAL(R) oral tablets, oral suspension,

2) 4 to 16 years old, maintenance, target maintenance dose of oxc should be achieved over 2 weeks, and is dependent upon patient w 29 kg, 900 mg/day); (29.1 to 39 kg, 1200 mg/day); and (greater tha mg/day) (Prod Info TRILEPTAL(R) oral tablets, oral suspension, 20

3) 2 to less than 4 years old, initial, 8-10 mg/kg/day ORALLY in 2 d MAX: 600 mg/day; patients under 20 kg, consider initial dose of 16- in 2 divided doses (Prod Info TRILEPTAL(R) oral tablets, oral suspe

4) 2 to less than 4 years old, maintenance, should be titrated over 2
MAX: 60 mg/kg/day in 2 divided doses (Prod Info TRILEPTAL(R) or
suspension, 2005)

3) Contraindications
a) hypersensitivity to oxcarbazepine, or to any product component (Prod Info TR
oral tablets, suspension, 2007)

4) Serious Adverse Effects
a) Anaphylaxis
b) Angioedema
c) Hyponatremia
d) Immune hypersensitivity reaction, multiorgan
e) Stevens-Johnson syndrome
f) Toxic epidermal necrolysis

5) Clinical Applications
a) FDA Approved Indications
1) Partial seizure, monotherapy
2) Partial seizure; Adjunct

1.0 Dosing Information

1.1 Drug Properties

A) Information on specific products and dosage forms can be obtained by referri
Tradename List (Product Index)

B) Synonyms
Oxcarbazepine

C) Physicochemical Properties
1) Molecular Weight
a) 252.27 (Prod Info Trileptal™, 00)
2) Solubility
a) Systemic: Oxcarbazepine is slightly soluble in acetone, chloroform,
dichloromethane, and methanol. It is practically insoluble in ethanol, eth
(Prod Info Trileptal™, 00)

1.2 Storage and Stability

A) Oral route
1) Oral suspension of oxcarbazepine should be stored between 15 and 30 d
Celsius (59 and 86 degrees Fahrenheit) (Prod Info Trileptal(R), 2003).

1.3 Adult Dosage

1.3.1 Normal Dosage

Oral route

Trigeminal neuralgia

1.3.1.A Oral route

Partial seizure, monotherapy

Partial seizure; Adjunct

1.3.1.A.1 Partial seizure, monotherapy

a) Conversion

1) For conversion of therapy from other antiepileptic drugs (AE
oxcarbazepine monotherapy, oxcarbazepine therapy should be
a dose of 600 milligrams/day (mg/day) in two divided doses; sir
reduction of the dosage of the concomitant AEDs should begin.
oxcarbazepine dose may be increased at weekly intervals, as c
indicated, by a maximum of 600 mg/day to achieve a daily dose
mg/day. The maximum dose of oxcarbazepine should be reach
approximately 2 to 4 weeks while therapy with concomitant AEI
terminated gradually over approximately 3 to 6 weeks. Close m
the patient is recommended during the transition phase (Prod I
TRILEPTAL(R) oral tablets, oral suspension, 2005).

b) Initiation

1) In patients not currently treated with any antiepileptic drugs,
oxcarbazepine therapy should be initiated at a dose of 600 milli
(mg/day) in two divided doses. This dose is then increased eve
300 mg/day to achieve a dose of 1200 mg/day (Prod Info TRILI
tablets, oral suspension, 2005).

c) Withdrawal

1) Withdrawal of oxcarbazepine therapy should be gradual (Pr
TRILEPTAL(R) oral tablets, oral suspension, 2005).

1.3.1.A.2 Partial seizure; Adjunct

a) Oxcarbazepine should be initiated with a dose of 600 milligrams
(mg/day), in two divided doses. This dose may be increased at wee
as clinically indicated, by a maximum of 600 mg/day. The recomme
maintenance dose of oxcarbazepine for adjunctive use is 1200 milli
(mg/day) in 2 divided doses. Although daily doses greater than 120
more effective, most patients are not able to tolerate the 2400 mg/d
to adverse central nervous system effects. Close monitoring of the p
plasma concentrations of concomitant antiepileptic drugs is recomm
the titration phase, especially at doses greater than 1200 mg/day (P
TRILEPTAL(R) oral tablets, oral suspension, 2005).

1.3.1.B Trigeminal neuralgia

1) Effective oral doses of oxcarbazepine in the treatment of trigeminal n
been 300 milligrams 2 to 4 times daily initially, with the dose increased w
adequate pain control was achieved (Zakrzewska & Patsalos, 1989b).

2) Daily maintenance doses associated with pain relief have ranged fro
milligrams/day (Zakrzewska & Patsalos, 1989b; Farago, 1987b). In one
required for effective relief of pain were less than 10 milligrams/kilogram
patients, 11 to 20 milligrams/kilogram/day in 46%, and greater than 20
milligrams/kilogram/day in 31% (Farago, 1987b).

1.3.1.C Equivalent Doses

1) Oxcarbazepine oral suspension and film-coated tablets may be interc
equal doses (Prod Info TRILEPTAL(R) oral tablets, oral suspension, 200

1.3.2 Dosage in Renal Failure

A) For patients with impaired renal function (creatinine clearance less than 3
milliliters/minute), oxcarbazepine therapy should be initiated at 300 milligram
half the usual starting dose, and increased at a slower rate than usual based
response (Prod Info TRILEPTAL(R) oral tablets, oral suspension, 2005).

1.3.3 Dosage in Hepatic Insufficiency

A) Dose adjustments are generally not required in patients with mild to mode impairment (Prod Info TRILEPTAL(R) oral tablets, oral suspension, 2005).

1.3.4 Dosage in Geriatric Patients

A) No specific guidelines exist for oxcarbazepine dosing in the elderly. Maxi concentrations and values for area under the concentration-time curve were higher in elderly volunteers (60 to 82 years of age) than in younger volunteer years of age). Differences are presumed to be due to age-related reductions clearance (Prod Info TRILEPTAL(R) oral tablets, oral suspension, 2005). Be oxcarbazepine is initiated at a low dosage and titrated until a maintenance d reached, these pharmacokinetic differences are felt to have no significant cli implications (van Heiningen et al, 1991).

1.3.6 Dosage in Other Disease States

A) Pregnancy

1) Dose-normalized plasma concentrations of oxcarbazepine and mono carbazepine (MHD), the active metabolite, decreased during pregnancy to return to prepregnancy levels during the postpartum period in a pharm study in 5 pregnant women on oxcarbazepine monotherapy. Although p concentrations were not available in any of the women, plasma concentr MHD and oxcarbazepine were measured during each trimester in 4 wom the last trimester in 1 woman, and at least once during the 3 months afte all women. The lowest dose-normalized concentrations were noted after gestation-week. Furthermore, postpartum dose-normalized plasma conc MHD and oxcarbazepine increased between 1.7 to 2.9 fold compared w trimester in 4 of the 5 pregnant women. The postpartum increase was ob soon as 7 to 8 days after delivery. In 1 out of the 5 women no increase i postpartum concentrations were noted (Tomson & Battino, 2007).

1.4 Pediatric Dosage

Normal Dosage

Dosage in Renal Failure

Dosage in Hepatic Insufficiency

1.4.1 Normal Dosage

1.4.1.A Oral route

Partial seizure, monotherapy

Partial seizure; Adjunct

1.4.1.A.1 Partial seizure, monotherapy

a) Conversion

1) For conversion of therapy from other antiepileptic drugs (AE oxcarbazepine monotherapy in children 4 to 16 years, oxcarba should be initiated with a dose of 8 to 10 milligrams/kilogram/da in two divided doses; simultaneously, reduction of the dosage c concomitant AEDs should begin. The oxcarbazepine dose may at weekly intervals, as clinically indicated, by a maximum of 10 achieve the recommended daily dose. Concomitant AEDs shou terminated gradually over approximately 3 to 6 weeks. Close m the patient is recommended during the transition phase. The re total daily dose of oxcarbazepine is as follows (Prod Info Trilep

Patient Weight (in kg)	Target Maintenance Dose Range
20	600 to 900
25	900 to 1200

30	900 to 1200
35	900 to 1500
40	900 to 1500
45	1200 to 1500
50	1200 to 1800
55	1200 to 1800
60	1200 to 2100
65	1200 to 2100
70	1500 to 2100

b) Initiation

1) In children 4 to 16 years not currently treated with any antiep oxcarbazepine therapy should be initiated at 8 to 10 milligrams/ (mg/kg/day) in two divided doses. Doses should be increased b mg/kg/day every 3 days until the recommended daily dose is re recommended total daily dose of oxcarbazepine is as follows (F Trileptal(R), 2003a):

Patient Weight (in kg)	Target Maintenance Dose Rang (mg/day)
20	600 to 900
25	900 to 1200
30	900 to 1200
35	900 to 1500
40	900 to 1500
45	1200 to 1500
50	1200 to 1800
55	1200 to 1800
60	1200 to 2100
65	1200 to 2100
70	1500 to 2100

1.4.1.A.2 Partial seizure; Adjunct

a) 4 to 16 Year Olds

For adjunctive therapy in pediatric patients aged between 4 to oxcarbazepine should be initiated at a daily dose of 8 to 10 milligrams/kilogram/day (mg/kg/day) in two divided doses, usua exceed 600 mg/day. The target maintenance dose, according t below, should be attained within 2 weeks. The median dose rea clinical trials was 31 mg/kg/day (6 to 51 mg/kg/day) (Prod Info T (R) oral tablets, oral suspension, 2005):

Patient Weight (in kg)	Target Maintenance Dose (mg/day)
20 to 29	900
29.1 to 39	1200
greater than 39	1800

Children 4 to less than or equal to 12 years of age may require oxcarbazepine dose per body weight compared to adults. Child higher dose per body weight relative to adults because the app clearance increases with decreasing age (Prod Info TRILEPTA tablets, oral suspension, 2005).

b) 2 to 4 Year Olds

1) For adjunctive therapy in pediatric patients 2 years old to les years old, oxcarbazepine should be initiated at a daily dose of 8 milligrams/kilogram/day (mg/kg/day) in two divided doses, usua exceed 600 mg/day. For patients under 20 kilogram, a starting 20 mg/kg/day in 2 divided doses may be considered. The maxi maintenance dose of oxcarbazepine should be achieved over 2 and should not exceed 60 mg/kg/day in two divided doses. The reached during clinical trials in children 2 to 4 years of age was (Prod Info TRILEPTAL(R) oral tablets, oral suspension, 2005).

2) Children 2 to less than 4 years of age may require up to twic oxcarbazepine dose per body weight compared to adults. Child

higher dose per body weight relative to adults because the app clearance increases with decreasing age (Prod Info TRILEPTA tablets, oral suspension, 2005).

3) Children 2 to 4 years of age may require up to twice the oxc dose per body weight compared to adults. Children require a hi body weight relative to adults because the apparent clearance decreasing age (Prod Info TRILEPTAL(R) oral tablets, oral sus 2005).

c) In children beginning oxcarbazepine therapy, doses have been t 30 milligrams/kilogram/day (mg/kg/day) over 1 to 3 weeks (Gaily et those switching from carbamazepine, an overnight change of 1.5 tin carbamazepine dose has been utilized. The mean effective dose fo achieving at least a 50% decrease in seizures has been 47 mg/kg/d range of 21 to 75 mg/kg/day.

1.4.1.B Equivalent Doses

1) Oxcarbazepine oral suspension and film-coated tablets may be interc equal doses (Prod Info TRILEPTAL(R) oral tablets, oral suspension, 200

1.4.2 Dosage in Renal Failure

A) For patients with impaired renal function (creatinine clearance less than 3 milliliters/minute), oxcarbazepine therapy should be initiated at one-half the u dose, and increased slowly according to the clinical response (Prod Info TRIL oral tablets, oral suspension, 2005).

1.4.3 Dosage in Hepatic Insufficiency

A) Dose adjustments are generally not required in patients with mild to mode impairment (Prod Info TRILEPTAL(R) oral tablets, oral suspension, 2005).

2.0 Pharmacokinetics

Onset and Duration

Drug Concentration Levels

ADME

2.1 Onset and Duration

A) Onset

1) Initial Response

a) Trigeminal neuralgia, oral: 24 hours (Zakrzewska & Patsalos, 1989).

2.2 Drug Concentration Levels

A) Therapeutic Drug Concentration

1) Epilepsy, not established (Zakrzewska & Patsalos, 1989).

B) Time to Peak Concentration

1) Oral: 4.5 hours (tablets), 6 hours (suspension) (Prod Info TRILEPTAL(R) oral suspension, 2005).

a) After the administration of a single dose of oxcarbazepine tablets, un conditions, in healthy, male volunteers, the median time to peak concent was 4.5 hours (range 3 to 13 hours). The median Tmax was 6 hours in h volunteers administered a single-dose of oxcarbazepine suspension, un conditions (Prod Info TRILEPTAL(R) oral tablets, oral suspension, 2005) metabolite, 10-hydroxy-carbazepine, reaches peak levels at 4.5 to 8 hou 1990; Kristensen et al, 1983; Theisohn & Heimann, 1982a).

b) After the administration of a single dose of oxcarbazepine oral suspe fasted conditions, in healthy, male volunteers, the median time to peak c (Tmax) was 6 hours (Prod Info Trileptal(R), 2003b).

2) Steady-state plasma concentrations of 10-hydroxy-carbazepine, the activ are achieved within 2 to 3 days with twice-a-day dosing (Prod Info TRILEPTA tablets, oral suspension, 2005).

3) Maximum serum concentrations of the S- and R- enantiomers of 10-hydro carbazepine were 4.49 and 0.99 mg/L, respectively, but the median time to p concentration was similar for both (Volosov et al, 1999).

C) Area Under the Curve

1) 129.8 mg/L/hr (S-enantiomer); 26.3 mg/L/hr (R-enantiomer) (Volosov et a
a) Approximately 5-fold greater AUC for S-10-hydroxy-carbazepine thar hydroxy-carbazepine (Volosov et al, 1999).
b) AUC values were 30% to 60% higher in elderly volunteers (60 to 82 y than in younger volunteers (18 to 32 years of age). Differences are presi due to age-related reductions in creatinine clearance (Prod Info Trileptal
c) Dose adjusted AUC values were 30% to 40% lower in children below years than in children above 8 years of age (Prod Info Trileptal(R), 2003

2.3 ADME

Absorption

Distribution

Metabolism

Excretion

Elimination Half-life

2.3.1 Absorption

A) Bioavailability
1) Oral: rapidly absorbed (Anon, 1990; Theisohn & Heimann, 1982a).
B) Effects of Food
1) none (Prod Info TRILEPTAL(R) oral tablets, oral suspension, 2005).

2.3.2 Distribution

A) Distribution Sites
1) Protein Binding
a) 40% to 60% (Prod Info TRILEPTAL(R) oral tablets, oral suspens Patsalos et al, 1990a).
1) Approximately 33% to 40% of 10-hydroxy-carbazepine is bc proteins, predominantly albumin (Prod Info TRILEPTAL(R) oral suspension, 2005; Patsalos et al, 1990a).
2) Serum concentration within the therapeutically relevant rang influence protein binding (Prod Info TRILEPTAL(R) oral tablets, suspension, 2005).
3) No difference in binding between males and females was ob (Patsalos et al, 1990a).
2) OTHER DISTRIBUTION SITES
a) SALIVA, correlates to serum concentrations (Kristensen et al, 19
1) A good correlation between saliva and serum concentration hydroxy-carbazepine has been reported from 8 to 72 hours follc administration of oxcarbazepine (Kristensen et al, 1983).
B) Distribution Kinetics
1) Volume of Distribution
a) 49 L (10-hydroxy-carbazepine) (Prod Info Trileptal(R), 2003b)

2.3.3 Metabolism

A) Metabolism Sites and Kinetics
1) LIVER, rapid and extensive metabolism (Faigle & Menge, 1990; Anor Schutz et al, 1986a; Theisohn & Heimann, 1982a).
a) Metabolized via stereoselective reduction by cystolic enzymes o group in position 10 of oxcarbazepine (Faigle & Menge, 1990; Anon Schutz et al, 1986a; Theisohn & Heimann, 1982a).
b) Lacks auto-inducing properties (Anon, 1990; Brodie et al, 1989a
c) Dose-dependent enzyme induction has been reported with highe producing effects similar to carbamazepine (Patsalos et al, 1990d).
B) Metabolites
1) 10-monohydroxy-carbazepine, active (Prod Info TRILEPTAL(R) oral suspension, 2005; Faigle & Menge, 1990; Anon, 1990; Schutz et al, 198 & Heimann, 1982a).
a) Primarily responsible for the therapeutic effects of oxcarbazepine

TRILEPTAL(R) oral tablets, oral suspension, 2005; Faigle & Menge
Patsalos et al, 1990d; Anon, 1990; Anon, 1989; Theisohn & Heimar
b) The metabolite 10-hydroxy-carbazepine is primarily excreted in t
the glucuronide conjugate (Dickinson et al, 1989; Anon, 1989; Schu
1986a; Theisohn & Heimann, 1982a).

2) Two isomeric 10,11-diols, inactive (Dickinson et al, 1989; Anon, 1989
1986a; Theisohn & Heimann, 1982a).

a) The trans-diol (10,11-dihydro-10,11-trans-dihydroxy-carbamazep
predominates (Dickinson et al, 1989; Anon, 1989; Schutz et al, 1986
& Heimann, 1982a).

3) Other minor metabolic pathways include direct O-glucuronidation and
with the enol form (Anon, 1990).

2.3.4 Excretion

A) Kidney

1) Renal Excretion (%)

a) 95% to 96% (Prod Info TRILEPTAL(R) oral tablets, oral suspens
Schutz et al, 1986a).

2) Only small amounts of unchanged oxcarbazepine are recovered (less
and the majority of renal excretion is accounted for by 10-hydroxy-carba
80%), primarily as the glucuronide conjugate. Only negligible amounts o
and cis-10,11-diol are found in the urine (approximately 3%) (Prod Info T
oral tablets, oral suspension, 2005; Anon, 1990; Schutz et al, 1986a).

B) Total Body Clearance

1) The younger and lower in weight the faster the weight-adjusted clear
monohydroxy-carbazepine (MHD). In children 2 years to less than 4 yea
weight-adjusted clearance is approximately 80% higher on average than
adults. When treated with a similar weight-adjusted dose, the correspon
exposure in these children is expected to be about 50% of adult exposu
4 to 12 years of age, weight-adjusted clearance is approximately 40% hi
average than that of adults. When treated with a similar weight-adjusted
corresponding MHD exposure in these children is expected to be about
exposure. The weight-adjusted MHD clearance in children 13 years and
expected to reach that of adults (Prod Info TRILEPTAL(R) oral tablets, o
suspension, 2005).

C) Other

1) OTHER EXCRETION

a) FECES, less than 4% (Prod Info TRILEPTAL(R) oral tablets, ora
2005).

2.3.5 Elimination Half-life

A) Parent Compound

1) ELIMINATION HALF-LIFE

a) 1 to 2.5 hours (Prod Info TRILEPTAL(R) oral tablets, oral suspen
Dickinson et al, 1989).

1) The half-life is prolonged to 19 hours in patients with renal in
(creatinine clearance less than 30 mL/min) (Prod Info TRILEPT
tablets, oral suspension, 2005).

B) Metabolites

1) 10-hydroxy-carbazepine, 8 to 11 hours (Prod Info TRILEPTAL(R) ora
suspension, 2005; Anon, 1990; Dickinson et al, 1989; Theisohn & Heima

a) The half-life of 10-monohydoxy-carbazepine was 9 hours (Prod I
TRILEPTAL(R) oral tablets, oral suspension, 2005).

b) Half-lives of the R- and S- enantiomers were 11.9 and 13 hours,
(Volosov et al, 1999).

3.0 Cautions

Contraindications

Precautions

Adverse Reactions

Teratogenicity/Effects in Pregnancy/Breastfeeding

Drug Interactions

3.1 Contraindications

A) hypersensitivity to oxcarbazepine, or to any product component (Prod Info TR oral tablets, suspension, 2007)

3.2 Precautions

A) anaphylaxis and angioedema of larynx, glottis, lips, and eyelids may occur; in fatalities if laryngeal involvement (Prod Info TRILEPTAL(R) oral tablets, suspensi
B) concomitant alcohol consumption; may cause additive sedative effect (Prod Ir TRILEPTAL(R) oral tablets, suspension, 2007)
C) concomitant medications known to decrease serum sodium levels; hyponatre Info TRILEPTAL(R) oral tablets, suspension, 2007)
D) concomitant use with hormonal contraceptives; therapy renders hormonal cor less effective (Prod Info TRILEPTAL(R) oral tablets, suspension, 2007)
E) decreases in T4 may occur; without decreases in T3 or TSH (Prod Info TRILE tablets, suspension, 2007)
F) hypersensitivity to carbamazepine (25% to 35% of those hypersensitive to car also have hypersensitivity reaction to oxcarbazepine) (Prod Info TRILEPTAL(R) c suspension, 2007)
G) hyponatremia (sodium less than 125 mmol/L); especially during the first 3 mo therapy, but may occur more than 1 year after therapy initiation (Prod Info TRILE tablets, suspension, 2007)
H) multiorgan hypersensitivity reactions have occurred; median time to detection (Prod Info TRILEPTAL(R) oral tablets, suspension, 2007)
I) rapid withdrawal of oxcarbazepine therapy; may result in increased seizure fre Info TRILEPTAL(R) oral tablets, suspension, 2007)
J) renal impairment (creatinine clearance less than 30 mL/minute); elimination of metabolite is slowed resulting in a 2-fold increase in exposure (Prod Info TRILEP tablets, suspension, 2007)
K) serious skin reactions, including Stevens-Johnson syndrome and toxic epider necrolysis, have occurred (median time to onset 19 days) (Prod Info TRILEPTAL tablets, suspension, 2007)
L) suicidality, increased risk of; based on data analysis of 199 placebo-controllec antiepileptic drugs, small elevated risk occurred as early as 1 week after starting continued to at least 24 weeks (US Food and Drug Administration, 2008)

3.3 Adverse Reactions

Dermatologic Effects

Endocrine/Metabolic Effects

Gastrointestinal Effects

Hematologic Effects

Hepatic Effects

Immunologic Effects

Neurologic Effects

Ophthalmic Effects

Psychiatric Effects

Renal Effects

Reproductive Effects

3.3.2 Dermatologic Effects

3.3.2.A Cutaneous hypersensitivity

1) Summary

a) Allergic skin reactions are described with the administration of ox
(Dam et al, 1989a; Dam, 1990a; Houtkooper et al, 1987c); (Zakrzev
1988)(Houtkooper et al, 1987c; Zakrzewska & Patsalos, 1989a; And
Watts & Bird, 1991).

2) LITERATURE REPORTS

a) Desensitization to oxcarbazepine, following the development of a
pruritic rash, was accomplished using a dose of 0.1 milligram (mg) o
doubling the dose every 2 days until a therapeutic dosage was reac
Bird, 1991).

b) Allergic skin reactions have been reported less frequently with ox
as compared to carbamazepine in some clinical studies (Dam et al,
1990a; Houtkooper et al, 1987c).

c) There is evidence that oxcarbazepine can be used safely as an a
some patients with carbamazepine induced hypersensitivity (Zakrze
Ivanni, 1988)(Houtkooper et al, 1987c; Zakrzewska & Patsalos, 198

d) In 1 Danish study, a cross-reaction to oxcarbazepine was seen i
47 patients (25%) with allergic skin reactions to carbamazepine (An

3.3.2.B Dermatological finding

1) Skin rash, Stevens-Johnson syndrome, toxic epidermal necrolysis, u
allergic skin reactions have been reported with the administration of oxc

3.3.2.C Erythema multiforme

1) Summary

a) Although not observed in controlled clinical trials, erythema multi
been observed in post-marketing studies or named patient program
oxcarbazepine (Prod Info Trileptal(R), 2003).

3.3.2.D Rash

1) Summary

a) Skin rash has been a frequently described adverse effect of oxc
therapy, also occurring with the discontinuation of oxcarbazepine th
may be associated with a mild eosinophilia, and was reported in 7%
on oxcarbazepine monotherapy in one study (Prod Info Trileptal(R),
al, 1993a; Watts & Bird, 1991).

3.3.2.E Stevens-Johnson syndrome

1) A 9-year-old Taiwanese boy developed Stevens-Johnson syndrome
14 days of initiating oxcarbazepine for treatment of seizures. The patient
of seizures first occurring at the age of 6 months and was treated with pl
several months and then the phenytoin was discontinued without recurre

seizures until he was 9 years old. Upon presentation, the patient's seizu
characterized by clonic movement of his hands and legs, with loss of co
The results of the electroencephalogram and physical examination were
unremarkable. The patient was started on oxcarbazepine 300 milligrams
and the dose was increased to 600 mg daily after one week. Fourteen d
beginning therapy with oxcarbazepine, the patient developed maculopap
his face and thigh along with high fever. Two days later, he developed b
thigh, multiple oral ulcers and hyperemic conjunctivae. The patient was
the emergency department with the diagnosis of presumed SJS. Labora
revealed leukocytosis (white blood cell (WBC) 13,930/mcL; normal rang
10,000/mcL), elevated C-reactive protein (50.59 mcg/mL; range, 0 to 5 r
Human leukocyte antigen (HLA) genotyping showed HLA-B*1518/B*400
pathology finding revealed lymphohistiocytic infiltration around the blood
scanty eosinophils, which was consistent with SJS. The patient improve
and antihistamine treatment for 7 days and was discharged 12 days late
concluded that similar to carbamazepine-induced SJS, the role of the HL
may be associated with the development of oxcarbazepine-induced SJS
2009).

2) Serious, sometimes life-threatening, cases of Stevens-Johnson synd
been reported with the use of oxcarbazepine in children and adults. Som
have required hospitalization, and rare cases of death have been report
Additionally, re-challenge with the drug has resulted in recurrence of the
reactions. The rate at which these dermatologic events have been repor
association with oxcarbazepine use exceeds the rate at which these eve
reported in the general population by 3- to 10-fold. The median time of o
reported cases was 19 days. Discontinuation of oxcarbazepine should b
in any patient who develops a skin reaction while using the drug (Prod Ir
TRILEPTAL(R) oral tablets, suspension, 2007).

3.3.2.F Toxic epidermal necrolysis

1) Serious, sometimes life-threatening, cases of toxic epidermal necroly
reported with the use of oxcarbazepine in children and adults. Some pat
required hospitalization, and rare cases of death have been reported. Ac
challenge with the drug has resulted in recurrence of the dermatologic re
rate at which these dermatologic events have been reported in associati
oxcarbazepine use exceeds the rate at which these events are reported
population by 3- to 10-fold. The median time of onset in reported cases
Discontinuation of oxcarbazepine should be considered in any patient w
skin reaction while using the drug(Prod Info TRILEPTAL(R) oral tablets,
2007).

3.3.3 Endocrine/Metabolic Effects

Abnormal thyroid hormone

Acute intermittent porphyria

Body temperature above normal

Hormone level - finding, Reproductive

Hyperlipidemia

Hyponatremia

Hypothermia

Weight gain

3.3.3.A Abnormal thyroid hormone

1) Summary

a) Use of oxcarbazepine has been associated with decreases in T4

or thyroid stimulating hormone (TSH) (Prod Info TRILEPTAL(R) ora suspension, 2007).

2) LITERATURE REPORTS

a) One study found that carbamazepine and oxcarbazepine both de serum thyroxine (T4) and free thyroxine (FT4) in girls with epilepsy. were reversible upon discontinuation of therapy. Patients, between and 18 years, were compared to 54 age-matched controls. Mean T4 levels in patients receiving carbamazepine (n=19) was 11.5 nM and compared to 14.4 nM and 96.6 nM in the control group (p less than 0.001, respectively). Mean T4 and FT4 in patients receiving oxcarba (n=18) were 11.3 nM and 74.9 nM (p less than 0.001 for both meas compared control). Thyrotropin and free triiodothyronine levels were significantly different. A second evaluation, taken a mean of 5.8 yea performed. Thyroid hormone levels in patients who had discontinue carbamazepine patients and 10 oxcarbazepine patients) did not sig from the controls. Patients had been off therapy for a mean of 5 and respectively (Vainionpaa et al, 2004).

3.3.3.B Acute intermittent porphyria

See Drug Consult reference: DRUGS CONSIDERED UNSAFE- ACUTE PORPHYRIAS

3.3.3.C Body temperature above normal

1) Case report- Despite several changes in drug therapy, a fever was re 20-year-old female which persisted for a follow-up period of approximate following the initial occurrence during oxcarbazepine therapy. The autho that the patient had actually experienced a change in "set point" for body regulation rather than having a febrile reaction. The oxcarbazepine dose milligrams (mg) twice a day for 2 weeks then increased to 300 milligrams times a day. The patient's body temperature had steadily ranged betwee 36.8 degrees Celsius (C) for several years. After oxcarbazepine treatme achieved good seizure control, but her temperature rose to over 37 degr oxcarbazepine was gradually reduced and valproate 1500 milligrams (m substituted resulting into a gradual return to pre-treatment temperature b increase in simple seizures. After a return to temperatures over 37 degre 37.6 degrees C) 4 months later, the valproate was reduced to 800 milligr (mg/day) and vigabatrin 1500 mg was added. Eventually, good seizure c achieved with doses of lamotrigine up to 150 mg/day and vigabatrin 200 however, the patient's temperature never returned to the pre-treatment r mechanism for this effect was hypothesized to be the influence of antiep on ion concentration, as the inherent ratio of sodium to calcium ions in th hypothalamus has been suggested as the physiological basis for the "se temperature control (Gatzonis et al, 1999).

3.3.3.D Hormone level - finding, Reproductive

1) LITERATURE REPORTS

a) Antiepileptic agents have been associated with changes in serur concentrations of male reproductive hormones. When compared to controls (n=41), carbamazepine treated men with partial epilepsy (n lower serum dehydroepiandrosterone sulfate concentrations (3068 r controls versus 1952 ng/mL for carbamazepine; p less than 0.001). statistically significant differences in dehydroepiandrosterone levels detected between controls and oxcarbazepine treated (n=18) or valp treated (n=27) men with generalized epilepsy. It was also found that valproic acid group had higher androstendione levels (5.9 ng/mL) w to the control group (2.2 ng/mL; p less than 0.001) whereas the othe not. Serum testosterone, sex hormone binding globulin, free androg luteinizing hormone, follicle stimulating hormone, prolactin and inhib measurements were not statistically significantly different between a Whether the differences in reproductive hormones are epilepsy-indu or antiepileptic agent-induced changes remains to be determined (Is 2004).

b) Reproductive hormone levels in men with epilepsy may be affec valproic acid or carbamazepine, with some effect shown by oxcarba doses. In valproate-treated men (n=21), androstenedione levels we increased compared with controls (n=25) (p less than 0.001), and m of the cohort taking valproate (57%) had serum concentrations of te

androstenedione, or dehydroepiandrosterone (DHEA) above the ref
(p less than 0.001). Follicle stimulating hormone levels were abnorm
valproate- treated men (p less than 0.05). Among carbamazepine-tr
(n=40), serum concentrations of DHEA were low (p less than 0.001)
hormone-binding globulin (SHBG) levels were high (p less than 0.05
taking high doses of oxcarbazepine (900 milligrams/day (mg/day) o
concentrations of testosterone, luteinizing hormone, and SHBG wer
(p=0.008, p=0.02, p=0.005, respectively). The authors noted that se
levels were high across all groups (Rattya et al, 2001).

3.3.3.E Hyperlipidemia

1) Case report - increased serum lipids, specifically low-density lipoprot
serum cholesterol were reported in 16-year-old girl. High-density lipopro
triglycerides, and liver function tests remained within normal limits. Oxca
metabolized primarily by ketone reductase and glucuronosyltransferase
minimal hepatic enzyme-induction in humans. An increase in lipid levels
previously in the patient when she was treated with carbamazepine, but
to be less probable with oxcarbazepine. The authors suggest monitoring
patients treated with oxcarbazepine as well as in those treated with carb
(Papacostas, 2000).

3.3.3.F Hyponatremia

1) Summary

a) Significant hyponatremia (sodium less than 125 mmol/L) genera
during the first 3 months of therapy, but may occur more than one y
therapy initiation. Dose reduction, therapy discontinuation, or restric
intake may be required. In patients who discontinued therapy in clin
sodium levels normalized within a few days without further treatmen
of serum sodium should be considered especially in patients at risk
who develop symptoms of hyponatremia. Patients are at risk if they
concomitant medications known to decrease serum sodium levels (
TRILEPTAL(R) oral tablets, suspension, 2007).

b) Hyponatremia has occurred with the administration of oxcarbaze
associated with a greater incidence of hyponatremia as compared w
carbamazepine (Dong et al, 2005). The mechanism is thought to be
antidiuretic hormone-like action on the kidney. HYPONATREMIC C
been described with oxcarbazepine use. Some investigators feel tha
hyponatremia from oxcarbazepine may severely limit its use as an a
Most patients with hyponatremia remain asymptomatic but some ma
drowsiness, increase in seizure frequency, and impaired consciousn
Hyponatremia with oxcarbazepine occurs most commonly in elderly
during administration of high doses of the drug (Kloster et al, 1998;
Amelsvoort et al, 1994; Steinhoff et al, 1992; Anon, 1990b; Pendleb
1989; Houtkooper et al, 1987c; Anon, 1989b; Zakrzewska & Patsalo
Johannessen & Nielson, 1987; Nielson et al, 1988).

2) Incidence: 2.5% to 29.9% (Dong et al, 2005; Prod Info TRILEPTAL(P
suspension, 2007)

3) LITERATURE REPORTS

a) The results of one study indicate that oxcarbazepine use is asso
greater incidence of hyponatremia as compared with the use of carb
In a cross-sectional study, the sodium levels of patients receiving tre
either oxcarbazepine (n=97; mean age, 36.3 years) or carbamazepi
mean age, 38.2 years) were evaluated for the presence of hyponatr
Hyponatremia was defined as a sodium level less than or equal to 1
milliequivalents/liter (mEq/L); severe hyponatremia was defined as a
less than or equal to 128 mEq/L. Hyponatremia was observed in a s
greater number of oxcarbazepine-treated patients, as compared wit
receiving carbamazepine therapy (29.9% (29/97) vs 13.5% (61/451)
p less than 0.0001). The incidence of severe hyponatremia was also
oxcarbazepine group as compared with the carbamazepine group (
vs 2.8%(13/451), respectively). Severe hyponatremia accounted for
(12/29) of all hyponatremia cases in oxcarbazepine-treated patients
accounting for 21.3% (13/61) of all hyponatremia cases reported in
receiving carbamazepine therapy (p less than 0.0001). The investig
found that, for both groups, hyponatremia was more likely to occur i
patients. Hyponatremia was observed in 62.2% and 20.6% of oxcar
carbamazepine-treated patients 40 years of age or older, as compa

and 7.9% of oxcarbazepine- and carbamazepine-treated patients le
years of age, respectively (p less than 0.0001, both values) (Dong e
b) In controlled epilepsy clinical studies, 38 of 1524 patients (2.5%)
oxcarbazepine developed clinically significant hyponatremia (sodiur
125 millimoles/liter (mmol/L), generally within the first 3 months of tr
patients who developed the condition were asymptomatic, but patie
frequently monitored and some had their oxcarbazepine dose reduc
discontinued or had their fluid intake restricted. When oxcarbazepin
discontinued, serum sodium concentrations generally returned to nc
few days without additional treatment (Prod Info Trileptal(R), 2003).
c) Hyponatremia, defined as at least one serum sodium measurem
micromoles/liter (mcmol/L), was observed in 8 of 34 children (24%)
intellectual disability given oxcarbazepine (Gaily et al, 1998).
d) Two cases of impaired water homeostasis and death after inges
oxcarbazepine are reported (Kloster et al, 1998).
e) In a study involving children, hyponatremia occurred in 7 out of 5
given oxcarbazepine (Gaily et al, 1997).
f) Hyponatremia was reported in 80 of 350 (23%) patients whose s
concentrations were monitored during oxcarbazepine therapy. Ten
patients had low serum sodium prior to receiving oxcarbazepine tre
et al, 1993a).
g) Hyponatremic coma, with a serum sodium level of 115 millimole
(mmol/L), was reported in a 50-year-old female following almost one
therapy with oxcarbazepine 2100 milligrams/day (mg/day). On disc
the drug, serum sodium levels improved after 2 days, with resolutio
somnolence and coma (Steinhoff et al, 1992).
h) Significant reductions in mean serum sodium levels (less than 1
millimoles/liter (mmol/L) have been reported in 50% to 80% of patie
studies. Available data suggests that the incidence of hyponatremia
oxcarbazepine may be greater than that observed with carbamazep
(Pendlebury et al, 1989; Nielson et al, 1988).

3.3.3.G Hypothermia

1) Transient hypothermia has been reported rarely during administratio
oxcarbazepine (Sillanpaa & Pihlaja, 1989).

3.3.3.H Weight gain

1) Weight gain has been reported as a relatively frequent adverse effec
oxcarbazepine therapy (Anon, 1990b).

3.3.4 Gastrointestinal Effects

Diarrhea

Gastrointestinal tract finding

Nausea and vomiting

3.3.4.A Diarrhea

1) Summary

a) Diarrhea is described with the administration of oxcarbazepine ir
patients, which stopped as therapy continued (Anon, 1990b; Farago
Sillanpaa & Pihlaja, 1989; Philbert et al, 1986a; Steinhoff et al, 1992
et al, 1989).

3.3.4.B Gastrointestinal tract finding

1) Summary

a) CONSTIPATION, ANOREXIA and a sensation of heat in the sto
described with the administration of oxcarbazepine (Steinhoff et al,
1990b; Pendlebury et al, 1989; Sillanpaa & Pihlaja, 1989; Farago, 1
et al, 1986a).

2) Nausea and vomiting, diarrhea, constipation, anorexia, and a sensati
the stomach are described with the administration of oxcarbazepine.

3.3.4.C Nausea and vomiting

1) Summary

a) Nausea and vomiting are described with the use of oxcarbazepi series, nausea and vomiting occurred with the discontinuation of ox therapy. In another trial, nausea and vomiting occurred with oxcarb at the maximum dosage (2400 mg/day) (Prod Info Trileptal(R), 200

3.3.5 Hematologic Effects

3.3.5.A Thrombocytopenia

1) A case report described thrombocytopenia in a 63-year-old woman a treated with oxcarbazepine. The patient, who had a history of depressio psychotic features and multiple psychiatric hospitalizations, presented to with increasingly disorganized behavior and paranoid ideation. Platelet c of admission was 300,000/microliter. Initial treatment with nortriptyline a was unsuccessful, and the patient was switched to aripiprazole and venl an inadequate response, oxcarbazepine 300 milligrams twice daily was ongoing treatment of aripiprazole and venlafaxine. The patient responde displaying an improvement in mood and energy levels. Following oxcarb therapy for a few days, the patient developed a low-grade fever and plat dropped to 208,000/microliter. Idiopathic thrombocytopenic purpura was partial thromboplastin time, prothrombin time, and international normaliz within normal limits. Platelet count continued to drop and was 18,000/mi 10 of treatment. Oxcarbazepine was discontinued and 4 days later, plate increased to 250,000/microliter and was within normal limits 7 days after oxcarbazepine (Mahmud et al, 2006).

3.3.6 Hepatic Effects

Increased liver function test

Liver finding

3.3.6.A Increased liver function test

1) Summary

a) Elevations in serum gamma-glutaryl transpeptidase (GGT) have observed in some patients treated with oxcarbazepine or 10-hydrox (Farago, 1987b). Although no severe hepatotoxic reactions have be monitoring of liver function tests is advised during therapy.

3.3.6.B Liver finding

1) Elevated liver function tests are described with the administration of oxcarbazepine.

3.3.7 Immunologic Effects

Anaphylaxis

Cross sensitivity reaction

Immune hypersensitivity reaction, multiorgan

3.3.7.A Anaphylaxis

1) Rare cases of anaphylaxis have been reported in patients following i subsequent oxcarbazepine use. In the event of this reaction, therapy sh discontinued and the patient should not be rechallenged with oxcarbaze Info TRILEPTAL(R) oral tablets, suspension, 2007).

3.3.7.B Cross sensitivity reaction

1) Summary

a) Cross-sensitivity reactions are described with the administration oxcarbazepine (Anon, 1990b; Prod Info Trileptal(R), 2003; Beran, 1

2) LITERATURE REPORTS

a) In 1 Danish study, a cross-reaction to oxcarbazepine was seen i patients (25%) with allergic skin reactions to carbamazepine (Anon,

b) Caution is advised in using oxcarbazepine in patients with a hist sensitivity to carbamazepine (Prod Info Trileptal(R), 2003).

c) Although only a 25% cross-sensitivity has been reported betwee oxcarbazepine and carbamazepine, dermatological reactions occur patients treated with oxcarbazepine who had previously discontinue carbamazepine because of the development of skin reactions. Two developed a pruritic skin rash and 1 patient developed exfoliative de following 2 or 3 doses of oxcarbazepine (Beran, 1993).

3.3.7.C Immune hypersensitivity reaction, multiorgan

1) Although the number of cases has been limited, multiorgan hypersen disorders, often considered life-threatening and resulting in hospitalizatic reported in association with the initiation of oxcarbazepine therapy (med detection 13 days, range 4-60 days). Multiorgan hypersensitivity reactior characterized by features such as rash, fever, lymphadenopathy, abnorr function tests, hepatitis, thrombocytopenia, neutropenia, eosinophilia, pr nephritis, oliguria, hepato-renal syndrome, asthenia, and arthralgia. Oxc treatment should be discontinued and replaced with an alternative thera hypersensitivity reaction is suspected. Although there are no reports tha sensitivity with other agents (ie, carbamazepine) has caused this reactio possibility cannot be ruled out (Prod Info TRILEPTAL(R) oral tablets, sus 2007).

3.3.9 Neurologic Effects

Encephalopathy

Neurological finding

Seizure

3.3.9.A Encephalopathy

1) Summary

a) Metabolic encephalopathy has been reported in a patient due to oxcarbazepine-induced hyponatremia (Rosendahl & Friis, 1991).

3.3.9.B Neurological finding

1) Summary

a) Severe HEADACHE (2.9%), DROWSINESS, DIZZINESS (6.4% (5.2%), TREMOR (1.8%), ABNORMAL GAIT (1.7%), and FATIGUE the most frequent adverse effects observed during therapy with oral oxcarbazepine and oral 10-hydroxy carbazepine and were among tl most commonly associated with discontinuation of oxcarbazepine ir studies. Sedation, DIFFICULTY IN CONCENTRATION, and MEMO IMPAIRMENT are also described with the administration of oxcarba is some evidence that the incidence and severity of central nervous effects, including sedation, is less with oxcarbazepine than with carl (Prod Info Trileptal(R), 2003; Anon, 1990b; Dam, 1990a; Sillanpaa & 1989; Farago, 1987b; Houtkooper et al, 1987c; Bulau et al, 1987a; I 1986a; Dickinson et al, 1988; Anon, 1989b; Farago, 1987b; Zakrzev Patsalos, 1989a; Curran & Java, 1993).

2) Headache, drowsiness, dizziness, ataxia, tremor, abnormal gait, fatig encephalopathy, and oculogyric crises are described with the administra oxcarbazepine. Psychomotor slowing, concentration difficulties, speech problems, somnolence or fatigue and coordination abnormalities such as disturbances have also been associated with oxcarbazepine use.

3) LITERATURE REPORTS

a) The incidence of dizziness, drowsiness, headache, and ataxia ha similar with oxcarbazepine as compared to carbamazepine in other 1990a; Houtkooper et al, 1987c).

b) In one study, substitution of carbamazepine with oxcarbazepine

receiving polytherapy was associated with increased alertness and to concentrate (Anon, 1990b).

3.3.9.C Seizure

1) Summary

a) In a case report, a 9-year-old female developed absence-like sei after initiating oxcarbazepine therapy. The patient had been diagnos benign focal epilepsy of childhood with centrotemporal spikes and h language delay. Her seizures were activated by drowsiness and we generalized tonic-clonic or hemi-clonic seizures with occasional pos paralysis. Over a 6-month period, she had 3 nocturnal seizures follc multiple nocturnal seizures over 3 days. She was then prescribed o monotherapy. Soon after, she developed multiple daily episodes of fluttering with loss of awareness. A 30-minute electroencephalogran recorded 6 seizures and benign focal epileptiform discharges of chil (BFEDC) occurring at a rate of 9 per minute. Oxcarbazepine was th discontinued and a 24-hour EEG was performed. BFEDC decrease minute and no seizures were recorded. The patient remained off an medications for 6 months and did not experience a recurrence of ab seizures (Chapman et al, 2003).

3.3.10 Ophthalmic Effects

Eye / vision finding

Oculogyric crisis

3.3.10.A Eye / vision finding

1) Summary

a) DIPLOPIA and ABNORMAL VISION were among the adverse ef frequently associated with discontinuation of oxcarbazepine therapy trials. Diplopia has been a relatively frequent adverse effect of oxca clinical trials abnormal vision and diplopia have been reported in 14 respectively, of patients treated with oxcarbazepine (n=86) (Prod In (TM), 2002)(Anon, 1990b).

2) Visual changes including diplopia, abnormal vision, and oculogyric cr described with the administration of oxcarbazepine.

3.3.10.B Oculogyric crisis

1) Summary

a) CASE REPORT - Oculogyric crisis, which occurred with carbam ceased following its discontinuance, recurred following onset of ther oxcarbazepine in a 31-year-old male. The oculogyric crisis occurrec related event, with as many as 30 episodes daily at higher oxcarbaz of 1800 milligrams/day (mg/day). Following implantation of a vagus stimulator, oculogyric crisis ceased, although oxcarbazepine therap continued (Gatzonis et al, 1999).

b) Dose-related oculogyric crisis has been described with the admi oxcarbazepine (Gatzonis et al, 1999).

3.3.12 Psychiatric Effects

3.3.12.A Suicidal thoughts

1) Data reviewed by the US Food and Drug Administration suggest an i of suicidal behavior or ideation may exist in patients receiving therapy w antiepileptic drugs (AEDs). The analysis included 199 placebo-controllec studies covering 11 different AEDs used for several different indications epilepsy, selected psychiatric illnesses, and other conditions, including n neuropathic pain syndromes. The analysis included 27,863 patients trea and 16,029 patients who received placebo, and patients were aged 5 ye There were 4 completed suicides among patients in the AED treatment g (vs) none in the placebo groups. Suicidal behavior or ideation occurred i patients in the AED treatment groups compared to 0.22% of patients in t groups. This corresponded to an estimated 2.1 per 1000 (95% confidenc to 4.2) more patients in the AED treatment groups having suicidal behav

than the placebo groups. The increased risk of suicidality was noted at 1 starting an AED and continued to at least 24 weeks. When compared to results were generally consistent among the drugs and were seen in all subgroups. Patients treated for epilepsy, psychiatric disorders, or other were all at an increased risk for suicidality compared to placebo. Closely patients treated with AEDs for emergence or worsening of depression, s other unusual changes in behavior, which may include symptoms such a agitation, hostility, mania, and hypomania (US Food and Drug Administr

3.3.13 Renal Effects

3.3.13.A Urogenital finding

1) When compared to healthy controls (n=41), valproic acid treated mer generalized epilepsy (n=27) had smaller testicular volumes (p=0.01). Wi study however, the testicular volumes of carbamazepine treated men wi epilepsy (n=15) or oxcarbazepine treated men with partial epilepsy (n=1 differ from controls. When further examined, valproic acid treated men w sperm morphology had smaller testicular volumes than control whereas volumes of valproic acid treated men with normal sperm were similar to (Isojarvi et al, 2004).

3.3.14 Reproductive Effects

3.3.14.A Semen exam: abnormal

1) Antiepileptic agents have been associated with changes in sperm mo motility. A lower frequency of morphologically normal sperm was found i carbamazepine treated men with partial epilepsy (n=15), in valproic acid with generalized epilepsy and in oxcarbazepine treated men with genera (n=18) (p less than 0.01 for carbamazepine and valproic acid and p less oxcarbazepine) compared to healthy controls (n=41). A statistically signi decrease in the frequency of motile sperm was also found with all treatm combined when compared to the healthy controls (p less than 0.05). Wit various treatment groups, valproic acid treated patients had a statisticall decrease in the frequency of motile sperm than in the control group (p le Carbamazepine treated men had high frequencies of abnormally low spe concentration (p less than 0.001) and poorly motile sperm (p less than 0 compared to controls (Isojarvi et al, 2004).

3.3.15 Respiratory Effects

Respiratory finding

Respiratory tract infection

3.3.15.A Respiratory finding

1) Upper respiratory tract infection has been reported with the administr oxcarbazepine.

3.3.15.B Respiratory tract infection

1) Summary

a) Upper respiratory tract infection has been reported in 7% of patie clinical trials (Prod Info Trileptal(TM), 2002).

3.3.16 Other

Angioedema

Withdrawal sign or symptom

3.3.16.A Angioedema

1) Rare cases of angioedema involving the larynx, glottis, lips, and eyel reported in patients following initial or subsequent oxcarbazepine use ar fatalities in cases with laryngeal involvement . In the event of this reactio

should be discontinued and the patient should not be rechallenged with oxcarbazepine (Prod Info TRILEPTAL(R) oral tablets, suspension, 2007

3.3.16.B Withdrawal sign or symptom

1) Rapid withdrawal of antiepileptic drugs including oxcarbazepine may increased seizure frequency (Prod Info TRILEPTAL(R) oral tablets, susp 2007).

3.4 Teratogenicity/Effects in Pregnancy/Breastfeeding

A) Teratogenicity/Effects in Pregnancy

1) U.S. Food and Drug Administration's Pregnancy Category: Category C (P TRILEPTAL(R) oral tablets, suspension, 2007a) (All Trimesters)

a) Either studies in animals have revealed adverse effects on the fetus (embryocidal or other) and there are no controlled studies in women or st women and animals are not available. Drugs should be given only if the benefit justifies the potential risk to the fetus.

2) Australian Drug Evaluation Committee's (ADEC) Category: D (Australian Department of Health and Ageing Therapeutic Goods Administration, 2006)

a) Drugs which have caused, are suspected to have caused, or may be cause an increased incidence of human fetal malformations or irreversib These drugs may also have adverse pharmacological effects. Accompar should be consulted for further details.

See Drug Consult reference: PREGNANCY RISK CATEGORIES

3) Crosses Placenta: Unknown

4) Clinical Management

a) There are no adequate and well-controlled clinical studies in pregnar Limited data on the safety of oxcarbazepine during pregnancy demonstr evidence of toxicity (Gentile, 2003; Friis et al, 1993). Animal studies hav demonstrated developmental toxicities in the offspring at oral oxcarbaze similar to the maximum recommended human dose. Because oxcarbaze structurally similar to carbamazepine, which is considered to be teratoge humans, it is likely that oxcarbazepine is a human teratogen. Use oxcarb during pregnancy only if the potential benefit outweighs the potential risk (Prod Info TRILEPTAL(R) oral tablets, suspension, 2007a).

5) Literature Reports

a) In a case report of a 34-year-old woman with a 2-year history of idiop (subtype partial seizures evolving to secondary generalized seizures), tr oxcarbazepine 600 mg twice daily before and during pregnancy resulted spontaneous, uncomplicated vaginal delivery of a female infant without a effects. The patient began oxcarbazepine treatment after her diagnosis a seizure-free following the first month of therapy. During week 4 of the 39 gestation and 13 months after she started oxcarbazepine, pregnancy wa According to the patient, there was no other drug intake, no history of sm alcohol or caffeine use or infections during pregnancy. Obstetrical findin fetoprotein concentration, and three ultrasounds at weeks 22, 26, and 3(were all normal. Oxcarbazepine therapy was continued. The patient gav spontaneous and uncomplicated vaginal delivery to a female infant weig and measuring 49 cm with Apgar scores of 8 and 9 at one minute and 5 respectively, and no adverse effects. There was no exacerbation of seiz delivery (Gentile, 2003)

b) No congenital malformations were reported in 9 infants born to mothe oxcarbazepine during the first trimester of pregnancy (Friis et al, 1993).

c) Fetal structural abnormalities and other developmental toxicities were the offspring of rats and rabbits treated with either oral oxcarbazepine or monohydroxy metabolite during pregnancy at doses similar to the maxim recommended human dose. Maternal toxicity was also reported in the ra oxcarbazepine use during pregnancy (Prod Info TRILEPTAL(R) oral tabl suspension, 2007a). In mice, a malformation incidence of 8% was report pregnant mice were given the highest tolerable oxcarbazepine dose of 1 mg/kg/day on days 6 through 18 of gestation compared with a 5% incide mice given no drugs (Bennett et al, 1996)

d) .

B) Breastfeeding

1) Thomson Lactation Rating: Infant risk cannot be ruled out.

a) Available evidence and/or expert consensus is inconclusive or is inac determining infant risk when used during breastfeeding. Weigh the poter of drug treatment against potential risks before prescribing this drug duri

breastfeeding.

2) Clinical Management

a) Oxcarbazepine and its active metabolite, 10-hydroxy metabolite (MH excreted in human breast milk. The milk-to-plasma concentration ratio w be 0.5 for both drug and metabolite. Due to the potential for serious adv the nursing infant, a decision should be made to discontinue oxcarbazep discontinue nursing taking into consideration the importance of the drug mother (Prod Info TRILEPTAL(R) oral tablets, suspension, 2007a; Genti

3) Literature Reports

a) In a case report of a 34-year-old woman with a 2-year history of idiop (subtype partial seizures evolving to secondary generalized seizures), tr oxcarbazepine 600 mg twice daily before and during pregnancy and lact demonstrated no developmental abnormalities in the nursing infant after breast-feeding. The patient began oxcarbazepine treatment after her dia was seizure-free following the first month of therapy. During week 4 of th gestation and 13 months after she started oxcarbazepine, pregnancy wa Oxcarbazepine treatment was maintained throughout gestation. The pat via spontaneous and uncomplicated vaginal delivery to a female infant w kg and measuring 49 cm with Apgar scores of 8 and 9 at one minute an respectively, and no adverse effects. There was no exacerbation of seiz delivery and breast-feeding was successfully initiated with concomitant c treatment. During the first four months of nursing, the infant's developme normal (Gentile, 2003).

3.5 Drug Interactions

3.5.1 Drug-Drug Combinations

Carbamazepine

Clopidogrel

Cyclosporine

Ethinyl Estradiol

Etonogestrel

Evening Primrose

Felodipine

Fosphenytoin

Ginkgo

Lamotrigine

Levonorgestrel

Mestranol

Norelgestromin

Norethindrone

Norgestrel

Phenobarbital

Phenytoin

Selegiline

Simvastatin

Tolvaptan

Valproic Acid

Verapamil

3.5.1.A Carbamazepine

1) Interaction Effect: decreased plasma concentration of the active 10-n
metabolite of oxcarbazepine

2) Summary: Concurrent administration of oxcarbazepine and carbama
has resulted in a 40% decrease in the plasma concentration of the active
monohydroxy derivative (MHD) of oxcarbazepine (Prod Info TRILEPTAL
tablets, oral suspension, 2005). Although the exact mechanism for this c
unknown, it is believed to be partially due to the potential induction of ox
metabolism by CBZ, which is strong inducer of cytochrome P450 enzym
al, 1994). Although, the clinical significance of this interaction is unknow
plasma MHD concentrations may result in a potential loss of oxcarbazep
oxcarbazepine and carbamazepine are administered concurrently, clinic
oxcarbazepine may need to be monitored.

3) Severity: moderate

4) Onset: delayed

5) Substantiation: established

6) Clinical Management: Coadministration of oxcarbazepine and carbar
result in a decreased concentration of the active 10-monohydroxy metab
oxcarbazepine. Monitor patients for clinical response to oxcarbazepine.

7) Probable Mechanism: potential induction of cytochrome P450-mediat
oxcarbazepine metabolism

8) Literature Reports

a) In a randomized, double-blind, placebo-controlled trial in adults,
coadministration of carbamazepine (CBZ) and oxcarbazepine result
decreased levels of the pharmacologically active 10-monohydroxy c
(MHD) of oxcarbazepine. Patients (n=12) being treated with a mear
1025 milligrams (mg) (range 400 to 2000 mg) were administered a s
oral dose of oxcarbazepine and were randomized, a week later, to r
300 mg oxcarbazepine three times daily or matched placebo for 3 w
controls (n=7) were untreated patients who received the single 600
oxcarbazepine dose and 3 weeks active treatment. Study results sh
area under the concentration-time curve (AUC) for MHD at steady s
reduced by 40% (90% confidence interval: 17% decrease, 57% dec
CBZ-treated group compared to the active controls (p less than 0.05
for CBZ did not alter significantly. Although the exact mechanism fo
decrease is unknown, it was partially attributed to a potential inducti
oxcarbazepine metabolism by carbamazepine, a strong inducer of c
P450 enzymes (McKee et al, 1994; Prod Info TRILEPTAL(R) oral ta
suspension, 2005).

3.5.1.B Clopidogrel

1) Interaction Effect: reduction in clinical efficacy of clopidogrel

2) Summary: Clopidogrel is metabolized to its active metabolite by CYP
Concomitant use of CYP2C19 inhibitors, such as oxcarbazepine, would
to result in reduced levels of the active metabolite, and therefore a reduc
clinical efficacy of clopidogrel. Concomitant use of CYP2C19 inhibitors w
clopidogrel is discouraged (Prod Info PLAVIX(R) oral tablet, 2009).

3) Severity: moderate

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Concomitant use of clopidogrel and oxcarbaze
discouraged (Prod Info PLAVIX(R) oral tablet, 2009).

7) Probable Mechanism: inhibition of CYP2C19- mediated clopidogrel m
oxcarbazepine

3.5.1.C Cyclosporine

1) Interaction Effect: decreased cyclosporine concentrations
2) Summary: Cyclosporine is extensively metabolized by CYP3A isozyn
Coadministration with oxcarbazepine, a CYP3A inducer, may result in de
cyclosporine concentrations. If concomitant therapy is required, the clinic
monitor circulating cyclosporine levels and make appropriate cyclosporin
adjustments (Prod Info ESTRADERM(R) transdermal system, 2005).
3) Severity: moderate
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: Concomitant use of cyclosporine and oxcarbaz
result in decreased cyclosporine plasma concentrations. If concurrent th
required, monitor circulating cyclosporine levels and make appropriate d
adjustments as necessary (Prod Info ESTRADERM(R) transdermal syst
Monitor the patient for decreased response to cyclosporine.
7) Probable Mechanism: induction of CYP3A-mediated cyclosporine me

3.5.1.D Ethinyl Estradiol

1) Interaction Effect: decreased contraceptive effectiveness
2) Summary: In studies conducted with oral contraceptives, concurrent
of oxcarbazepine with an oral contraceptive has decreased plasma conc
2 hormonal components: ethinyl estradiol (EE) and levonorgestrel (LNG)
TRILEPTAL(R) oral tablets, oral suspension, 2005). Contraceptive effec
be reduced when hormonal contraceptives (oral, transdermal, or vaginal
coadministered with some drugs, such as oxcarbazepine, that increase t
metabolism of contraceptive steroids. This could result in unintended pre
breakthrough bleeding. Caution is advised when oxcarbazepine is admi
concurrently with hormonal contraceptives (Prod Info ORTHO EVRA(R)
system, 2005). Patients should be advised about using additional contra
methods (Prod Info NUVARING(R) vaginal ring, 2005).
3) Severity: moderate
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: Concurrent use of oxcarbazepine with hormon
contraceptives (oral, transdermal, or vaginal ring) may result in decrease
contraceptive efficacy, leading to unintended pregnancy or breakthrough
Use caution if oxcarbazepine is administered concomitantly with a comb
contraceptive.
7) Probable Mechanism: increased metabolism of contraceptive steroid
8) Literature Reports
a) The effects of oxcarbazepine (OCBZ) on the pharmacokinetics o
estradiol (EE) and levonorgestrel (LNG) were studied in 10 healthy
had taken triphasic oral contraceptives for at least three menstrual c
300 mg was administered once on day 16 of the first study cycle, tw
day 17, and three times daily from day 18 of the first cycle through c
second cycle. Combined use resulted in a significant decrease in th
the concentration-time curve (AUC) for both EE (3 +/- 1.2 vs 1.6 +/-
and LNG (29.3 +/- 94.6 vs 189.5 +/- 71.7 nmol/h) (p = 0.006 for both
not a significant change in mean maximum concentration (Cmax) va
EE or LNG. Progesterone levels were low throughout the study indi
anovulation, but one subject had prolonged menstrual bleeding and
experienced breakthrough bleeding which indicates a potential loss
contraceptive efficacy (Klosterskov-Jensen et al, 1992).
b) The effects of oxcarbazepine (OCBZ) on the pharmacokinetics o
estradiol (EE) and levonorgestrel (LN) were studied on 16 healthy w
18 to 44 years in a randomized double-blind cross-over design. Dur
different menstrual cycles, each woman was given placebo or 1200
in random sequence for 26 consecutive days with a one cycle wash
between. An oral contraceptive containing 50 mcg EE and 250 mcg
for the first 21 days of each cycle. Plasma concentrations of EE and
measured at regular intervals on days 21 to 23 of each cycle. Comp
placebo, a 47% decrease in area under the concentration-time curv
both EE and LN was seen during OCBZ treatment. Peak plasma EE
concentrations decreased from 180 pg/ml to 117 pg/ml during the p

OCBZ cycle, respectively (p less than 0.01) and the LN concentratic
from 10.2 to 7.7 ng/ml (p less than 0.01). In addition, the half-lives o
decreased from 13.6 to 7.9 hours (p less than 0.01) and from 28.8 t
respectively (p less than 0.01) (Fattore et al, 1999).
c) Concurrent administration of oxcarbazepine with an oral contrac
affected plasma concentrations 2 hormonal components: ethinyl est
and levonorgestrel (LNG). In studies conducted with oral combinatic
contraceptives, the mean area under the concentration-time curve (
for EE were reduced by 48% (90% confidence interval (CI): 22 to 65
and 52% (90% CI: 38 to 52) in another study. The mean AUC value
were reduced by 32% (90% CI: 20 to 45) in one study and 52% (90
52) in another study (Prod Info TRILEPTAL(R) oral tablets, oral sus
2005).

3.5.1.E Etonogestrel

1) Interaction Effect: decreased contraceptive effectiveness
2) Summary: In studies conducted with oral contraceptives, concurrent
of oxcarbazepine with an oral contraceptive has decreased plasma conc
2 hormonal components: ethinyl estradiol (EE) and levonorgestrel (LNG)
TRILEPTAL(R) oral tablets, oral suspension, 2005). Contraceptive effec
be reduced when hormonal contraceptives (oral, transdermal, or vaginal
coadministered with some drugs, such as oxcarbazepine, that increase
metabolism of contraceptive steroids. This could result in unintended pre
breakthrough bleeding. Caution is advised when oxcarbazepine is admi
concurrently with hormonal contraceptives (Prod Info ORTHO EVRA(R)
system, 2005). Patients should be advised about using additional contra
methods (Prod Info NUVARING(R) vaginal ring, 2005).
3) Severity: moderate
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: Concurrent use of oxcarbazepine with hormon
contraceptives (oral, transdermal, or vaginal ring) may result in decrease
contraceptive efficacy, leading to unintended pregnancy or breakthrough
Use caution if oxcarbazepine is administered concomitantly with a comb
contraceptive.
7) Probable Mechanism: increased metabolism of contraceptive steroid
8) Literature Reports
a) The effects of oxcarbazepine (OCBZ) on the pharmacokinetics c
estradiol (EE) and levonorgestrel (LNG) were studied in 10 healthy
had taken triphasic oral contraceptives for at least three menstrual c
300 mg was administered once on day 16 of the first study cycle, tw
day 17, and three times daily from day 18 of the first cycle through c
second cycle. Combined use resulted in a significant decrease in th
the concentration-time curve (AUC) for both EE (3 +/- 1.2 vs 1.6 +/-
and LNG (29.3 +/- 94.6 vs 189.5 +/- 71.7 nmol/h) (p = 0.006 for both
not a significant change in mean maximum concentration (Cmax) va
EE or LNG. Progesterone levels were low throughout the study indi
anovulation, but one subject had prolonged menstrual bleeding and
experienced breakthrough bleeding which indicates a potential loss
contraceptive efficacy (Klosterskov-Jensen et al, 1992).
b) The effects of oxcarbazepine (OCBZ) on the pharmacokinetics c
estradiol (EE) and levonorgestrel (LN) were studied on 16 healthy w
18 to 44 years in a randomized double-blind cross-over design. Dur
different menstrual cycles, each woman was given placebo or 1200
in random sequence for 26 consecutive days with a one cycle wash
between. An oral contraceptive containing 50 mcg EE and 250 mcg
for the first 21 days of each cycle. Plasma concentrations of EE and
measured at regular intervals on days 21 to 23 of each cycle. Comp
placebo, a 47% decrease in area under the concentration-time curv
both EE and LN was seen during OCBZ treatment. Peak plasma EE
concentrations decreased from 180 pg/ml to 117 pg/ml during the p
OCBZ cycle, respectively (p less than 0.01) and the LN concentratic
from 10.2 to 7.7 ng/ml (p less than 0.01). In addition, the half-lives o
decreased from 13.6 to 7.9 hours (p less than 0.01) and from 28.8 t
respectively (p less than 0.01) (Fattore et al, 1999).
c) Concurrent administration of oxcarbazepine with an oral contrac
affected plasma concentrations 2 hormonal components: ethinyl est

and levonorgestrel (LNG). In studies conducted with oral combinatic contraceptives, the mean area under the concentration-time curve (for EE were reduced by 48% (90% confidence interval (CI): 22 to 6 and 52% (90% CI: 38 to 52) in another study. The mean AUC value were reduced by 32% (90% CI: 20 to 45) in one study and 52% (90 52) in another study (Prod Info TRILEPTAL(R) oral tablets, oral sus 2005).

3.5.1.F Evening Primrose

1) Interaction Effect: reduced anticonvulsant effectiveness

2) Summary: Theoretically, evening primrose oil may reduce the effecti anticonvulsants by lowering the seizure threshold. Evening primrose oil i contraindicated in patients with epilepsy (Barber, 1998; Newall et al, 199

3) Severity: moderate

4) Onset: delayed

5) Substantiation: theoretical

6) Clinical Management: Avoid concomitant use of evening primrose oil anticonvulsants.

7) Probable Mechanism: evening primrose oil may reduce the seizure th

3.5.1.G Felodipine

1) Interaction Effect: decreased felodipine exposure

2) Summary: Oxcarbazepine and its active 10-monohydroxy metabolite subgroup of cytochrome P450 3A family of enzymes which are utilized ir metabolism of felodipine. A small study indicated that repeated coadmin felodipine and oxcarbazepine decreased exposure to felodipine; howeve plasma concentrations remained within the recommended therapeutic ra et al, 1993; Prod Info TRILEPTAL(R) oral tablets, oral suspension, 2005 and oxcarbazepine are coadministered, it is advisable to monitor clinical felodipine.

3) Severity: moderate

4) Onset: delayed

5) Substantiation: probable

6) Clinical Management: Coadministration of felodipine and oxcarbazep resulted in decreased exposure to felodipine. If felodipine and oxcarbaze administered concurrently, monitor clinical response to felodipine.

7) Probable Mechanism: induction of cytochrome P450-mediated felodi metabolism

8) Literature Reports

a) A pharmacokinetic study was conducted with seven healthy subj were given felodipine 10 mg daily for 13 days; on day 6 oxcarbazep was given and was increased to 450 mg twice daily from day 7 to 1 dose of oxcarbazepine had no effect on felodipine pharmacokinetic compared with felodipine alone, but the week-long coadministration decrease of felodipine area under the concentration-time curve (AU (110.2 +/- 35.9 vs 79.2 +/- 25.7; p less than 0.05) and maximum pla concentration by 34% (9.7 +/- 3.2 vs 6.4 +/- 2 nmol/L). Similar result obtained for the inactive felodipine pyridine metabolite. Despite thes in felodipine AUC and Cmax, the felodipine plasma concentrations r within the recommended therapeutic range (Zaccara et al, 1993).

3.5.1.H Fosphenytoin

1) Interaction Effect: an increased risk of phenytoin toxicity (ataxia, hype nystagmus, tremor)

2) Summary: Fosphenytoin is a prodrug of phenytoin and the same inte occur with phenytoin are expected to occur with fosphenytoin (Prod Info 1999). When phenytoin in doses of 250 mg to 500 mg daily was combin oxcarbazepine in doses of 600 mg to 1800 mg daily, there was less thar change in the concentration of phenytoin. Additionally, concentrations of monohydroxy metabolite (MHD) of oxcarbazepine, which possesses pha activity, were decreased by 30%. This effect is most likely due to inducti cytochrome P450 enzyme system by phenytoin. When the same doses were combined with oxcarbazepine in doses greater than 1200 mg daily to a 40% increase in plasma phenytoin concentrations (Prod Info Trilept

3) Severity: moderate

4) Onset: delayed

5) Substantiation: probable

6) Clinical Management: Patients should be monitored for phenytoin tox
receiving oxcarbazepine concurrently, especially when oxcarbazepine d
1200 mg daily. A decrease in the phenytoin dose may be required.
7) Probable Mechanism: inhibition of cytochrome P450 2C19-mediated
metabolism
8) Literature Reports
a) In polypharmacy studies employing add-on oxcarbazepine and
carbamazepine, increased serum levels of valproic acid and phenyt
observed with patients receiving oxcarbazepine. This was attributec
enzyme induction (Bulau et al, 1987; Houtkooper et al, 1987). Alterr
dependent enzyme induction has been reported by some investigat
doses of oxcarbazepine produced enzyme induction that was simila
carbamazepine (Patsalos et al, 1990a). Further studies are requirec
if oxcarbazepine will offer a significant advantage over carbamazep
regard to enzyme induction.

3.5.1.l Ginkgo

1) Interaction Effect: decreased anticonvulsant effectiveness
2) Summary: In a case report, 2 patients with epilepsy previously well c
valproate sodium developed a recurrence of seizures after ingesting ginl
Seizure control was regained after ginkgo was withdrawn (Granger, 200
developed seizures after exposure to 4'-O-methylpyridoxine arising from
ginkgo seeds (Yagi et al, 1993a). The compound 4'-O-methylpyridoxine,
is found in ginkgo seeds (used as food in Japan) as well as in leaves, th
component from which commercially available extracts are derived (Arer
1996a). The majority of ginkgo leaf products should not contain sufficien
4'-O-methylpyridoxine to cause seizures. However, ginkgo products are
assayed to assure that 4'-O-methylpyridixone is not contained in the con
product. Of concern are those instances where, depending on the harve
the potential introduction of contamination, 4'-O-methylpyridoxine may b
sufficient amounts to be problematic in vulnerable populations (eg, infan
with known seizure disorders).
3) Severity: moderate
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: Avoid concomitant use of ginkgo and anticonv
patients with epilepsy. If seizures occur for the first time or recur in patie
controlled by anticonvulsant medication, inquire about the use of ginkgo
extract. If possible, an assay should be conducted on the specific produc
if 4'-O-methylpyridoxine is present.
7) Probable Mechanism: neurotoxin 4'-O-methylpyridoxine (found in lea
seeds of ginkgo biloba) may cause seizures
8) Literature Reports
a) The serum of a 21-month-old patient with gin-nan food poisoning
for 4'-O-methylpyridoxine levels. The serum concentration was 0.9
micrograms/milliliter (mcg/mL) at 8.5 hours after ingesting ginkgo se
decreasing to 0.05 mcg/mL at 15.5 hours. The authors concluded th
methylpyridoxine content was responsible for the tonic/clonic convu
loss of consciousness observed. They further observed that infants
particularly vulnerable (Yagi et al, 1993).
b) Four to six milligrams of the neurotoxin 4'-O-methylpyridoxine ha
isolated from 2 kilograms of Ginkgo biloba leaves which is the sourc
commercially-available products. Highest amounts were found in se
micrograms (mcg)/seed) and leaves (5 mcg/leaf) derived from the tr
of July and beginning of August. The albumen of the seed can conta
mcg/gram dry weight, but this is reduced to 0.75-1.32 mcg/gram dry
boiled. The unprocessed seed coats contain from 5.44-7.15 mcg/gr
The neurotoxin in ginkgo leaf was detected in medications and it wa
detectable in homeopathic preparations. Specifically, 8.13 mcg/mL
methylpyridoxine was found in Tebonin Forte(R), 9.77 mcg/mL in R
mcg/mL in Kaveri Forte(R), and 7.18 mcg/mL in Gingium(R). Based
recommended daily intake, this translates into a maximum daily inta
methylpyridoxine of 48.78 mcg, 58.62 mcg, 11.40 mcg, and 43.08 m
Tebonin Forte(R), Rokan(R), Kaveri Forte(R), and Gingium(R), resp
Among the homeopathic products, Ginkgo biloba Urtinktur Hanosar
Ginkgo biloba Urtinktur DHU(R) contained 0.301 mcg/mL and 0.589
4'-O-methylpyridoxine, respectively. However, the authors note that

contained in medicinal extracts of ginkgo leaves may be too low to b
significance. Concern remains with the variance in 4'-O-methylpyrid
depending on the season during which the ginkgo was harvested (A
1996).

c) Seizures recurred in 2 patients, both with epilepsy that was well
prior to ingesting ginkgo biloba (Gb). The patients (an 84-year-old w
78-year-old man) had been free of seizures for at least 18 months p
beginning therapy with Gb 120 milligrams daily to treat cognitive de
patients developed seizures within 2 weeks of beginning Gb therapy
remained seizure-free (without changing anticonvulsant therapy) aft
discontinuing Gb (Granger, 2001).

3.5.1.J Lamotrigine

1) Interaction Effect: reduced lamotrigine concentrations and possible lo
control

2) Summary: Oxcarbazepine is structurally similar to carbamazepine bu
form an epoxide metabolite, which is considered responsible for the neu
of carbamazepine. When lamotrigine and oxcarbazepine were administe
concurrently to 14 epileptic patients, plasma concentrations of lamotrigin
decreased 28.7% compared to lamotrigine monotherapy (May et al, 199
patients who had received lamotrigine and oxcarbazepine concurrently,
occurred several weeks after oxcarbazepine discontinuation or dose red
Induction of lamotrigine metabolism by oxcarbazepine was postulated to
mechanism, such oxcarbazepine discontinuation or a dose reduction ma
resulted in a slow increase in lamotrigine levels, thereby increasing its to
& deLeon, 2007). Concomitant use of lamotrigine and oxcarbazepine ma
monitoring the patient closely for seizure control and increasing the lamo
as necessary. Conversely, in patients receiving these agents concurrent
oxcarbazepine is discontinued or its dose is reduced, lamotrigine doses
be reduced. Additionally, the patient may need to be monitored over sev
signs/symptoms of lamotrigine toxicity.

3) Severity: moderate

4) Onset: delayed

5) Substantiation: probable

6) Clinical Management: Monitor seizure control and anticipate a possib
increase lamotrigine doses if oxcarbazepine is added to therapy. Conver
oxcarbazepine is withdrawn from therapy or if dosage is reduced, lamotr
may need to be reduced and the patient may need to be monitored over
weeks for symptoms of lamotrigine toxicity.

7) Probable Mechanism: hepatic induction by oxcarbazepine of lamotrig
metabolism

8) Literature Reports

a) Two patients, receiving lamotrigine and oxcarbazepine concurre
experienced oral ulcers several weeks after oxcarbazepine discontin
dose reduction. In the first case, a 35-year-old woman being treated
disorder (BD II), hypothyroidism, gastritis, migraines, and asthma w
after experiencing one week of worsening depression and two days
thoughts and treated with oxcarbazepine 600 mg/day, topiramate, fl
aripiprazole, quetiapine, lithium, naproxen, pantoprazole, amoxicillin
levothyroxine. On day 2, lamotrigine 50 mg/day was initiated and titr
200 mg/day by day 6. Oxcarbazepine dose was decreased and stop
and she was discharged on day 8 with lamotrigine 200 mg, topirama
aripiprazole, escitalopram, naproxen, pantoprazole, levothyroxine, a
hydroxyzine. On day 42 (41 days after starting lamotrigine and 39 d
stopping oxcarbazepine), she developed painful tongue ulcers. Sub
lamotrigine was stopped and the ulcers resolved in 4 days. In the se
36-year-old man with BD II, hypertension, and GERD was admitted
suicide attempt and prescribed oxcarbazepine 600 mg/day, phenyto
venlafaxine, mirtazapine, metoprolol, and famotidine. Lamotrigine 5
initiated on day 11 and titrated up to 100 mg/day by day 14. He was
on day 14 with lamotrigine 100 mg and oxcarbazepine 1200 mg (alo
medications); however, he reduced the oxcarbazepine dose to 600
discharge. On day 44 (22 days after oxcarbazepine dose decrease)
developed several painful mouth sores on his lips, gums, and tongu
lamotrigine and oxcarbazepine were discontinued and the ulcers res
completely (O'Neill & deLeon, 2007).

b) Lamotrigine serum concentrations from 222 patients receiving la

monotherapy (n = 64) or combination therapy with another antiepile
were evaluated. Fourteen patients were being treated with lamotrigi
oxcarbazepine. In the lamotrigine monotherapy group, the lamotrigi
concentration was 7.14 mcg/mL while the mean dose was 7.27 mg/
lamotrigine level-to-dose ratio (LDR) in this group calculated out to
mcg/mL/mg/kg. In the subjects receiving oxcarbazepine in addition
the plasma concentration was 4.73 mcg/mL while the mean dose w
mg/dose/kg. The lamotrigine LDR in this group was 0.71 mcg/mL/m
demonstrating the inducing properties of oxcarbazepine on lamotrig
metabolism (May et al, 1999).

3.5.1.K Levonorgestrel

1) Interaction Effect: decreased contraceptive effectiveness

2) Summary: In studies conducted with oral contraceptives, concurrent
of oxcarbazepine with an oral contraceptive has decreased plasma conc
2 hormonal components: ethinyl estradiol (EE) and levonorgestrel (LNG)
TRILEPTAL(R) oral tablets, oral suspension, 2005). Contraceptive effec
be reduced when hormonal contraceptives (oral, transdermal, or vaginal
coadministered with some drugs, such as oxcarbazepine, that increase
metabolism of contraceptive steroids. This could result in unintended pre
breakthrough bleeding. Caution is advised when oxcarbazepine is admi
concurrently with hormonal contraceptives (Prod Info ORTHO EVRA(R)
system, 2005). Patients should be advised about using additional contra
methods (Prod Info NUVARING(R) vaginal ring, 2005).

3) Severity: moderate

4) Onset: delayed

5) Substantiation: probable

6) Clinical Management: Concurrent use of oxcarbazepine with hormon
contraceptives (oral, transdermal, or vaginal ring) may result in decrease
contraceptive efficacy, leading to unintended pregnancy or breakthrough
Use caution if oxcarbazepine is administered concomitantly with a comb
contraceptive.

7) Probable Mechanism: increased metabolism of contraceptive steroid

8) Literature Reports

a) The effects of oxcarbazepine (OCBZ) on the pharmacokinetics o
estradiol (EE) and levonorgestrel (LNG) were studied in 10 healthy
had taken triphasic oral contraceptives for at least three menstrual c
300 mg was administered once on day 16 of the first study cycle, tw
day 17, and three times daily from day 18 of the first cycle through c
second cycle. Combined use resulted in a significant decrease in th
the concentration-time curve (AUC) for both EE (3 +/- 1.2 vs 1.6 +/-
and LNG (29.3 +/- 94.6 vs 189.5 +/- 71.7 nmol/h) (p = 0.006 for both
not a significant change in mean maximum concentration (Cmax) va
EE or LNG. Progesterone levels were low throughout the study indi
anovulation, but one subject had prolonged menstrual bleeding and
experienced breakthrough bleeding which indicates a potential loss
contraceptive efficacy (Klosterskov-Jensen et al, 1992).

b) The effects of oxcarbazepine (OCBZ) on the pharmacokinetics o
estradiol (EE) and levonorgestrel (LN) were studied on 16 healthy w
18 to 44 years in a randomized double-blind cross-over design. Dur
different menstrual cycles, each woman was given placebo or 1200
in random sequence for 26 consecutive days with a one cycle wash
between. An oral contraceptive containing 50 mcg EE and 250 mcg
for the first 21 days of each cycle. Plasma concentrations of EE and
measured at regular intervals on days 21 to 23 of each cycle. Comp
placebo, a 47% decrease in area under the concentration-time curv
both EE and LN was seen during OCBZ treatment. Peak plasma EE
concentrations decreased from 180 pg/ml to 117 pg/ml during the p
OCBZ cycle, respectively (p less than 0.01) and the LN concentratio
from 10.2 to 7.7 ng/ml (p less than 0.01). In addition, the half-lives o
decreased from 13.6 to 7.9 hours (p less than 0.01) and from 28.8 t
respectively (p less than 0.01) (Fattore et al, 1999).

c) Concurrent administration of oxcarbazepine with an oral contrac
affected plasma concentrations 2 hormonal components: ethinyl est
and levonorgestrel (LNG). In studies conducted with oral combinatio
contraceptives, the mean area under the concentration-time curve (
for EE were reduced by 48% (90% confidence interval (CI): 22 to 65

and 52% (90% CI: 38 to 52) in another study. The mean AUC value were reduced by 32% (90% CI: 20 to 45) in one study and 52% (90 52) in another study (Prod Info TRILEPTAL(R) oral tablets, oral sus 2005).

3.5.1.L Mestranol

1) Interaction Effect: decreased contraceptive effectiveness

2) Summary: In studies conducted with oral contraceptives, concurrent of oxcarbazepine with an oral contraceptive has decreased plasma conc 2 hormonal components: ethinyl estradiol (EE) and levonorgestrel (LNG) TRILEPTAL(R) oral tablets, oral suspension, 2005). Contraceptive effec be reduced when hormonal contraceptives (oral, transdermal, or vaginal coadministered with some drugs, such as oxcarbazepine, that increase t metabolism of contraceptive steroids. This could result in unintended pre breakthrough bleeding. Caution is advised when oxcarbazepine is admi concurrently with hormonal contraceptives (Prod Info ORTHO EVRA(R) system, 2005). Patients should be advised about using additional contra methods (Prod Info NUVARING(R) vaginal ring, 2005).

3) Severity: moderate

4) Onset: delayed

5) Substantiation: probable

6) Clinical Management: Concurrent use of oxcarbazepine with hormon contraceptives (oral, transdermal, or vaginal ring) may result in decrease contraceptive efficacy, leading to unintended pregnancy or breakthrough Use caution if oxcarbazepine is administered concomitantly with a comb contraceptive.

7) Probable Mechanism: increased metabolism of contraceptive steroid

8) Literature Reports

a) The effects of oxcarbazepine (OCBZ) on the pharmacokinetics o estradiol (EE) and levonorgestrel (LNG) were studied in 10 healthy had taken triphasic oral contraceptives for at least three menstrual c 300 mg was administered once on day 16 of the first study cycle, tw day 17, and three times daily from day 18 of the first cycle through c second cycle. Combined use resulted in a significant decrease in th the concentration-time curve (AUC) for both EE (3 +/- 1.2 vs 1.6 +/- and LNG (29.3 +/- 94.6 vs 189.5 +/- 71.7 nmol/h) (p = 0.006 for both not a significant change in mean maximum concentration (Cmax) va EE or LNG. Progesterone levels were low throughout the study indi anovulation, but one subject had prolonged menstrual bleeding and experienced breakthrough bleeding which indicates a potential loss contraceptive efficacy (Klosterskov-Jensen et al, 1992).

b) The effects of oxcarbazepine (OCBZ) on the pharmacokinetics o estradiol (EE) and levonorgestrel (LN) were studied on 16 healthy w 18 to 44 years in a randomized double-blind cross-over design. Dur different menstrual cycles, each woman was given placebo or 1200 in random sequence for 26 consecutive days with a one cycle wash between. An oral contraceptive containing 50 mcg EE and 250 mcg for the first 21 days of each cycle. Plasma concentrations of EE and measured at regular intervals on days 21 to 23 of each cycle. Comp placebo, a 47% decrease in area under the concentration-time curv both EE and LN was seen during OCBZ treatment. Peak plasma EE concentrations decreased from 180 pg/ml to 117 pg/ml during the p OCBZ cycle, respectively (p less than 0.01) and the LN concentratio from 10.2 to 7.7 ng/ml (p less than 0.01). In addition, the half-lives o decreased from 13.6 to 7.9 hours (p less than 0.01) and from 28.8 t respectively (p less than 0.01) (Fattore et al, 1999).

c) Concurrent administration of oxcarbazepine with an oral contrac affected plasma concentrations 2 hormonal components: ethinyl est and levonorgestrel (LNG). In studies conducted with oral combinatio contraceptives, the mean area under the concentration-time curve (for EE were reduced by 48% (90% confidence interval (CI): 22 to 65 and 52% (90% CI: 38 to 52) in another study. The mean AUC value were reduced by 32% (90% CI: 20 to 45) in one study and 52% (90 52) in another study (Prod Info TRILEPTAL(R) oral tablets, oral sus 2005).

3.5.1.M Norelgestromin

1) Interaction Effect: decreased contraceptive effectiveness
2) Summary: In studies conducted with oral contraceptives, concurrent
of oxcarbazepine with an oral contraceptive has decreased plasma conc
2 hormonal components: ethinyl estradiol (EE) and levonorgestrel (LNG)
TRILEPTAL(R) oral tablets, oral suspension, 2005). Contraceptive effec
be reduced when hormonal contraceptives (oral, transdermal, or vaginal
coadministered with some drugs, such as oxcarbazepine, that increase
metabolism of contraceptive steroids. This could result in unintended pre
breakthrough bleeding. Caution is advised when oxcarbazepine is admi
concurrently with hormonal contraceptives (Prod Info ORTHO EVRA(R)
system, 2005). Patients should be advised about using additional contra
methods (Prod Info NUVARING(R) vaginal ring, 2005).
3) Severity: moderate
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: Concurrent use of oxcarbazepine with hormon
contraceptives (oral, transdermal, or vaginal ring) may result in decrease
contraceptive efficacy, leading to unintended pregnancy or breakthrough
Use caution if oxcarbazepine is administered concomitantly with a comb
contraceptive.
7) Probable Mechanism: increased metabolism of contraceptive steroid
8) Literature Reports
a) The effects of oxcarbazepine (OCBZ) on the pharmacokinetics o
estradiol (EE) and levonorgestrel (LNG) were studied in 10 healthy
had taken triphasic oral contraceptives for at least three menstrual c
300 mg was administered once on day 16 of the first study cycle, tw
day 17, and three times daily from day 18 of the first cycle through c
second cycle. Combined use resulted in a significant decrease in th
the concentration-time curve (AUC) for both EE (3 +/- 1.2 vs 1.6 +/-
and LNG (29.3 +/- 94.6 vs 189.5 +/- 71.7 nmol/h) (p = 0.006 for both
not a significant change in mean maximum concentration (Cmax) va
EE or LNG. Progesterone levels were low throughout the study indi
anovulation, but one subject had prolonged menstrual bleeding and
experienced breakthrough bleeding which indicates a potential loss
contraceptive efficacy (Klosterskov-Jensen et al, 1992).
b) The effects of oxcarbazepine (OCBZ) on the pharmacokinetics o
estradiol (EE) and levonorgestrel (LN) were studied on 16 healthy w
18 to 44 years in a randomized double-blind cross-over design. Dur
different menstrual cycles, each woman was given placebo or 1200
in random sequence for 26 consecutive days with a one cycle wash
between. An oral contraceptive containing 50 mcg EE and 250 mcg
for the first 21 days of each cycle. Plasma concentrations of EE and
measured at regular intervals on days 21 to 23 of each cycle. Comp
placebo, a 47% decrease in area under the concentration-time curv
both EE and LN was seen during OCBZ treatment. Peak plasma EE
concentrations decreased from 180 pg/ml to 117 pg/ml during the p
OCBZ cycle, respectively (p less than 0.01) and the LN concentratio
from 10.2 to 7.7 ng/ml (p less than 0.01). In addition, the half-lives o
decreased from 13.6 to 7.9 hours (p less than 0.01) and from 28.8 t
respectively (p less than 0.01) (Fattore et al, 1999).
c) Concurrent administration of oxcarbazepine with an oral contrac
affected plasma concentrations 2 hormonal components: ethinyl est
and levonorgestrel (LNG). In studies conducted with oral combinatio
contraceptives, the mean area under the concentration-time curve (
for EE were reduced by 48% (90% confidence interval (CI): 22 to 65
and 52% (90% CI: 38 to 52) in another study. The mean AUC value
were reduced by 32% (90% CI: 20 to 45) in one study and 52% (90
52) in another study (Prod Info TRILEPTAL(R) oral tablets, oral susp
2005).

3.5.1.N Norethindrone

1) Interaction Effect: decreased contraceptive effectiveness
2) Summary: In studies conducted with oral contraceptives, concurrent
of oxcarbazepine with an oral contraceptive has decreased plasma conc
2 hormonal components: ethinyl estradiol (EE) and levonorgestrel (LNG)
TRILEPTAL(R) oral tablets, oral suspension, 2005). Contraceptive effec
be reduced when hormonal contraceptives (oral, transdermal, or vaginal

coadministered with some drugs, such as oxcarbazepine, that increase t
metabolism of contraceptive steroids. This could result in unintended pre
breakthrough bleeding. Caution is advised when oxcarbazepine is admi
concurrently with hormonal contraceptives (Prod Info ORTHO EVRA(R)
system, 2005). Patients should be advised about using additional contra
methods (Prod Info NUVARING(R) vaginal ring, 2005).

3) Severity: moderate

4) Onset: delayed

5) Substantiation: probable

6) Clinical Management: Concurrent use of oxcarbazepine with hormon
contraceptives (oral, transdermal, or vaginal ring) may result in decrease
contraceptive efficacy, leading to unintended pregnancy or breakthrough
Use caution if oxcarbazepine is administered concomitantly with a comb
contraceptive.

7) Probable Mechanism: increased metabolism of contraceptive steroid

8) Literature Reports

a) The effects of oxcarbazepine (OCBZ) on the pharmacokinetics c
estradiol (EE) and levonorgestrel (LNG) were studied in 10 healthy
had taken triphasic oral contraceptives for at least three menstrual c
300 mg was administered once on day 16 of the first study cycle, tw
day 17, and three times daily from day 18 of the first cycle through c
second cycle. Combined use resulted in a significant decrease in th
the concentration-time curve (AUC) for both EE (3 +/- 1.2 vs 1.6 +/-
and LNG (29.3 +/- 94.6 vs 189.5 +/- 71.7 nmol/h) (p = 0.006 for both
not a significant change in mean maximum concentration (Cmax) va
EE or LNG. Progesterone levels were low throughout the study indi
anovulation, but one subject had prolonged menstrual bleeding and
experienced breakthrough bleeding which indicates a potential loss
contraceptive efficacy (Klosterskov-Jensen et al, 1992).

b) The effects of oxcarbazepine (OCBZ) on the pharmacokinetics c
estradiol (EE) and levonorgestrel (LN) were studied on 16 healthy w
18 to 44 years in a randomized double-blind cross-over design. Dur
different menstrual cycles, each woman was given placebo or 1200
in random sequence for 26 consecutive days with a one cycle wash
between. An oral contraceptive containing 50 mcg EE and 250 mcg
for the first 21 days of each cycle. Plasma concentrations of EE and
measured at regular intervals on days 21 to 23 of each cycle. Comp
placebo, a 47% decrease in area under the concentration-time curv
both EE and LN was seen during OCBZ treatment. Peak plasma EE
concentrations decreased from 180 pg/ml to 117 pg/ml during the p
OCBZ cycle, respectively (p less than 0.01) and the LN concentratio
from 10.2 to 7.7 ng/ml (p less than 0.01). In addition, the half-lives o
decreased from 13.6 to 7.9 hours (p less than 0.01) and from 28.8 t
respectively (p less than 0.01) (Fattore et al, 1999).

c) Concurrent administration of oxcarbazepine with an oral contrac
affected plasma concentrations 2 hormonal components: ethinyl est
and levonorgestrel (LNG). In studies conducted with oral combinatio
contraceptives, the mean area under the concentration-time curve (
for EE were reduced by 48% (90% confidence interval (CI): 22 to 65
and 52% (90% CI: 38 to 52) in another study. The mean AUC value
were reduced by 32% (90% CI: 20 to 45) in one study and 52% (90
52) in another study (Prod Info TRILEPTAL(R) oral tablets, oral susp
2005).

3.5.1.O Norgestrel

1) Interaction Effect: decreased contraceptive effectiveness

2) Summary: In studies conducted with oral contraceptives, concurrent
of oxcarbazepine with an oral contraceptive has decreased plasma conc
2 hormonal components: ethinyl estradiol (EE) and levonorgestrel (LNG)
TRILEPTAL(R) oral tablets, oral suspension, 2005). Contraceptive effec
be reduced when hormonal contraceptives (oral, transdermal, or vaginal
coadministered with some drugs, such as oxcarbazepine, that increase t
metabolism of contraceptive steroids. This could result in unintended pre
breakthrough bleeding. Caution is advised when oxcarbazepine is admi
concurrently with hormonal contraceptives (Prod Info ORTHO EVRA(R)
system, 2005). Patients should be advised about using additional contra
methods (Prod Info NUVARING(R) vaginal ring, 2005).

3) Severity: moderate
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: Concurrent use of oxcarbazepine with hormon contraceptives (oral, transdermal, or vaginal ring) may result in decrease contraceptive efficacy, leading to unintended pregnancy or breakthrough Use caution if oxcarbazepine is administered concomitantly with a comb contraceptive.
7) Probable Mechanism: increased metabolism of contraceptive steroid
8) Literature Reports
a) The effects of oxcarbazepine (OCBZ) on the pharmacokinetics c estradiol (EE) and levonorgestrel (LNG) were studied in 10 healthy had taken triphasic oral contraceptives for at least three menstrual c 300 mg was administered once on day 16 of the first study cycle, tw day 17, and three times daily from day 18 of the first cycle through c second cycle. Combined use resulted in a significant decrease in th the concentration-time curve (AUC) for both EE (3 +/- 1.2 vs 1.6 +/- and LNG (29.3 +/- 94.6 vs 189.5 +/- 71.7 nmol/h) (p = 0.006 for both not a significant change in mean maximum concentration (Cmax) va EE or LNG. Progesterone levels were low throughout the study indi anovulation, but one subject had prolonged menstrual bleeding and experienced breakthrough bleeding which indicates a potential loss contraceptive efficacy (Klosterskov-Jensen et al, 1992).
b) The effects of oxcarbazepine (OCBZ) on the pharmacokinetics c estradiol (EE) and levonorgestrel (LN) were studied on 16 healthy w 18 to 44 years in a randomized double-blind cross-over design. Dur different menstrual cycles, each woman was given placebo or 1200 in random sequence for 26 consecutive days with a one cycle wash between. An oral contraceptive containing 50 mcg EE and 250 mcg for the first 21 days of each cycle. Plasma concentrations of EE anc measured at regular intervals on days 21 to 23 of each cycle. Comp placebo, a 47% decrease in area under the concentration-time curv both EE and LN was seen during OCBZ treatment. Peak plasma EE concentrations decreased from 180 pg/ml to 117 pg/ml during the p OCBZ cycle, respectively (p less than 0.01) and the LN concentratic from 10.2 to 7.7 ng/ml (p less than 0.01). In addition, the half-lives o decreased from 13.6 to 7.9 hours (p less than 0.01) and from 28.8 t respectively (p less than 0.01) (Fattore et al, 1999).
c) Concurrent administration of oxcarbazepine with an oral contrac affected plasma concentrations 2 hormonal components: ethinyl est and levonorgestrel (LNG). In studies conducted with oral combinatic contraceptives, the mean area under the concentration-time curve (for EE were reduced by 48% (90% confidence interval (CI): 22 to 65 and 52% (90% CI: 38 to 52) in another study. The mean AUC value were reduced by 32% (90% CI: 20 to 45) in one study and 52% (90 52) in another study (Prod Info TRILEPTAL(R) oral tablets, oral sus 2005).

3.5.1.P Phenobarbital
1) Interaction Effect: decreased concentration of the active 10-monohyc metabolite of oxcarbazepine and potential loss of oxcarbazepine efficacy
2) Summary: Concurrent administration of oxcarbazepine (600 to 1,800 (mg)/day) in patients receiving treatment with phenobarbital (100 to 150 resulted in a 25% decrease (90% confidence interval (CI), 12% decrease decrease) in the plasma concentration of oxcarbazepine's 10-monohydr (MHD) and a 14% increase (90% confidence interval (CI), 2% increase t increase) in the phenobarbital concentration (Prod Info TRILEPTAL(R) c oral suspension, 2005). Although the clinical significance of this interacti unknown, MHD is the pharmacologically active metabolite of oxcarbazep decreased plasma MHD concentrations may result in potential loss of ox efficacy. If oxcarbazepine and phenobarbital are administered concurrer response to oxcarbazepine may need to be monitored.
3) Severity: moderate
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: Coadministration of oxcarbazepine and pheno resulted in decreased concentrations of the active 10-monohydroxy met

oxcarbazepine. Monitor patients for clinical response to oxcarbazepine.
7) Probable Mechanism: potential induction of cytochrome P450-mediat oxcarbazepine metabolism

3.5.1.Q Phenytoin

1) Interaction Effect: an increased risk of phenytoin toxicity (ataxia, hype nystagmus, tremor)
2) Summary: Coadministration of phenytoin and oxcarbazepine (600 to milligrams (mg)/day) resulted in decreased levels of the pharmacologica monohydroxy derivative (MHD) of oxcarbazepine while oxcarbazepine d 1200 to 2400 mg/day resulted in increased levels of phenytoin plasma c Patients should be monitored for signs of phenytoin toxicity (ataxia, hype nystagmus, tremor) when receiving oxcarbazepine concurrently, especia oxcarbazepine doses exceed 1200 mg daily. A decrease in the phenytoi be required (Prod Info TRILEPTAL(R) oral tablets, oral suspension, 200
3) Severity: moderate
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: Concurrent administration of oxcarbazepine ar have resulted in increased plasma levels of phenytoin. Monitor patients f phenytoin toxicity (ataxia, hyperreflexia, nystagmus, tremor) when receiv oxcarbazepine concurrently, especially when oxcarbazepine doses exce daily. A decrease in the phenytoin dose may be required.
7) Probable Mechanism: potential inhibition of cytochrome P450 -media metabolism
8) Literature Reports
a) Administration of phenytoin in doses of 250 to 500 milligrams (m patients concurrently receiving oxcarbazepine in doses of 600 to 18 resulted in a less than 10% change in the concentration of phenytoi concentrations of the active 10-monohydroxy derivative (MHD) of ox were decreased by 30% (90% confidence interval (CI): 3% decreas decrease). When the same doses of phenytoin were combined with oxcarbazepine in doses greater than 1200 to 2400 mg daily, there v 40% increase (90% CI: 12% increase to 60% increase) in phenytoir concentrations (Prod Info TRILEPTAL(R) oral tablets, oral suspensi
b) In polypharmacy studies employing add-on oxcarbazepine and carbamazepine, increased serum levels of valproic acid and phenyt observed with patients receiving oxcarbazepine. This was attributec enzyme induction (Bulau et al, 1987; Houtkooper et al, 1987a). Alte dose-dependent enzyme induction has been reported by some inve higher doses of oxcarbazepine produced enzyme induction that was carbamazepine (Patsalos et al, 1990b). Further studies are required if oxcarbazepine will offer a significant advantage over carbamazep regard to enzyme induction.

3.5.1.R Selegiline

1) Interaction Effect: an increase in selegiline plasma concentration
2) Summary: In subjects who had received carbamazepine 400 mg/day slightly increased levels of selegiline and its metabolites were seen after application of selegiline transdermal patch 6 mg/24 hr. Changes in the s plasma levels were nearly 2-fold and variable across the subject populat EMSAM(R) transdermal patch, 2008). Although not studied with oxcarba similar interaction would be expected. Concomitant use of oxcarbazepin selegiline is contraindicated. It is recommended that selegiline be discor minimum of 14 days prior to initiation of oxcarbazepine when necessary EMSAM(R) transdermal patch, 2008).
3) Severity: contraindicated
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Concomitant use of oxcarbazepine and selegil contraindicated. Selegiline should be discontinued for a minimum of 14 d oxcarbazepine therapy is initiated (Prod Info EMSAM(R) transdermal pa
7) Probable Mechanism: unknown

3.5.1.S Simvastatin

1) Interaction Effect: reduced simvastatin exposure
2) Summary: Oxcarbazepine is a molecular derivative of carbamazepin

a similar ability to induce cytochrome P450/3A4. Theoretically, oxcarbaz
expected to induce the metabolism of simvastatin, a cytochrome P450/3
In a controlled study, the concurrent administration of carbamazepine wi
significantly reduced maximum serum concentration, serum half-life, and
the concentration-time curve for both simvastatin and its active metaboli
acid (Ucar et al, 2004).
3) Severity: moderate
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: Monitor cholesterol levels in patients receiving
therapy with oxcarbazepine and simvastatin. Simvastatin dose may nee
adjusted.
7) Probable Mechanism: induction of CYP3A4-mediated first-pass meta
simvastatin by oxcarbazepine
8) Literature Reports
a) Concurrent administration of simvastatin with carbamazepine (a
anticonvulsant chemically related to oxcarbazepine) significantly red
simvastatin exposure. In a randomized, crossover study with a 2-we
period, healthy subjects (n=12) received either no drug or carbamaz
milligrams (mg) once daily for 2 days, after which the active drug gr
carbamazepine 300 mg twice daily for the next 12 days. On day 15
after the last carbamazepine dose), subjects fasted for 2 hours prio
single dose of simvastatin 80 mg. Serial blood samples were obtain
immediately prior to and for 24 hours after simvastatin administratio
Carbamazepine co-administration significantly reduced the mean m
serum concentration for both simvastatin and its active metabolite s
acid (from 18.7 nanograms/milliliter (ng/mL) to 6.0 ng/mL and from
1.1 ng/mL, respectively; p less than 0.01, both values). Simvastatin
simvastatin acid mean areas under the concentration-time curves (A
declined from 88.8 ng/mL x hour to 22.6 ng/mL x hour and from 33.
hour to 6.8 ng/mL x hour, respectively (p less than 0.001, both value
Concurrent administration with carbamazepine also significantly red
simvastatin acid serum mean half-life (from 5.9 hours to 3.7 hours, p
0.01) (Ucar et al, 2004).

3.5.1.T Tolvaptan

1) Interaction Effect: decreased tolvaptan plasma concentrations
2) Summary: Concomitant use of tolvaptan (primarily metabolized by CY
oxcarbazepine (a CYP3A inducer) may reduce tolvaptan exposure and s
avoided. If concomitant use is required, tolvaptan dose increases may b
to achieve the same clinical effect (Prod Info SAMSCA(TM) oral tablets,
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Concomitant use of oxcarbazepine and tolvapt
avoided due to a risk of reduced plasma concentrations of tolvaptan. If c
use is required, the dose of tolvaptan may need to be increased to achie
clinical effect (Prod Info SAMSCA(TM) oral tablets, 2009).
7) Probable Mechanism: induction of CYP3A-mediated tolvaptan metab
oxcarbazepine

3.5.1.U Valproic Acid

1) Interaction Effect: decreased plasma concentration of the active 10-m
metabolite of oxcarbazepine
2) Summary: Concurrent administration of oxcarbazepine (600 to 1,800
(mg)/day) in patients receiving treatment with valproic acid (400 to 2,800
resulted in a 18% decrease (90% confidence interval, 13% decrease to
decrease) in the plasma concentration of oxcarbazepine's 10-monohydr
(MHD) and a less than 10% change in the valproic acid concentration (P
TRILEPTAL(R) oral tablets, oral suspension, 2005). Although, the clinica
of this interaction is unknown, decreased plasma MHD concentrations m
potential loss of oxcarbazepine efficacy. If oxcarbazepine and valproic a
administered concurrently, clinical response to oxcarbazepine may neec
monitored.
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable

6) Clinical Management: Coadministration of oxcarbazepine and valproi result in a decreased concentration of the active 10-monohydroxy metab oxcarbazepine. Monitor patients for clinical response to oxcarbazepine.
7) Probable Mechanism: unknown

3.5.1.V Verapamil

1) Interaction Effect: decreased plasma levels of the active 10-monohyc metabolite of oxcarbazepine and potential loss of oxcarbazepine efficacy
2) Summary: Concurrent administration of oxcarbazepine (OCBZ) and v resulted in a 20% decrease in the plasma concentration of 10-monohydr (MHD) (Prod Info TRILEPTAL(R) oral tablets, oral suspension, 2005; Ba 1994). Although the clinical significance of this interaction is unknown, M active metabolite of OCBZ and decreased plasma MHD concentrations r potential loss of OCBZ efficacy. If OCBZ and verapamil are administered clinical response to OCBZ may need to be monitored.
3) Severity: moderate
4) Onset: delayed
5) Substantiation: established
6) Clinical Management: Coadministration of oxcarbazepine and verapa in decreased plasma levels of the active 10-monohydroxy metabolite of oxcarbazepine. Although the clinical significance of this interaction is unl oxcarbazepine and verapamil are coadministered, monitor clinical respo oxcarbazepine.
7) Probable Mechanism: unknown
8) Literature Reports
a) Concurrent administration of oxcarbazepine (OCBZ) and verapa decreased plasma concentration of the 10-monohydroxy derivative active metabolite of OCBZ. In healthy volunteers (n=10), upon titrati to 900 milligrams/day (mg/day), verapamil (240 mg/day) was admin week. The area under the concentration-time curve (AUC) of MHD c 20%; however, AUC was unchanged for OCBZ. The mechanism for in MHD plasma concentration and its clinical significance are unkno al, 1994).

4.0 Clinical Applications

4.1 Monitoring Parameters

A) Therapeutic

1) Laboratory Parameters

a) In patients with epilepsy, therapeutic serum levels have not been ade established.
b) In women who plan on becoming pregnant, obtaining concentrations oxcarbazepine and mono-hydroxy-carbazepine (MHD) before becoming during the pregnancy may be beneficial. Although, therapeutic concentra not been established, prepregnancy concentrations in an optimally-treat provide a reference concentration for comparison to concentrations duri when concentrations decrease due to changes in the pharmacokinetic c of oxcarbazepine. Possible sampling times could be once monthly, with in patients with mild and stable epilepsy, and every 3 to 4 days for 2 wee delivery in patients who had their dosage adjusted during pregnancy (To Battino, 2007).

c) In patients with trigeminal neuralgia, therapeutic serum concentration metabolite of oxcarbazepine (10-hydroxy-carbazepine) have ranged fror micromoles/L (Zakrzewska & Patsalos, 1989a).

2) Physical Findings

a) In patients with epilepsy, seizure frequency and electroencephalogra

b) A reduction or elimination of pain is indicative of a therapeutic respor with trigeminal neuralgia.

B) Toxic

1) Laboratory Parameters

a) Serum sodium, during maintenance treatment, particularly if the patie receiving other medications known to decrease serum sodium levels or i hyponatremia (nausea, malaise, headache, lethargy, confusion, obtunda increase in seizure frequency or severity) (Prod Info TRILEPTAL(R) oral suspension, 2005)

b) Liver function tests

c) Blood counts

d) Serum lipid levels

e) Serum levels of concomitant antiepileptic drugs (AEDs) during oxcarb titration. Levels of AEDs may change, especially at oxcarbazepine doses than 1200 milligrams/day (Prod Info TRILEPTAL(R) oral tablets, oral sus 2005)

2) Physical Findings

a) Body weight

b) Temperature

c) Blood pressure

d) Data reviewed by the US Food and Drug Administration suggest an i of suicidal behavior or ideation may exist in patients receiving therapy w antiepileptic drugs (AEDs). The increased risk of suicidality was noted at starting an AED and continued to at least 24 weeks. Patients treated for psychiatric disorders, or other conditions were all at an increased risk for compared to placebo. Closely monitor patients treated with AEDs for em worsening of depression, suicidality, and other unusual changes in beha may include symptoms such as anxiety, agitation, hostility, mania, and h (US Food and Drug Administration, 2008).

4.2 Patient Instructions

A) Oxcarbazepine (By mouth)

Oxcarbazepine

Treats seizures caused by epilepsy in adults and children.

When This Medicine Should Not Be Used:
You should not use this medicine if you have had an allergic reaction to oxca

How to Use This Medicine:
Tablet, Liquid

Your doctor will tell you how much of this medicine to use and how often may need to be changed several times in order to find out what works be not use more medicine or use it more often than your doctor tells you to.
You may take this medicine with or without food.
Measure the oral liquid medicine with a marked measuring spoon, oral s medicine cup.
Shake the oral liquid well just before using. You can take the medicine d the oral syringe, or you can mix the medicine in a glass with a small amo
If you mix the medicine, drink the mixture right away. Do not save any m later.

If a Dose is Missed:

If you miss a dose or forget to use your medicine, use it as soon as you almost time for your next dose, wait until then to use the medicine and s dose. Do not use extra medicine to make up for a missed dose.

How to Store and Dispose of This Medicine:

Store the medicine in a closed container at room temperature, away fror moisture, and direct light.
Ask your pharmacist, doctor, or health caregiver about the best way to d outdated medicine or medicine no longer needed. Dispose of any leftove

medicine 7 weeks after you open the bottle.
Keep all medicine away from children and never share your medicine wi

Drugs and Foods to Avoid:
Ask your doctor or pharmacist before using any other medicine, including ov
medicines, vitamins, and herbal products.
Make sure your doctor knows if you are also using any other medicines
seizures. Seizure medicine includes carbamazepine (Tegretol®), phenol
phenytoin (Dilantin®), or valproic acid (Depakote®).
Tell your doctor if you also use felodipine (Plendil®) or verapamil (Calan
Do not drink alcohol while you are using this medicine.

Warnings While Using This Medicine:
Make sure your doctor knows if you are pregnant or breast feeding.
Tell your doctor if you have kidney disease, or if you have ever had an a
reaction to carbamazepine (Tegretol®).
Birth control pills may not work while you are using oxcarbazepine. To k
getting pregnant, use another form of birth control. Other forms include c
diaphragm, or contraceptive foam or jelly.
This medicine may make you dizzy or drowsy. Avoid driving, using mach
anything else that could be dangerous if you are not alert.
Do not stop using this medicine suddenly without asking your doctor. Yo
slowly decrease your dose before stopping it completely.

Possible Side Effects While Using This Medicine:
Call your doctor right away if you notice any of these side effects:
Allergic reaction: Itching or hives, swelling in your face or hands, swellin
your mouth or throat, chest tightness, trouble breathing.
Blistering, peeling, red skin rash.
Blurred vision or double vision.
Change in how much or how often you urinate.
Confusion, weakness, and muscle twitching.
Fast, slow, or pounding heartbeat.
Fever with rash, swollen glands in your neck.
Nausea, vomiting, loss of appetite, pain in your upper stomach.
Rapid eye movements (especially in children).
Seizures.
Trouble walking, speaking, or controlling body movement.
Uncontrollable shaking.
Unusual bleeding, bruising, or weakness.
Visual changes.

If you notice these less serious side effects, talk with your doctor:
Dizziness or drowsiness.
Headache.
Joint pain.
Mild nausea, vomiting, stomach pain, belching, or gas.
Stomach pain or indigestion

If you notice other side effects that you think are caused by this medicine, tel

4.3 Place In Therapy

A) Oxcarbazepine appears to be as effective as carbamazepine in the treatment and slightly better tolerated. It should be considered an alternative in epileptic pat to tolerate carbamazepine, including those with hypersensitivity, although caution these patients.

B) In the treatment of trigeminal neuralgia, oxcarbazepine has been effective in p unresponsive to, or intolerant of, carbamazepine, which is currently the drug of ch superiority of oxcarbazepine over carbamazepine has been suggested, but these employed small numbers of patients and were not adequately controlled.

C) Dose-dependent enzyme induction has been reported by some investigators, doses of oxcarbazepine producing effects similar to carbamazepine (Patsalos et the optimal dose of oxcarbazepine remains undefined, further studies will also be determine if the drug will offer a significant advantage in regard to enzyme inducti autoinduction.

D) Hyponatremia is a concern with oxcarbazepine therapy, and may limit its use anticonvulsant and antineuralgic. The use of oxcarbazepine in diabetes insipidus

suggested, although data is not available for this indication (Pendlebury et al, 198

4.4 Mechanism of Action / Pharmacology

A) MECHANISM OF ACTION

1) Oxcarbazepine, an anticonvulsant, is the 10-keto derivative of carbamaze Chemically, oxcarbazepine is 10,11-dihydro-10-oxo-5H-dibenz(b,f)azepine 5 (Prod Info TRILEPTAL(R) oral tablets, oral suspension, 2005; Anon, 1989; A The metabolite 10-hydroxy-carbazepine is primarily responsible for the pharr activity of oxcarbazepine. However, the exact mechanism of action for its ant is unknown. In vitro electrophysiological studies suggest that drug-induced bl voltage-sensitive sodium channels may prevent repetitive neuronal firing and stabilization of hyperexcited neural membranes and the diminution of synapti propagation. Increased potassium conductance and high-voltage calcium cha modulation may also play a role (Prod Info TRILEPTAL(R) oral tablets, oral s 2005).

2) Animal studies have demonstrated that the mechanism of action of oxcarl similar to that of carbamazepine, which is inhibition of seizure propagation via posttetanic potentiation of synaptic transmission (Baltzer & Schmutz, 1978; A Anon, 1990). The spectrum of antiepileptic activity of each agent is also simil Schmutz, 1978; Anon, 1989). Antineuralgic properties of oxcarbazepine have demonstrated (Farago, 1987; Zakrzewska & Patsalos, 1989).

B) REVIEW ARTICLES

1) Dosages and formulations of antiepileptic drugs used to treat pediatric ep been reviewed (Bourgeois, 2002).

2) The pharmacology and therapeutic use of oxcarbazepine has been reviev 1999; Grant & Faulds, 1992; Bulau & Froscher, 1991; Perucca, 1993; Benete

3) A review of newer antiepileptic medications, including a summary of clinic and recommendations for use, has been published (Dichter & Brodie, 1996).

4) The pharmacokinetic interaction profile of oxcarbazepine and its importan has been reviewed (Baruzzi et al, 1993).

4.5 Therapeutic Uses

Antineoplastic adverse reaction - Peripheral neuropathy; Prophylaxis

Bipolar disorder

Panic disorder

Partial seizure, monotherapy

Partial seizure; Adjunct

Spasticity

Trigeminal neuralgia

4.5.A Antineoplastic adverse reaction - Peripheral neuropathy; Prophylaxis

1) Overview

FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence favors efficacy
Recommendation: Adult, Class IIb
Strength of Evidence: Adult, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RA

2) Summary:

A randomized, open-label trial (n=40) found that oxcarbazepine may oxaliplatin-induced peripheral neuropathy symptoms (Argyriou et al,

3) Adult:

a) A randomized, open-label trial found that oxcarbazepine may preven induced peripheral neuropathy symptoms. Adult patients (age 61.8 years deviation (SD) +/- 9.1) with advanced colon cancer were randomly assig chemotherapy with the FOLFOX-4 regimen plus oxcarbazepine (150 mil (mg) /day initially, doubled weekly for 4 weeks to a maximum dose of 60

daily), or the FOLFOX-4 regimen alone. The oxcarbazepine titration peri
followed by a 20-week maintenance period. The primary endpoint meas
incidence of peripheral neuropathy. Investigators also evaluated differen
total neuropathy scores (TNS; 1-11 = mild, 12-23 = moderate, greater th
severe), neurologic disability scores (NDS) and neurologic symptom sco
The incidence of oxaliplatin-induced neuropathy among the patients who
the trial (n=32) was 5 of 16 patients receiving oxcarbazepine (31.2%) , w
incidence of oxaliplatin-induced neuropathy occurred in 12 of 16 of the c
(75%). This represents a relative risk of 0.42 (95% confidence interval (C
0.91, p=0.033). The intention-to-treat analysis (n=40) also demonstrated
significant results favoring oxaliplatin (p=0.05). The mean TNS scores w
in the patients treated with oxacarbazepine vs 11.2 +/- 9.05 in the patien
with oxcarbazepine (p=0.016). The mean NDS (5.1 +/- 8.2 vs 20 +/- 23.1
and the mean NSS (0.6 +/- 0.9 vs 1.5 +/- 1.3, p=0.025) were both lower
treated with oxcarbazepine. Adverse effects were mild to moderate in se
occurred at similar rates in both treatment groups; the most common effe
diarrhea, myelosuppression, dizziness, nausea, vomiting, and headache
Two patients in the oxcarbazepine group experienced acute headache a
during the titration period that caused them to withdraw from the study; t
symptoms improved shortly after oxcarbazepine discontinuation (Argyric

4.5.B Bipolar disorder

1) Overview

FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence favors efficacy
Recommendation: Adult, Class IIb
Strength of Evidence: Adult, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RA

2) Summary:

Comparable results to other mood stabilizing agents (Ghaemi et al,
et al, 1983)
Limited data on usefulness as add-on therapy to lithium (Vieta et al,
Benedetti et al, 2004; Vieta et al, 2008)

3) Adult:

a) In a 52-week, multicenter, double-blind, randomized, placebo-control
prophylaxis trial (n=55), the addition of oxcarbazepine as adjunctive trea
maintenance lithium therapy of bipolar I and II disorder did not significan
onset of first relapse. Patients (aged 43.5 +/- 12 years, 65% female) with
of bipolar I or II disorder, who were not in an acute phase, but had at lea
episodes in the past year (with the last episode over 6 months prior to en
study) and receiving concomitant lithium (lithium levels greater than or e
milliequivalents/liter) during the past year were assigned to adjunctive ox
(n=26) treatment or placebo (n=29). Oxcarbazepine was started at 300 m
(mg) once a day for 3 days and titrated up by 300 mg increments every
administered twice a day, to a total daily dose of 1200 mg per day. After
week titration, the dose was maintained until the end of the study. Lithiu
administered open label throughout the study with levels monitored for a
months. Patients were required to stop all psychoactive, antipsychotic an
antidepressant medications 72 hours before the start of the study. Loraz
allowed as a concomitant medication up to 5 mg per day for insomnia or
primary efficacy variable was the length of the remission period (time to
manic or depressive episode). Based on an intent-to-treat analysis, the a
until first relapse of any type was not significantly different with the additi
oxcarbazepine compared with placebo (19.2 weeks vs 18.6 weeks; p=0.
of 38.5% and 58.6% patients in the oxcarbazepine and placebo arm, res
relapsed (p=0.1354). The number needed to treat (NNT) with oxcarbaze
any kind of relapse was 5 (odds ratio 0.44; 95% confidence interval, 0.1
study showed a statistically significant difference on the Barratt Impulsiv
Scale (BIS) (p=0.044) with a positive effect of oxcarbazepine in preventi
impulsivity. Overall, oxcarbazepine was well tolerated with no statistical
incidence of adverse events between the 2 groups. Larger trials are nee
evaluating oxcarbazepine in bipolar disorder (Vieta et al, 2008).

b) Adjunctive oxcarbazepine may be useful in the treatment of bipolar d
satisfactorily controlled by lithium. In an open-label study, patients with b
disorder taking lithium for at least 1 month (lithium levels ranging from 0.
milliequivalents/liter) were prescribed oxcarbazepine 300 milligrams/day
Doses of oxcarbazepine were increased to a maximum dose of 2400 mg

maintenance dose 919 mg/day). Patients had bipolar I (n=16) or bipolar
had a Clinical Global Impression Severity score of 4 to 6 at baseline. Oth
psychotropic agents were allowed but were not modified or changed dur
weeks of study. Sedation (66.7%), increased appetite (50%), weight gai
tremors (27.8%), constipation (16.7%), nausea/vomiting (16.7%), dry mo
and insomnia (11.1%) were reported with the use of oxcarbazepine. The
Clinical Global Impression-Bipolar Version Improvement (CGI-BP-I) scor
significantly from baseline at week 2, 4 and 8 (p less than 0.0001). Of th
61.1% were considered to be "responders" (CGI-BP-I score of 2 or 1 at
(Benedetti et al, 2004).
c) Authors of a retrospective chart review concluded that adjunctive or
oxcarbazepine was useful as a mood stabilizer in patients with bipolar di
Charts of patients treated with either adjunctive (n=31) or monotherapy
oxcarbazepine in a private practice clinic were reviewed. The mean oxca
dose was 1056.6 milligrams/day (mg/day) (range 150 to 2400 mg/day).
length ranged from 1 to 71 weeks (mean 16.2 weeks). Clinical response
assessed retrospectively using the Clinical Global Impressions-Improver
the patients receiving monotherapy oxcarbazepine, 36% experienced no
worsening of their symptoms, and 64% experienced mild to marked impr
patients receiving adjunctive oxcarbazepine, 39% experienced a worser
effect, and 61% experienced mild to marked improvement. Overall, 52%
discontinued treatment; 29% due to side effects and 24% due to lack of
Reported side effects included: sedation (40%), dizziness (7%), headacl
cognitive difficulty (5%), paresthesia, twitching, tactile impairment, diplop
nausea, weight gain and leg edema (2% each) (Ghaemi et al, 2003).
d) Comparable results to other mood stabilizing agents was found with
oxcarbazepine in 6 patients with acute mania (Emrich et al, 1983). Dose
2100 milligrams daily produced average decreases in the mania rating o
Multidimensional Psychiatric Scale of 50%.

4.5.C Panic disorder

1) Overview

FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence is inconclusive
Recommendation: Adult, Class IIb
Strength of Evidence: Adult, Category C

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RA

2) Summary:

Effective in one case report (Windhaber et al, 1997)

3) Adult:

a) A 23-year-old man with alcohol-related seizures developed panic dis
was successfully treated with an increased dose of oxcarbazepine (Winc
1997). The patient was already receiving oxcarbazepine 600 milligrams
this was increased to 900 mg/day. The patient remained symptom-free
month follow-up period.

4.5.D Partial seizure, monotherapy

FDA Labeled Indication

1) Overview

FDA Approval: Adult, yes; Pediatric, yes (4 years and older)
Efficacy: Adult, Effective; Pediatric, Effective
Recommendation: Adult, Class IIa; Pediatric, Class IIa
Strength of Evidence: Adult, Category B; Pediatric, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RA

2) Summary:

Indicated for use as monotherapy in the treatment of partial seizures
children 4 years and older (Prod Info TRILEPTAL(R) oral tablets, or
2005)
In an observational study (n=673; mean age 42.5 years) of adult ma
with partial epilepsy, oxcarbazepine improved sexual dysfunction in
preexisting sexual function disorders at baseline (Luef et al, 2009).

3) Adult:

a) Oxcarbazepine (OXC) was an effective monotherapeutic substitute w
to replace antiepileptic drugs (AED) used to maintain patients with medi
refractory partial epilepsy, in a randomized, double-blind, multicenter clir
compared two doses of oxcarbazepine (OXC 300 milligrams (mg)/day a
mg/day). Patients with a history of 2 to 40 seizures per 28-day period re

OXC 300 mg/day (n=46), or OXC 2400 mg/day (n=41) throughout a 126
treatment phase; all prior AED's were tapered and discontinued by day 4
receiving 2400 mg/day were titrated from an initial dose of 1200 mg up t
dose in 600 mg weekly increments; those patients unable to tolerate the
dose were adjusted to either 2100 mg or 1800 mg daily. Efficacy was me
the number of patients meeting one of 4 protocol-defined exit criteria (pr
variable) and the time required to meet one of the exit criteria (secondar
The number of patients meeting one of the 4 exit criteria was significantl
OXC 2400 mg cohort compared with the OXC 300 mg cohort (41.2% ve
less than 0.0001), while significantly greater time was required by the OX
group to meet an exit criterion compared with the OXC 300 mg group (p
intent-to-treat analysis revealed at least a 50% reduction in seizure incid
of OXC 2400 mg-treated patients (12% rendered seizure-free) compared
patients receiving OXC 300 mg (none seizure-free). Dizziness, headach
somnolence, nausea, and vomiting were the adverse events most freque
most were transient, and mild or moderate in severity (Beydoun et al, 20
b) Oxcarbazepine, 2400 milligrams/day (mg/day) in 2 divided doses, wa
monotherapy for the treatment of refractory partial seizures in 102 patien
62 years of age) in a placebo-controlled, double-blind trial. The primary e
variable was time to meet one of the exit criteria, defined as: completion
treatment phase; 4 partial seizures; 2 new-onset secondarily generalized
serial seizures; or status epilepticus. This variable was statistically signif
of oxcarbazepine (p=0.0001; by day 2.5 of the study period, 75% of the p
treated patients had met one of the exit criteria versus (vs) 25% of the pa
with oxcarbazepine. The secondary efficacy variable was the percentage
meet one of the exit criteria and was also statistically significantly lower (
0.0001) for the patients treated with oxcarbazepine (47%) vs 84% for the
treated group (Schachter et al, 1999).
c) Oxcarbazepine initiated at 600 milligrams/day, titrated to 1200 milligr
dosages in 2 daily divided doses), and maintained at the higher dose for
statistically significantly superior to placebo (p=0.046) in previously untre
(n=67; 8 to 69 years of age). The primary efficacy measure was a compa
to first seizure (Prod Info Trileptal(R), 2003a).
d) In 2 trials comparing oxcarbazepine in daily doses of 300 or 2400 mil
in patients previously treated with carbamazepine or other antiepileptic d
higher dose of oxcarbazepine was statistically significantly superior to th
(p=0.0001). Primary efficacy measures differed between the 2 studies; th
to meet exit criteria in 1 study and percentage of patients meeting exit cr
other (Prod Info Trileptal(R), 2003a).
e) Seizure frequency decreased in 32% to 48% of patients treated with
oxcarbazepine in a multicenter trial conducted over 10 years in 947 patie
al, 1993b). Patients were diagnosed with simple partial or complex partia
with or without secondary generalization and primary generalized seizur
daily doses employed were 30 milligrams/kilogram/day in children and 1
milligrams/kilogram/day in adults, usually given in 2 or 3 divided doses. (
patients experienced adverse reactions such as dizziness, sedation, fati
hyponatremia. Oxcarbazepine was used as monotherapy in 63% of the p
as part of polytherapy in 37%.
f) Similar decreases in seizure frequency were seen in a double-blind st
oxcarbazepine and carbamazepine in 16 epileptic patients inadequately
at least 1 anticonvulsant (other than carbamazepine) (Bulau et al, 1987b
patient had experienced at least 1 tonic-clonic or complex partial seizure
Oxcarbazepine or carbamazepine were added sequentially in randomize
during a 1-month titration period; therapy was continued for an additiona
Mean doses were 1111.5 and 788.5 milligrams daily for oxcarbazepine a
carbamazepine, respectively. Concomitant anticonvulsants were continu
the study. Seizure frequency was reduced by 90% during therapy with b
with 28% of all patients becoming seizure-free. Adverse effects were les
treated with oxcarbazepine. Increases in serum levels of valproic acid, p
primidone were observed in the oxcarbazepine group, presumably secon
lesser degree of enzyme induction as compared to carbamazepine.

1) Sexual Dysfunction Improvement in Male Patients with Epilepsy

a) In an observational study (n=673; mean age 42.5 years) of a
patients with partial epilepsy, oxcarbazepine improved sexual c
patients with preexisting sexual function disorders at baseline. I
received oxcarbazepine monotherapy either as initial treatment
changed from other antiepileptic drug (AED) pretreatment to ox

monotherapy; doses were titrated to the optimal therapeutic do
patients were assessed regarding their sexual dysfunction at ba
again 12 weeks later at the final examination. Seizure occurren
ratings of efficacy, and tolerability were also assessed. At base
dysfunction was reported in 228 (34%) patients, with 27 patient
antiepileptic pretreatment, 168 patients receiving enzyme-induc
pretreatment, and 33 patients receiving non-enzyme inducing A
pretreatment. Sexual dysfunction improvement was reported in
(n=181/228) of patients with preexisting sexual function disorde
months of treatment with oxcarbazepine, with no impairment re
10.1% (n=23/228) of patients at final assessment. The improve
most significant in patients receiving enzyme-inducing AED pre
Seizure occurrence per 28 days decreased during the retrospe
from a mean of 1.8 +/- 4.9 (95% CI, 1.43 to 2.17) to 0.4 +/- 1.8
to 0.54) after 3 months of therapy. Carbamazepine-treated pati
were excluded from results; however, in the patients who repor
dysfunction (n=147) with carbamazepine, 110 (75%) patients ir
switched to oxcarbazepine (Luef et al, 2009).

4) Pediatric:

a) An open-label study (n=92) failed to demonstrate the effectiveness o
oxcarbazepine monotherapy for children (1 month to 16 years of age) wi
inadequately-controlled or new-onset partial seizures; however, based o
pharmacokinetic and pharmacodynamic parameters, oxcarbazepine mo
was approved for children 4 years and older. Hospitalized children were
to either oxcarbazepine 10 milligrams/kilogram/day (mg/kg/day) or were
40 to 60 mg/kg/day within 3 days while withdrawing the previous antiepil
the second day of oxcarbazepine therapy. From day 3 to day 5, seizures
monitored by continuous video-electroencephalogram monitoring. The p
efficacy outcome was either completed the 5 day treatment or met one c
criteria. The exit criteria were: 1) 3 study specific seizures (ie, electrogra
seizures with a behavioral correlate) 2) a prolonged study specific seizu
children from both dose groups completed the 5-day study without exitin
between group comparison of the time to meet exit criteria was not statis
significant (p=0.904 for the difference between the curves). The manufa
the results were uninterpretable because of study limitations (no placebo
treatment and assessment period, and inadequate washout period) (Pro
TRILEPTAL(R) oral tablets, oral suspension, 2005).

b) Oxcarbazepine initiated at 600 milligrams/day, titrated to 1200 milligr
dosages in 2 daily divided doses), and maintained at the higher dose for
statistically significantly superior to placebo (p=0.046) in previously untre
(n=67; 8 to 69 years of age). The primary efficacy measure was a compa
to first seizure (Prod Info TRILEPTAL(R) oral tablets, oral suspension, 2

c) Oxcarbazepine, 2400 milligrams/day (mg/day) in 2 divided doses, wa
monotherapy for the treatment of refractory partial seizures in 102 patier
62 years of age) in a placebo-controlled, double-blind trial. The primary e
variable was time to meet one of the exit criteria, defined as: completion
treatment phase; 4 partial seizures; 2 new-onset secondarily generalized
serial seizures; or status epilepticus. This variable was statistically signif
of oxcarbazepine (p=0.0001; by day 2.5 of the study period, 75% of the
treated patients had met one of the exit criteria versus (vs) 25% of the pa
with oxcarbazepine. The secondary efficacy variable was the percentage
meet one of the exit criteria and was also statistically significantly lower
0.0001) for the patients treated with oxcarbazepine (47%) vs 84% for the
treated group (Schachter et al, 1999).

d) Oxcarbazepine was found to be useful in both adjunctive use and mo
children with seizures during a chart review (Gaily et al, 1997a). Children
3.9 years, range 0.6 to 6.9 years) had either localization-related seizures
generalized epilepsy (n=9) with the main seizure types being complex pa
simple partial (n=4), epileptic spasm (n=9), and generalized tonic-clonic
children, an overnight change was made from carbamazepine to oxcarb
times their previous carbamazepine dose. The other children were titrate
milligrams/kilogram/day (mg/kg/day) over 1 to 3 weeks. Out of the childr
localization-related seizures, 12 of 44 became seizure-free while 16 ach
reduction in seizures. No child with generalized seizures became seizure
9 had a 50% reduction in seizures. In children who had previously had a
response to carbamazepine, 4 of 30 children become seizure-free while
reduction in seizures of at least 50%. Of the 23 children receiving monot

became seizure-free, and 7 had a 50% reduction in seizures. The mean
for children achieving at least a 50% decrease in seizures was 47 mg/kg
Hyponatremia occurred in 7 of the 53 children.

4.5.E Partial seizure; Adjunct

FDA Labeled Indication

1) Overview

FDA Approval: Adult, yes; Pediatric, yes (2 years and older)
Efficacy: Adult, Effective; Pediatric, Effective
Recommendation: Adult, Class IIa; Pediatric, Class IIa
Strength of Evidence: Adult, Category B; Pediatric, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RA

2) Summary:

Indicated for use as adjunctive therapy in the treatment of partial se
adults and children 2 years and older (Prod Info TRILEPTAL(R) ora
suspension, 2005)
No evidence that oxcarbazepine was effective in children less than
(n=75) in an open-label, multicenter, rater-blind, randomized, paralle
(Prod Info TRILEPTAL(R) oral tablets, oral suspension, 2005)
During adjunctive therapy studies, median reductions in partial seizu
frequencies from baseline were 26% to 50% for oxcarbazepine and
placebo in adults, and 35% for oxcarbazepine and 9% for placebo i
(Prod Info TRILEPTAL(R) oral tablets, oral suspension, 2005)
No important differences in response due to gender were identified
adjunctive therapy trials (Prod Info TRILEPTAL(R) oral tablets, oral
2005)

3) Adult:

a) Efficacy for oxcarbazepine as adjunctive therapy for partial seizures i
demonstrated in a multicenter, double-blind, placebo-controlled trial (n=6
years of age). Patients who experienced 1 to 4 partial seizures per mont
baseline phase were randomized to receive placebo or fixed oxcarbazep
600, 1200, or 2400 milligrams/day (mg/day) in conjunction with 1 to 3 otl
antiepileptic drugs. A comparison between treatment groups of the perc
change in partial seizure frequency was the primary measure of efficacy
of oxcarbazepine were statistically significantly superior to placebo (p=0
high dose group, however, over 65% of patients discontinued treatment
adverse events (Prod Info TRILEPTAL(R) oral tablets, oral suspension,

b) Seizure frequency decreased in 32% to 48% of patients treated with
oxcarbazepine in a multicenter trial conducted over 10 years in 947 patie
al, 1993b). Patients were diagnosed with simple partial or complex partia
with or without secondary generalization and primary generalized seizur
daily doses employed were 30 milligrams/kilogram/day in children and 1
milligrams/kilogram/day in adults, usually given in 2 or 3 divided doses.
patients experienced adverse reactions such as dizziness, sedation, fati
hyponatremia. Oxcarbazepine was used as monotherapy in 63% of the
as part of polytherapy in 37%.

4) Pediatric:

a) Efficacy for oxcarbazepine as adjunctive therapy for inadequately-co
seizures in children was demonstrated in a multicenter, rater-blind, rand
parallel-group, open-label trial (n=128; 1 month to less than 4 years of a
criteria were at least 2 study specific seizures (ie, partial seizures identifi
electrograph with a behavioral correlate) during the 72 hour baseline pe
were randomized to either 10 milligrams/kilogram/day (mg/kg/day) or we
to 60 mg/kg/day within 26 days. After 9 days on their randomized target
seizures were monitored by continuous video-electroencephalogram mo
during the last 72 hours of the maintenance period. A between group co
the change in seizure frequency per 24 hours compared to the seizure fr
baseline was statistically better (results and p value not provided) in the
group vs 10 mg/kg/day group. No evidence that oxcarbazepine was effe
children less than 2 years of age (n=75) (Prod Info TRILEPTAL(R) oral t
suspension, 2005).

b) Oxcarbazepine (OXC) was safe and effective when used as an adjur
antiepileptic agent in the treatment of partial seizures in children, in a ra
double-blind, parallel-group study. Pediatric patients (ages 3 to 17 years
inadequately controlled partial seizures treated with one or two antiepile
(AED) were assigned to receive 98-day regimens of either OXC (titrated
of 30 to 46 milligrams (mg)/kilogram (kg)/day) two times a day (n=138) o

(n=129) in addition to their pre-established AED regimen. Patients in the experienced a baseline median partial seizure frequency of 12 per 28-da median OXC dose administered was 31.4 mg/kg/day. The addition of OX preexisting AED regimen produced a significantly greater median percer from baseline in 28-day partial seizure frequency compared with placebo 9%, respectively; p=0.0001). Forty-one percent of patients OXC-group p recorded a seizure frequency reduction from baseline of 50% or more pe period compared with 22% of patients receiving placebo (p=0.0005), and group patients were seizure- free throughout the double-blind treatment compared with 1 patient receiving placebo. OXC-treated patients also ex significantly greater median percentage reduction in the occurrence of s generalized seizures compared with patients receiving placebo (78% ve respectively; p=0.0012). The frequency of adverse events was similar be groups; somnolence, headache, dizziness, nausea and vomiting were m reported, with the majority being considered mild to moderate in severity TRILEPTAL(R) oral tablets, oral suspension, 2005; Glauser et al, 2000).

c) Oxcarbazepine, in a mean dose of 56.7 milligrams/kilogram/day (mg/ found to be efficacious for adjunctive therapy in epilepsy in a retrospecti review of 46 children and adolescents (mean age 10.3 years; range 1.3 Oxcarbazepine doses ranged from 19 to 123 mg/kg twice a day, valproic most common co-medication (32 of 46 patients) and no patients were m more than one other drug besides oxcarbazepine. After follow-up for 1 y oxcarbazepine was found to be of some benefit in 50% of the patients. S children experienced an exacerbation of seizures and 17 children exhibi change, but 4 children became seizure-free, 18 experienced a 75% to 9 in seizures, and 1 had a 50% to 74% reduction in seizures; 4 patients we follow-up. Adverse effects tended to occur in patients with blood serum c of 35 to 40 mg/L 10-hydroxy-carbazepine, the active metabolite of oxcar (Borusiak et al, 1998).

d) In a small study (n=40) in children with intellectual disability and intra epilepsy, seizure frequency was reduced by at least 50% in 48% (19) of treated with oxcarbazepine 49 milligrams/kilogram/day (mg/kg/day) (mea dosage), given in 2 or 3 divided doses. Nine of the children received oxc monotherapy and 31 received it concomitantly with other antiepileptic dr including vigabatrin, benzodiazepines, valproate, lamotrigine, phenytoin, acetazolamide. Oxcarbazepine therapy was initiated using several strate Oxcarbazepine was initiated in 10 children as an overnight change from carbamazepine (at 1.5 times the carbamazepine dosage). In the remaini who weighed under 40 kg, the oxcarbazepine dose was titrated over 1 to 30/mg/kg/day and then increased as necessary. For the other children w 40 kg, oxcarbazepine was initiated at 20/mg/kg/day and titrated accordir response. A greater than 50% response was reported in 14 of 28 childre localization-related epilepsy and 5 of 12 children (42%) with generalized Oxcarbazepine dose reduction or discontinuation occurred in 8 children adverse effects and at least one adverse effect was reported in 40% of p Hyponatremia occurred in 24% (Gaily et al, 1998a).

e) Oxcarbazepine was found to be useful in both adjunctive use and mo children with seizures during a chart review (Gaily et al, 1997a). Children 3.9 years, range 0.6 to 6.9 years) had either localization-related seizures generalized epilepsy (n=9) with the main seizure types being complex pa simple partial (n=4), epileptic spasm (n=9), and generalized tonic-clonic children, an overnight change was made from carbamazepine to oxcarb times their previous carbamazepine dose. The other children were titrate milligrams/kilogram/day (mg/kg/day) over 1 to 3 weeks. Out of the childr localization-related seizures, 12 of 44 became seizure-free while 16 ach reduction in seizures. No child with generalized seizures became seizure 9 had a 50% reduction in seizures. In children who had previously had a response to carbamazepine, 4 of 30 children become seizure-free while reduction in seizures of at least 50%. Of the 30 children receiving polyth became seizure free and seizure reduction occurred in 14. The mean eff for children achieving at least a 50% decrease in seizures was 47 mg/kg Hyponatremia occurred in 7 of the 53 children.

4.5.F Spasticity

1) Overview

FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence is inconclusive

Recommendation: Adult, Class III
Strength of Evidence: Adult, Category B
See Drug Consult reference: RECOMMENDATION AND EVIDENCE RA

2) Summary:
Suggested efficacy in the treatment of spasticity related to cerebral lesions (Bittencourt & Silvado, 1985)

3) Adult:
a) Limited data have suggested the efficacy of oral oxcarbazepine in the spasticity related to cerebral epileptogenic lesions. Oxcarbazepine has b doses up to 3900 milligrams daily (Bittencourt & Silvado, 1985). Controll studies are needed to more fully evaluate the efficacy of the drug in spas

4.5.G Trigeminal neuralgia

1) Overview
FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence favors efficacy
Recommendation: Adult, Class IIb
Strength of Evidence: Adult, Category C
See Drug Consult reference: RECOMMENDATION AND EVIDENCE RA

2) Summary:
Effective in the treatment of trigeminal neuralgia in patients unrespo intolerant of, carbamazepine (Zakrzewska & Patsalos, 1989b)

3) Adult:
a) Oxcarbazepine was effective in 6 patients with trigeminal neuralgia re carbamazepine therapy (Zakrzewska & Patsalos, 1989b). Oxcarbazepin administered in a dose of 300 milligrams 2 to 4 times daily, with prior me withdrawn over a 2-day period. The dose was adjusted weekly until adeq control was achieved, then patients were examined at 2 to 4 weekly inte were considered optimally managed after a pain free 2-week period; at t dose was reduced by 1 dose per week (300 milligrams). Re-titration was the event of relapse. Pain control was achieved in all patients, with onse effect being observed within 24 hours. Daily doses ranged from 600 to 2 milligrams. Both oxcarbazepine and 10-hydroxy-carbazepine serum leve with the dose and therapeutic effects. Effective pain relief was seen in al when serum levels of 10-hydroxy-carbazepine were between 50 and 11(micromoles/liter, corresponding to 1200 to 2400 milligrams daily of oxca

4.6 Comparative Efficacy / Evaluation With Other Therapies

Carbamazepine

Haloperidol

Lithium

Surgical procedure

4.6.A Carbamazepine

Epilepsy

Trigeminal neuralgia

4.6.A.1 Epilepsy

a) SUMMARY: Oxcarbazepine appears to be as effective as carbamaze treatment of epilepsy; severe adverse effects have occurred to a lesser oxcarbazepine in some studies. Further studies are needed to investigat inducing effects, particularly at higher doses.

b) Oxcarbazepine is similar in efficacy to carbamazepine as monothera therapy in epileptic patients (Dam et al, 1989; Reinikainen et al, 1987); (1987)(Houtkooper et al, 1987b; Houtkooper et al, 1984; Dam, 1990; Phil 1986; Anon, 1990a; Jensen, 1990). There is some evidence of efficacy i

unresponsive to carbamazepine. Doses associated with therapeutic equ
some studies have been 200 mg carbamazepine and 300 to 400 mg oxc
(Houtkooper et al, 1987b), however the ratio has been closer to 1:1 in ot
al, 1987).
c) Oxcarbazepine is at least as effective as carbamazepine in patients r
polytherapy, and oxcarbazepine may be better tolerated in some patient
efficacy of oxcarbazepine and carbamazepine was compared in 48 epile
poorly controlled on polytherapy, including carbamazepine, in a double-
crossover study (Houtkooper et al, 1987b). The types of seizures were g
patients), partial (10 patients), or both generalized and partial (29 patien
had at least 2 seizures/week despite therapy with 2 to 4 antiepileptic age
were randomly allocated to oxcarbazepine 300 mg/day or carbamazepir
mg/day. Following a titration period, where the dose of each was increas
optimal seizure control, therapy was continued for 12 weeks (steady- sta
trial period. As compared to carbamazepine, therapy with oxcarbazepine
total number of seizures by 9%; tonic-clonic and tonic seizures were furt
by 20% and 31%, respectively. In 5 patients, a shift from complex partial
partial seizures or atypical absence seizures was observed during oxcar
therapy. Other differences reported during oxcarbazepine therapy were
alertness and greater ability to concentrate in 5 patients and remission o
carbamazepine related allergic skin reactions in 2. Serum levels of valpr
phenytoin were higher in oxcarbazepine treated patients, and serum soc
concentration were lower. Other adverse effects were similar with each a
d) In a double-blind study, the efficacy of oxcarbazepine and carbamaz
epileptic patients inadequately controlled on at least 1 anticonvulsant (ot
carbamazepine) was evaluated (Bulau et al, 1987). Each patient had ex
least 1 tonic-clonic or complex partial seizure per month. Oxcarbazepine
carbamazepine were added sequentially in randomized fashion during a
titration period; therapy was continued for an additional 3 months. Mean
1111.5 and 788.5 mg daily for oxcarbazepine and carbamazepine, respe
Concomitant anticonvulsants were continued throughout. Seizure freque
reduced by 90% during therapy with both agents, with 28% of all patient
seizure-free. Adverse effects were less in oxcarbazepine treated patient
serum levels of valproic acid, phenytoin, and primidone were observed i
oxcarbazepine group, presumably secondary to a lesser degree of enzy
as compared to carbamazepine.

4.6.A.2 Trigeminal neuralgia

a) Oxcarbazepine and its 10-hydroxy-metabolite (10-hydroxy-carbazepi
dihydro-10-hydroxy carbamazepine) were compared with carbamazepin
patients with trigeminal neuralgia (Farago, 1987a). All patients had eithe
trigeminal neuralgia or other idiopathic facial neuralgias for at least 2 we
patients had been treated previously with carbamazepine. Oxcarbazepir
administered to 13 of the 24 patients for a mean of 11 months (mean ma
of 1100 milligrams daily), resulting in an adequate clinical response in 1(
moderate response in 3. Symptom recurrence, however, was seen in 1 p
months of treatment. Eleven patients were treated with the 10-hydroxy-n
oxcarbazepine (GP 47779) for a mean of 3.5 months (mean maximal do
milligrams daily), with 7 achieving alleviation of symptoms and 4 noticing
improvement. However, recurrence of symptoms occurred in 2 patients
and 2 months of treatment, respectively. In the 14 patients treated previc
carbamazepine, therapy with either oxcarbazepine or its metabolite was
be more effective than carbamazepine in 12; efficacy was considered ec
and worse in another. These overall results suggest the potential superi
oxcarbazepine over carbamazepine in trigeminal neuralgia. However, pl
controlled trials are required to confirm these findings.

4.6.A.3 Efficacy

a) The primary difference between oxcarbazepine and carbamazepine i
pharmacokinetic properties, which in turn affect the propensity of these a
adverse effects. Following absorption, oxcarbazepine is rapidly and exte
converted via reduction to 10-hydroxy-carbazepine, the active metabolit
excreted in the urine as the glucuronide conjugate. A portion of the 10-h
metabolite is hydroxylated to isomeric 10,11-diols, the trans-diol predom
(Theisohn & Heimann, 1982; Schutz et al, 1986; Anon, 1989a).
b) In contrast, carbamazepine is oxidized to the active carbamazepine-
epoxide; a portion of this metabolite is also converted to the inactive 10,
(Eichelbaum et al, 1985; Anon, 1989a; Anon, 1990a). The 10,11-epoxid

carbamazepine is responsible for dose-dependent adverse effects (Anon Anon, 1989a). Because an epoxide is not produced during oxcarbazepir metabolism, this drug is expected to be better tolerated than carbamaze 1990a).

4.6.A.4 Adverse Effects

a) A trend toward a lower incidence of severe adverse effects has been with oxcarbazepine as compared to carbamazepine in some studies (Bu 1987)(Dam, 1990; Houtkooper et al, 1987b), which at times reached sta significance (Dam, 1990).

b) Oxcarbazepine appears less likely than carbamazepine to influence processes, as the metabolism of oxcarbazepine is facilitated primarily by Studies have reported that oxcarbazepine lacks autoinducing properties carbamazepine, a feature which may decrease the incidence of breakthr (Anon, 1989a; Brodie et al, 1989; Anon, 1990a).

c) In some studies, oxcarbazepine has not influenced antipyrine kinetics an advantage with regard to drug interactions (Anon, 1989a). However, dependent enzyme induction has been reported by other investigators, v doses producing effects similar to carbamazepine (Patsalos et al, 1990c optimal dose of oxcarbazepine remains undefined, further studies will be determine if the drug will offer a significant advantage in regard to enzyn and autoinduction.

4.6.B Haloperidol

4.6.B.1 Bipolar disorder

a) Oxcarbazepine has been compared with with haloperidol in 42 patier mania; mean doses used were 2400 mg/day and 42 mg/day respectively the response to oxcarbazepine was slower, by the end of the second we treatment, results were similar in both treatment groups. Haloperidol-trea had a significantly higher incidence of adverse effects (Emrich, 1990).

4.6.C Lithium

4.6.C.1 Bipolar disorder

a) In a review of the results of a double-blind multicenter trial comparing oxcarbazepine with lithium in 58 acutely manic patients, oxcarbazepine be equally effective but with a higher incidence of side effects. Onset wa slower with oxcarbazepine (Grant & Faulds, 1992a).

b) Conversely, a 3-year randomized study of oxcarbazepine vs lithium p 18 patients with bipolar disorder demonstrated no clear responders in th oxcarbazepine-treated group. A reduction in relapses was clearly seen i treated group. This study was flawed by poor patient selection and the tr lithium nonresponders with oxcarbazepine (Wildegrube, 1990).

4.6.D Surgical procedure

4.6.D.1 Trigeminal neuralgia

a) Oxcarbazepine was initially efficacious for relieving pain of intractable neuralgia, but eventually surgery was necessary in most patients. Fifteen had not found relief of trigeminal neuralgia pain or had experienced adve with carbamazepine, phenytoin, and baclofen, either as monotherapy or combination, were transferred from their current medication to oxcarbaz followed for 13 years. Over a period of 3 days, oxcarbazepine 300 millig was substituted for each 200 mg dose of carbamazepine or 100 mg dos phenytoin. Patients were free to discontinue medication during remissior patients used oxcarbazepine continuously, and 7 stopped during remiss periods of 2 to 7 months and, in one case, for 26 months. The mean dail 17.9 mg/kilogram (range 3.9 to 46.5 mg/kg). The mean duration of treatr years (range 2.4 months to 10.8 years). Oxcarbazepine gave pain relief, surgery was considered necessary in 12 of the 13 surviving patients. Su immediately successful in 8 of those patients but had to be repeated in 3 because of pain recurrence or complete failure. Repeat surgery was suc 2 with pain recurrence, but the one whose initial surgery completely faile medication for pain relief after the second surgery. Three of the patients underwent surgery had numbness and one had deafness as a conseque mean time for recurrence of pain after oxcarbazepine treatment was 10 (median 7 months); the mean time for recurrence after surgery was 28 n

time of this report, 8 patients continued to be pain free. Most patients fel
have had surgery earlier (Zakrzewska & Patsalos, 2002).

6.0 References

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DRUGDEX® Evaluations

LISDEXAMFETAMINE

0.0 Overview

1) Class
- **a)** This drug is a member of the following class(es):
  Amphetamine (class)
  CNS Stimulant

2) Dosing Information
- **a)** Lisdexamfetamine Dimesylate
  - **1)** Adult
    - **a)** safety and efficacy have not been evaluated in the geriatric population (Prod Info VYVANSE(R) oral capsu
      - **1)** Attention deficit hyperactivity disorder
        - **a)** initial (lisdexamfetamine naive or switching from another medication): 30 mg ORALLY once daily capsules, 2008)
        - **b)** maintenance: may increase dose in increments of 10 mg or 20 mg ORALLY per day at approxim ORALLY per day (Prod Info VYVANSE(R) oral capsules, 2008)
  - **2)** Pediatric
    - **a)** long-term use of amphetamines has not been established in pediatric patients; effectiveness of lisdexamfe weeks duration (Prod Info VYVANSE(R) oral capsules, 2008)
    - **b)** lisdexamfetamine dimesylate has not been studied in children under the age of 6 years or adolescents; ar children under 3 years of age (Prod Info VYVANSE(R) oral capsules, 2008).
      - **1)** Attention deficit hyperactivity disorder
        - **a)** initial (lisdexamfetamine naive or switching from another medication): 30 mg ORALLY once daily capsules, 2008)
        - **b)** maintenance: may increase dose in increments of 10 mg or 20 mg ORALLY per day at approxim ORALLY per day (Prod Info VYVANSE(R) oral capsules, 2008)

3) Contraindications
- **a)** Lisdexamfetamine Dimesylate
  - **1)** cardiovascular disease, symptomatic (Prod Info VYVANSE(TM) oral capsules, 2007)
  - **2)** drug dependence, history of; potential for abuse (Prod Info VYVANSE(TM) oral capsules, 2007)
  - **3)** advanced arteriosclerosis (Prod Info VYVANSE(TM) oral capsules, 2007)
  - **4)** agitated states; may aggravate symptoms (Prod Info VYVANSE(TM) oral capsules, 2007)
  - **5)** concomitant use of monoamine oxidase inhibitors (MAOI), or within 14 days of MAOI use; hypertensive crisis r capsules, 2007)
  - **6)** glaucoma (Prod Info VYVANSE(TM) oral capsules, 2007)
  - **7)** hypersensitivity/idiosyncrasy to sympathomimetic amines (Prod Info VYVANSE(TM) oral capsules, 2007)
  - **8)** hypertension, moderate to severe (Prod Info VYVANSE(TM) oral capsules, 2007)
  - **9)** hyperthyroidism (Prod Info VYVANSE(TM) oral capsules, 2007)

4) Serious Adverse Effects
- **a)** Lisdexamfetamine Dimesylate
  - **1)** Cerebrovascular accident
  - **2)** Chest pain
  - **3)** Dead - sudden death
  - **4)** Gilles de la Tourette's syndrome
  - **5)** Myocardial infarction
  - **6)** Palpitations
  - **7)** Seizure
  - **8)** Stevens-Johnson syndrome
  - **9)** Tachycardia
  - **10)** Toxic epidermal necrolysis due to drug
  - **11)** Ventricular hypertrophy

5) Clinical Applications
- **a)** Lisdexamfetamine Dimesylate
  - **1)** FDA Approved Indications
    - **a)** Attention deficit hyperactivity disorder

1.0 Dosing Information

Drug Properties

Storage and Stability

Adult Dosage

Pediatric Dosage

1.1 Drug Properties

A) Information on specific products and dosage forms can be obtained by referring to the Tradename List (Product In

B) Synonyms

Lisdexamfetamine

Lisdexamfetamine Dimesylate

C) Physicochemical Properties

1) Lisdexamfetamine Dimesylate

a) Molecular Weight

1) 455.6 (Prod Info VYVANSE(TM) oral capsules, 2007)

b) Solubility

1) Lisdexamfetamine is soluble in water at 792 mg/mL (Prod Info VYVANSE(TM) oral capsules, 2007)

1.2 Storage and Stability

A) Lisdexamfetamine Dimesylate

1) Preparation

a) Oral route

1) Lisdexamfetamine dimesylate should be administered once daily in the morning. The dose may be ta swallowed whole, or the capsule may be opened and the entire contents dissolved in a glass of water to (Prod Info VYVANSE(R) oral capsules, 2008).

B) Lisdexamfetamine Dimesylate

1) Oral route

a) Capsule

1) Store at controlled room temperature, 25 degrees Celsius (77 degrees Fahrenheit); excursions permi 86 degrees Fahrenheit) (Prod Info VYVANSE(TM) oral capsules, 2007).

1.3 Adult Dosage

1.3.1 Normal Dosage

1.3.1.A Lisdexamfetamine Dimesylate

1.3.1.A.1 Oral route

1.3.1.A.1.a Attention deficit hyperactivity disorder

1) The recommended initial dose in lisdexamfetamine-naive patients or in patients switching from a once daily in the morning. According to therapeutic need and patient response, the initial dose may orally per day at approximately weekly intervals to a maximum of 70 mg orally per day. The lowest e should be periodically interrupted to determine the need for continued treatment (Prod Info VYVANS

2) Lisdexamfetamine dimesylate has not been studied in the geriatric population (Prod Info VYVANSE(R) ora

1.4 Pediatric Dosage

1.4.1 Normal Dosage

1.4.1.A Lisdexamfetamine Dimesylate

1.4.1.A.1 Oral route

1.4.1.A.1.a Attention deficit hyperactivity disorder

1) The recommended initial dose in lisdexamfetamine-naive patients or in patients switching from a once daily in the morning. According to therapeutic need and patient response, the initial dose may orally per day at approximately weekly intervals to a maximum of 70 mg orally per day. The lowest e should be periodically interrupted to determine the need for continued treatment (Prod Info VYVANS

2) The long-term effects of amphetamine use in the pediatric population have not been established. In clinica dimesylate was established for up to 4 weeks duration. Lisdexamfetamine dimesylate has not been studied ir adolescents. Amphetamines are not recommended for use in children under 3 years of age (Prod Info VYVAl

2.0 Pharmacokinetics

Drug Concentration Levels

ADME

2.2 Drug Concentration Levels

A) Lisdexamfetamine Dimesylate

1) Peak Concentration

a) When the dose of lisdexamfetamine dimesylate was normalized based on weight, the Cmax was 12% low
70 milligrams/day (mg/day) for 7 days. The weight/dose normalized Cmax were the same for girls and boys f
VYVANSE(TM) oral capsules, 2007).

2) Time to Peak Concentration

a) Oral, dextroamphetamine: 3.5 hours (Prod Info VYVANSE(TM) oral capsules, 2007)

b) Oral, lisdexamfetamine dimesylate: 1 hour (Prod Info VYVANSE(TM) oral capsules, 2007)

1) The Tmax of dextroamphetamine after a single oral 30, 50, or 70 milligram dose of lisdexamfetamine
(n=18; aged 6 to 12 years) after an 8-hour fast was approximately 3.5 hours. The Tmax of lisdexamfetan
Info VYVANSE(TM) oral capsules, 2007).

3) Area Under the Curve

a) After lisdexamfetamine dimesylate was administered as a solution and as capsules after an 8-hour fast, th
(Prod Info VYVANSE(TM) oral capsules, 2007).

b) When the dose of lisdexamfetamine dimesylate was normalized based on weight, the AUC was 22% lowe
70 milligrams/day (mg/day) for 7 days. The weight/dose normalized AUC were the same for girls and boys fo
VYVANSE(TM) oral capsules, 2007).

2.3 ADME

Absorption

Metabolism

Excretion

Elimination Half-life

2.3.1 Absorption

A) Lisdexamfetamine Dimesylate

1) Effects of Food

a) Increases Tmax by approximately 1 hr (Prod Info VYVANSE(TM) oral capsules, 2007).

b) Food has no effect on AUC or Cmax but does prolong the Tmax of dextroamphetamine by approxima
dose of lisdexamfetamine dimesylate was given to healthy adults after a high fat meal, the Tmax was 4.7
fasted state (Prod Info VYVANSE(TM) oral capsules, 2007).

2) Following oral administration, lisdexamfetamine dimesylate is rapidly absorbed from the gastrointestinal tr
2007).

2.3.3 Metabolism

A) Metabolism Sites and Kinetics

1) Lisdexamfetamine Dimesylate

a) Liver and/or intestinal metabolism (Prod Info VYVANSE(TM) oral capsules, 2007).

1) After oral administration, lisdexamfetamine dimesylate is converted to dextroamphetamine and L
intestinal and/or hepatic metabolism. Lisdexamfetamine dimesylate is not metabolized by CYP450 e
capsules, 2007).

B) Metabolites

1) Lisdexamfetamine Dimesylate

a) Dextroamphetamine, (active) (Prod Info VYVANSE(TM) oral capsules, 2007).

1) After oral administration, lisdexamfetamine dimesylate is converted to dextroamphetamine and L
intestinal and/or hepatic metabolism (Prod Info VYVANSE(TM) oral capsules, 2007).

b) L-lysine, (inactive) (Prod Info VYVANSE(TM) oral capsules, 2007)

1) After oral administration, lisdexamfetamine dimesylate is converted to dextroamphetamine and L
intestinal and/or hepatic metabolism (Prod Info VYVANSE(TM) oral capsules, 2007).

2.3.4 Excretion

A) Kidney

1) Lisdexamfetamine Dimesylate

a) Renal Excretion (%)

1) 96% (Prod Info VYVANSE(TM) oral capsules, 2007).

a) Following administration of a single 70 milligram dose of lisdexamfetamine dimesylate to 6 h

dose was recovered in the urine; 42% of which was amphetamine, 25% hippuric acid, and 2% i
(TM) oral capsules, 2007).

B) Feces
1) Lisdexamfetamine Dimesylate
a) 0.3% (Prod Info VYVANSE(TM) oral capsules, 2007).
1) Following administration of a single 70 milligram dose of lisdexamfetamine dimesylate to 6 healt
was recovered in the feces (Prod Info VYVANSE(TM) oral capsules, 2007).

2.3.5 Elimination Half-life

A) Parent Compound
1) Lisdexamfetamine Dimesylate
a) less than 1 hour (Prod Info VYVANSE(TM) oral capsules, 2007)
1) The elimination half-life of lisdexamfetamine dimesylate averaged less than one hour in studies i
VYVANSE(TM) oral capsules, 2007).

3.0 Cautions

Contraindications

Precautions

Adverse Reactions

Teratogenicity/Effects in Pregnancy/Breastfeeding

Drug Interactions

3.0.A Black Box WARNING
1) Lisdexamfetamine Dimesylate
a) Oral (Capsule)
1) Amphetamines have a high potential for abuse. Administration of amphetamines for prolonged periods of
attention should be paid to the possibility of subjects obtaining amphetamines for non-therapeutic use or distr
prescribed or dispensed sparingly.
2) Misuse of amphetamines may cause sudden death and serious cardiovascular adverse events (Prod Info

3.1 Contraindications

A) Lisdexamfetamine Dimesylate
1) cardiovascular disease, symptomatic (Prod Info VYVANSE(TM) oral capsules, 2007)
2) drug dependence, history of; potential for abuse (Prod Info VYVANSE(TM) oral capsules, 2007)
3) advanced arteriosclerosis (Prod Info VYVANSE(TM) oral capsules, 2007)
4) agitated states; may aggravate symptoms (Prod Info VYVANSE(TM) oral capsules, 2007)
5) concomitant use of monoamine oxidase inhibitors (MAOI), or within 14 days of MAOI use; hypertensive crisis r
capsules, 2007)
6) glaucoma (Prod Info VYVANSE(TM) oral capsules, 2007)
7) hypersensitivity/idiosyncrasy to sympathomimetic amines (Prod Info VYVANSE(TM) oral capsules, 2007)
8) hypertension, moderate to severe (Prod Info VYVANSE(TM) oral capsules, 2007)
9) hyperthyroidism (Prod Info VYVANSE(TM) oral capsules, 2007)

3.2 Precautions

A) Lisdexamfetamine Dimesylate
1) long duration of use; may lead to dependence (Prod Info VYVANSE(TM) oral capsules, 2007)
2) amphetamine misuse; may cause sudden death and serious cardiovascular events (Prod Info VYVANSE(TM)
3) bipolar disorder, comorbid; may precipitate a mixed/manic episode (Prod Info VYVANSE(TM) oral capsules, 2
4) cardiovascular conditions which may be compromised by increases in blood pressure or heart rate (eg, preexis
myocardial infarction, or ventricular arrhythmia) (Prod Info VYVANSE(TM) oral capsules, 2007)
5) EEG abnormalities, especially with history of; may lower convulsive threshold (Prod Info VYVANSE(TM) oral c
6) psychosis, preexisting; may exacerbate symptoms of behavior disturbance and thought disorder (Prod Info VY
7) seizures, especially with a history of; may lower convulsive threshold (Prod Info VYVANSE(TM) oral capsules,
8) structural cardiac abnormalities/conditions, serious, especially in children and adolescents; sudden death has
(Prod Info VYVANSE(TM) oral capsules, 2007)
9) tics, motor and phonic, history of; risk of exacerbation (Prod Info VYVANSE(TM) oral capsules, 2007)
10) Tourette's syndrome, history of; risk of exacerbation (Prod Info VYVANSE(TM) oral capsules, 2007)

3.3 Adverse Reactions

Cardiovascular Effects

Dermatologic Effects

Endocrine/Metabolic Effects

Gastrointestinal Effects

Musculoskeletal Effects

Neurologic Effects

Ophthalmic Effects

Psychiatric Effects

Reproductive Effects

Respiratory Effects

Other

3.3.1 Cardiovascular Effects

3.3.1.A Lisdexamfetamine Dimesylate

Chest pain

Dead - sudden death

Increased blood pressure

Increased heart rate

Myocardial infarction

Palpitations

Summary

Tachycardia

Ventricular hypertrophy

3.3.1.A.1 Chest pain

a) In a retrospective review of poison center databases in 8 states during the initial 10 months of produc
28) of patients between 4 and 44 years of age (median, 8 years) experiencing adverse events with lisde
reliably determined as concomitant drugs or conditions were not evaluated (Spiller et al, 2008).

3.3.1.A.2 Dead - sudden death

a) Incidence: rare

b) Children and Adolescents - With Preexisting Cardiac Risk

1) Following administration of CNS stimulant drugs at usual doses, sudden death has been reporte
cardiac abnormalities or other serious heart problems and adults being treated for ADHD . Sudden d
administration of amphetamines (Prod Info VYVANSE(TM) oral capsules, 2007).

c) Children and Adolescents - Healthy

1) A retrospective, case-controlled study examines the association between stimulant medication, i

unexplained sudden death in healthy children and adolescents. In a collection of data from state vita
States, 564 cases of sudden death in children and adolescents between the ages of 7 to 19 years w
who died as passengers in motor vehicle accidents. The study determined that 1.8% (n=10) of youth
were taking stimulant medication compared with only 0.4% (n=2) of youths in the motor vehicle acci
74.9; p=0.02). Limitations to this study included the time lag between the youths stimulant medicatio
recall of information regarding clinical diagnoses, inconsistent postmortem inquiry, and the exclusion
authors stated that this finding should be considered when evaluating the overall risk and benefit of
adolescents (Gould et al, 2009). Given the limitations of this study, the U.S. Food and Drug Adminis
and benefits associated with stimulant medications (US Food and Drug Administration, 2009).

3.3.1.A.3 Increased blood pressure

a) Incidence: adult patients, 3% (Prod Info VYVANSE(R) oral capsules, 2008)

b) Blood pressure increases were reported in 3% of adult patients who received lisdexamfetamine in fin
compared with 0% of patients who received placebo (n=62) in a 4-week, double-blind, randomized, place
patients diagnosed with ADHD (Prod Info VYVANSE(R) oral capsules, 2008).

c) Elevation of blood pressure has been reported following administration of amphetamines. Modest inc
mmHg), and average heart rate (about 3 to 6 bpm) are associated with stimulant medications, but larger
(R) oral capsules, 2008).

3.3.1.A.4 Increased heart rate

a) Incidence: adult patients, 2% (Prod Info VYVANSE(R) oral capsules, 2008)

b) Heart rate increases were reported in 2% of adult patients who received lisdexamfetamine in final dos
compared with 0% of patients who received placebo (n=62) in a 4-week, double-blind, randomized, place
patients diagnosed with ADHD (Prod Info VYVANSE(R) oral capsules, 2008).

3.3.1.A.5 Myocardial infarction

a) Myocardial infarction (MI) has been reported in adults being treated with CNS stimulant drugs at usua
following administration of amphetamines (Prod Info VYVANSE(TM) oral capsules, 2007).

3.3.1.A.6 Palpitations

a) Palpitations have been reported following administration of amphetamines (Prod Info VYVANSE(R) o

3.3.1.A.7 Summary

a) Serious cardiovascular events, including sudden cardiac death, myocardial infarction, and stroke hav
including lisdexamfetamine. It is recommended that stimulant drugs not be used in patients who have kn
serious heart rhythm irregularities, coronary artery disease, or other serious heart problems. Blood press
regular intervals in patients receiving lisdexamfetamine (Prod Info VYVANSE(TM) oral capsules, 2007).

3.3.1.A.8 Tachycardia

a) Tachycardia led to discontinuation of therapy in 1% (3/358) of adult patients receiving lisdexamfetami
rate compared with those receiving placebo (Prod Info VYVANSE(R) oral capsules, 2008).

b) Tachycardia has been reported following administration of amphetamines or lisdexamfetamine dimes
2008).

c) In a retrospective review of poison center databases in 8 states during the initial 10 months of produc
of 28) of patients between 4 and 44 years of age (median, 8 years) experiencing adverse events with lisd
reliably determined as concomitant drugs or conditions were not evaluated (Spiller et al, 2008).

3.3.1.A.9 Ventricular hypertrophy

a) Ventricular hypertrophy led to discontinuation of therapy in 1% (2/218) of pediatric patients receiving l
discontinuation rate compared with those receiving placebo (Prod Info VYVANSE(R) oral capsules, 2008

3.3.2 Dermatologic Effects

3.3.2.A Lisdexamfetamine Dimesylate

Rash

Stevens-Johnson syndrome

Toxic epidermal necrolysis due to drug

Urticaria

3.3.2.A.1 Rash

a) Incidence: pediatric patients, 3% (Prod Info VYVANSE(R) oral capsules, 2008)
b) During a 4-week, double-blind, randomized, placebo-controlled, parallel-group clinical trial of pediatric (n=290), rash was reported in 3% of pediatric patients receiving lisdexamfetamine (n=218) compared wit the most frequent adverse events leading to discontinuation of therapy was rash with an incidence of 1% which was at least twice the rate compared with placebo (Prod Info VYVANSE(R) oral capsules, 2008).

3.3.2.A.2 Stevens-Johnson syndrome
a) Stevens-Johnson syndrome has been reported following administration of amphetamines (Prod Info V

3.3.2.A.3 Toxic epidermal necrolysis due to drug
a) Toxic epidermal necrolysis has been reported following administration of amphetamines (Prod Info V

3.3.2.A.4 Urticaria
a) Urticaria has been reported following administration of amphetamines (Prod Info VYVANSE(R) oral c

3.3.3 Endocrine/Metabolic Effects

3.3.3.A Lisdexamfetamine Dimesylate

Decreased body growth

Diaphoresis

Problem of growth and development

Sexual dysfunction

Weight decreased

3.3.3.A.1 Decreased body growth
a) Suppression of growth has been reported with long-term use of stimulants in children and adolescent
b) It is recommended that pediatric patients being treated with lisdexamfetamine be monitored for growt (R) oral capsules, 2008).

3.3.3.A.2 Diaphoresis
a) Incidence: adult patients, 3% (Prod Info VYVANSE(R) oral capsules, 2008)
b) Hyperhidrosis was reported in 3% of adult patients who received lisdexamfetamine in final doses of 3 0% of patients who received placebo (n=62) in a 4-week, double-blind, randomized, placebo-controlled, diagnosed with ADHD (Prod Info VYVANSE(R) oral capsules, 2008).

3.3.3.A.3 Problem of growth and development
a) In patients receiving lisdexamfetamine 7 days per week for 1 year, there was a decrease in growth ra from baseline in percentile of -13.4 over 1 year. The average percentile at baseline was 60.6, and at 1 ye (R) oral capsules, 2008).
b) It is recommended that pediatric patients being treated with lisdexamfetamine be monitored for growt (R) oral capsules, 2008).

3.3.3.A.4 Sexual dysfunction
a) Changes in libido have been reported following administration of amphetamines (Prod Info VYVANSE

3.3.3.A.5 Weight decreased
a) Incidence: pediatric patients, 9% (Prod Info VYVANSE(R) oral capsules, 2008)
b) During a 4-week, double-blind, randomized, placebo-controlled, parallel-group clinical trial of pediatric (n=290), a decrease in weight was reported in 9% of pediatric patients receiving lisdexamfetamine (n=21 (n=72) (Prod Info VYVANSE(R) oral capsules, 2008).
c) In a controlled trial in pediatric patients age 6 to 12 years, the mean weight loss from baseline after 4 pounds for patients receiving 30, 50, and 70 mg of lisdexamfetamine, respectively, compared with a 1 pc Higher doses of lisdexamfetamine were associated with greater weight loss during the 4 weeks of therap per week for 1 year, there was a decrease in growth rate (measured by body weight) from mean change The average percentile at baseline was 60.6, and at 1 year was 47.2 (Prod Info VYVANSE(R) oral capsu
d) In a 4-week, double-blind, randomized, placebo-controlled, parallel group trial of 420 adult patients di baseline after 4 weeks of therapy was 2.8, 3.1, and 4.3 pounds in adult patients who received lisdexamfe (n=358), respectively, compared with a mean weight gain of 0.5 pound in patients who received placebo 2008).

3.3.4 Gastrointestinal Effects

3.3.4.A Lisdexamfetamine Dimesylate

Constipation

Diarrhea

Loss of appetite

Nausea

Taste sense altered

Upper abdominal pain

Vomiting

Xerostomia

3.3.4.A.1 Constipation

a) Constipation has been reported following administration of amphetamines (Prod Info VYVANSE(R) o

3.3.4.A.2 Diarrhea

a) Incidence: adult patients, 7% (Prod Info VYVANSE(R) oral capsules, 2008)

b) Diarrhea was reported in 7% of adult patients who received lisdexamfetamine in final doses of 30 mg patients who received placebo (n=62) in a 4-week, double-blind, randomized, placebo-controlled, paralle ADHD (Prod Info VYVANSE(R) oral capsules, 2008).

3.3.4.A.3 Loss of appetite

a) Incidence: pediatric patients, 39%; adult patients, 27% (Prod Info VYVANSE(R) oral capsules, 2008)

b) During a 4-week, double-blind, randomized, placebo-controlled, parallel-group clinical trial of pediatric (n=290), a decreased appetite was reported in 39% of pediatric patients receiving lisdexamfetamine (n=2 placebo (n=72) (Prod Info VYVANSE(R) oral capsules, 2008).

c) Decreased appetite was reported in 27% of adult patients who received lisdexamfetamine in final dos compared with 3% of patients who received placebo (n=62) in a 4-week, double-blind, randomized, place patients diagnosed with ADHD. In the same study, anorexia was reported in 5% of patients receiving lisc receiving placebo (Prod Info VYVANSE(R) oral capsules, 2008).

3.3.4.A.4 Nausea

a) Incidence: pediatric patients, 6%; adult patients, 7% (Prod Info VYVANSE(R) oral capsules, 2008)

b) During a 4-week, double-blind, randomized, placebo-controlled, parallel-group clinical trial of pediatric (n=290), nausea was reported in 6% of pediatric patients receiving lisdexamfetamine (n=218) compared Info VYVANSE(R) oral capsules, 2008).

c) Nausea was reported in 7% of adult patients who received lisdexamfetamine in final doses of 30 mg, patients who received placebo (n=62) in a 4-week, double-blind, randomized, placebo-controlled, paralle ADHD (Prod Info VYVANSE(R) oral capsules, 2008).

3.3.4.A.5 Taste sense altered

a) Unpleasant taste has been reported following administration of amphetamines (Prod Info VYVANSE(

3.3.4.A.6 Upper abdominal pain

a) Incidence: pediatric patients, 12%; adults, 5% or greater (Prod Info VYVANSE(R) oral capsules, 2008

b) During a 4-week, double-blind, randomized, placebo-controlled, parallel-group clinical trial of pediatric (n=290), upper abdominal pain was reported in 12% of pediatric patients receiving lisdexamfetamine (n= placebo (n=72). Abdominal pain was also reported in at least 5% or more adults patients receiving lisdex VYVANSE(R) oral capsules, 2008).

c) Further, in a retrospective review of poison center databases in 8 states during the initial 10 months o in 7% (2 of 28) of patients between 4 and 44 years of age (median, 8 years) experiencing adverse event not be reliably determined as concomitant drugs or conditions were not evaluated (Spiller et al, 2008).

3.3.4.A.7 Vomiting

a) Incidence: pediatric patients, 9% (Prod Info VYVANSE(R) oral capsules, 2008)
b) During a 4-week, double-blind, randomized, placebo-controlled, parallel-group clinical trial of pediatric (n=290), vomiting was reported in 9% of pediatric patients receiving lisdexamfetamine (n=218) compared Vomiting led to discontinuation of therapy in 1% (2/218) of pediatric patients receiving lisdexamfetamine, rate compared with those receiving placebo (Prod Info VYVANSE(R) oral capsules, 2008).
c) In a retrospective review of poison center databases in 8 states during the initial 10 months of produc of patients between 4 and 44 years of age (median, 8 years) experiencing adverse events with lisdexam determined as concomitant drugs or conditions were not evaluated (Spiller et al, 2008).

3.3.4.A.8 Xerostomia

a) Incidence: pediatric patients, 5%; adult patients, 26% (Prod Info VYVANSE(R) oral capsules, 2008)
b) During a 4-week, double-blind, randomized, placebo-controlled, parallel-group clinical trial of pediatric (n=290), dry mouth was reported in 5% of pediatric patients receiving lisdexamfetamine (n=218) compar (Prod Info VYVANSE(R) oral capsules, 2008).
c) Dry mouth was reported in 26% of adult patients who received lisdexamfetamine in final doses of 30 of patients who received placebo (n=62) in a 4-week, double-blind, randomized, placebo-controlled, para with ADHD (Prod Info VYVANSE(R) oral capsules, 2008).

3.3.8 Musculoskeletal Effects

3.3.8.A Lisdexamfetamine Dimesylate

3.3.8.A.1 Muscle fasciculation

a) In a retrospective review of poison center databases in 8 states during the initial 10 months of produc 28) of patients between 4 and 44 years of age (median, 8 years) experiencing adverse events with lisdex reliably determined as concomitant drugs or conditions were not evaluated (Spiller et al, 2008).

3.3.9 Neurologic Effects

3.3.9.A Lisdexamfetamine Dimesylate

Cerebrovascular accident

Confusion, acute

Dizziness

Dystonia

Gilles de la Tourette's syndrome

Headache

Insomnia

Seizure

Somnolence

Tic

Tremor

3.3.9.A.1 Cerebrovascular accident

a) Stroke has been reported in adults being treated with CNS stimulant drugs at usual doses for ADHD. administration of amphetamines (Prod Info VYVANSE(TM) oral capsules, 2007).

3.3.9.A.2 Confusion, acute

a) In a retrospective review of poison center databases in 8 states during the initial 10 months of produc of patients between 4 and 44 years of age (median, 8 years) experiencing adverse events with lisdexam determined as concomitant drugs or conditions were not evaluated (Spiller et al, 2008).

3.3.9.A.3 Dizziness

a) Incidence: pediatric patients, 5% (Prod Info VYVANSE(TM) oral capsules, 2007)

b) During a 4-week, double-blind, randomized, placebo-controlled, parallel-group clinical trial of pediatric (n=290), dizziness was reported in 5% of pediatric patients receiving lisdexamfetamine (n=218) compare (Prod Info VYVANSE(TM) oral capsules, 2007).

c) Further, in a retrospective review of poison center databases in 8 states during the initial 10 months c (2 of 28) of patients between 4 and 44 years of age (median, 8 years) experiencing adverse events with be reliably determined as concomitant drugs or conditions were not evaluated (Spiller et al, 2008).

3.3.9.A.4 Dystonia

a) Incidence: 29% (Spiller et al, 2008)

b) In a retrospective review of poison center databases in 8 states during the initial 10 months of produc 28) of patients between 4 and 44 years of age (median, 8 years) experiencing adverse events with lisde reliably determined as concomitant drugs or conditions were not evaluated (Spiller et al, 2008).

3.3.9.A.5 Gilles de la Tourette's syndrome

a) Exacerbation of Tourette's syndrome has been reported following administration of amphetamines. P be evaluated for Tourette's syndrome (Prod Info VYVANSE(R) oral capsules, 2008).

3.3.9.A.6 Headache

a) Incidence: adult patients, 5% or greater (Prod Info VYVANSE(R) oral capsules, 2008)

b) Headache occurred in at least 5% or more patients receiving lisdexamfetamine during clinical trials, l (2/358) of adult patients , which was at least twice the discontinuation rate compared with those receiving capsules, 2008).

3.3.9.A.7 Insomnia

a) Incidence: pediatric patients, 19%; adult patients, 27% (Prod Info VYVANSE(R) oral capsules, 2008;

b) During a 4-week, double-blind, randomized, placebo-controlled, parallel-group clinical trial of pediatric (n=290), insomnia was reported in 19% of pediatric patients receiving lisdexamfetamine (n=218) compar (Prod Info VYVANSE(R) oral capsules, 2008).

c) Insomnia was reported in 27% of adult patients who received lisdexamfetamine in final doses of 30 m of patients who received placebo (n=62) in a 4-week, double-blind, randomized, placebo-controlled, para with ADHD. In the same trial, initial insomnia was reported in 4% of adult patient receiving lisdexamfetam placebo (Prod Info VYVANSE(R) oral capsules, 2008).

d) Insomnia led to discontinuation of therapy in 1% (2/218) of pediatric patients and 2% (8/358) of adult at least twice the discontinuation rate compared with those receiving placebo (Prod Info VYVANSE(R) o

e) Further, in a retrospective review of poison center databases in 8 states during the initial 10 months c (8 of 28) of patients between 4 and 44 years of age (median, 8 years) experiencing adverse events with be reliably determined as concomitant drugs or conditions were not evaluated (Spiller et al, 2008).

3.3.9.A.8 Seizure

a) Incidence: 4% (Spiller et al, 2008)

b) In a retrospective review of poison center databases in 8 states during the initial 10 months of produc patients between 4 and 44 years of age (median, 8 years) experiencing adverse events with lisdexamfet concomitant trazodone and imipramine, but had not experienced any other seizures prior to the initiation

3.3.9.A.9 Somnolence

a) Incidence: pediatric patients, 2% (Prod Info VYVANSE(R) oral capsules, 2008)

b) During a 4-week, double-blind, randomized, placebo-controlled, parallel-group clinical trial of pediatric (n=290), somnolence was reported in 2% of pediatric patients receiving lisdexamfetamine (n=218) comp (Prod Info VYVANSE(TM) oral capsules, 2007).

3.3.9.A.10 Tic

a) Incidence: pediatric patients, 2% (Prod Info VYVANSE(R) oral capsules, 2008)

b) During a 4-week, double-blind, randomized, placebo-controlled, parallel-group clinical trial of pediatric (n=290), tics were reported in 2% of pediatric patients receiving lisdexamfetamine (n=218) compared wit the most frequent adverse events leading to discontinuation of therapy was exacerbation of motor and p patients receiving lisdexamfetamine, which was at least twice the rate compared with placebo (Prod Info

c) Tics led to discontinuation of therapy in 1% (2/218) of pediatric patients receiving lisdexamfetamine, v compared with those receiving placebo (Prod Info VYVANSE(R) oral capsules, 2008).

d) Exacerbation of motor and phonic tics has been reported following administration of amphetamines. I should be evaluated for tics (Prod Info VYVANSE(R) oral capsules, 2008).

3.3.9.A.11 Tremor

a) Incidence: adult patients, 2% (Prod Info VYVANSE(R) oral capsules, 2008)

b) Tremor was reported in 2% of adult patients who received lisdexamfetamine in final doses of 30 mg, patients who received placebo (n=62) in a 4-week, double-blind, randomized, placebo-controlled, paralle ADHD (Prod Info VYVANSE(R) oral capsules, 2008).

c) Further, in a retrospective review of poison center databases in 8 states during the initial 10 months c of 28) of patients between 4 and 44 years of age (median, 8 years) experiencing adverse events with lisc reliably determined as concomitant drugs or conditions were not evaluated (Spiller et al, 2008).
d) Tremor has been reported following administration of amphetamines (Prod Info VYVANSE(R) oral ca

3.3.10 Ophthalmic Effects

3.3.10.A Lisdexamfetamine Dimesylate

3.3.10.A.1 Blurred vision
a) In a retrospective review of poison center databases in 8 states during the initial 10 months of produc 28) of patients between 4 and 44 years of age (median, 8 years) experiencing adverse events with lisde reliably determined as concomitant drugs or conditions were not evaluated (Spiller et al, 2008).

3.3.12 Psychiatric Effects

3.3.12.A Lisdexamfetamine Dimesylate

Agitation

Anxiety

Dysphoric mood

Euphoria

Feeling nervous

Hallucinations

Irritability

Labile affect

Psychotic disorder

Restlessness

Summary

3.3.12.A.1 Agitation
a) Incidence: adult patients, 3% (Prod Info VYVANSE(R) oral capsules, 2008)
b) Agitation was reported in 3% of adult patients who received lisdexamfetamine in final doses of 30 mg patients who received placebo (n=62) in a 4-week, double-blind, randomized, placebo-controlled, paralle ADHD (Prod Info VYVANSE(R) oral capsules, 2008).
c) In a retrospective review of poison center databases in 8 states during the initial 10 months of produc 28) of patients between 4 and 44 years of age (median, 8 years) experiencing adverse events with lisde reliably determined as concomitant drugs or conditions were not evaluated (Spiller et al, 2008).

3.3.12.A.2 Anxiety
a) Incidence: adult patients, 6% (Prod Info VYVANSE(R) oral capsules, 2008)
b) Anxiety was reported in 6% of adult patients who received lisdexamfetamine in final doses of 30 mg, patients who received placebo (n=62) in a 4-week, double-blind, randomized, placebo-controlled, paralle ADHD. This led to a 1% discontinuation rate of lisdexamfetamine therapy (Prod Info VYVANSE(R) oral c

3.3.12.A.3 Dysphoric mood
a) Dysphoria has been reported following administration of amphetamines (Prod Info VYVANSE(R) oral

3.3.12.A.4 Euphoria
a) Euphoria has been reported following administration of amphetamines (Prod Info VYVANSE(R) oral c

3.3.12.A.5 Feeling nervous

a) Incidence: adult patients, 4% (Prod Info VYVANSE(R) oral capsules, 2008)
b) Feeling jittery was reported in 4% of adult patients who received lisdexamfetamine in final doses of 3
0% of patients who received placebo (n=62) in a 4-week, double-blind, randomized, placebo-controlled,
diagnosed with ADHD (Prod Info VYVANSE(R) oral capsules, 2008).
c) In a retrospective review of poison center databases in 8 states during the initial 10 months of produc
(3 of 28) of patients between 4 and 44 years of age (median, 8 years) experiencing adverse events with
be reliably determined as concomitant drugs or conditions were not evaluated (Spiller et al, 2008).

3.3.12.A.6 Hallucinations

a) Incidence: 11% (Spiller et al, 2008)
b) In a retrospective review of poison center databases in 8 states during the initial 10 months of produc
of 28) of patients between 4 and 44 years of age (median, 8 years) experiencing adverse events with lisc
reliably determined as concomitant drugs or conditions were not evaluated (Spiller et al, 2008).

3.3.12.A.7 Irritability

a) Incidence: pediatric patients, 10%; adults, 5% or greater (Prod Info VYVANSE(R) oral capsules, 2008
b) During a 4-week, double-blind, randomized, placebo-controlled, parallel-group clinical trial of pediatric
(n=290), irritability was reported in 10% of pediatric patients receiving lisdexamfetamine (n=218) compar
(Prod Info VYVANSE(R) oral capsules, 2008).
c) Irritability was also reported in at least 5% or more adults patients receiving lisdexamfetamine during
1% (Prod Info VYVANSE(R) oral capsules, 2008).

3.3.12.A.8 Labile affect

a) Incidence: pediatric patients, 3% (Prod Info VYVANSE(R) oral capsules, 2008)
b) During a 4-week, double-blind, randomized, placebo-controlled, parallel-group clinical trial of pediatric
(n=290), labile affect was reported in 3% of pediatric patients receiving lisdexamfetamine (n=218) compa
(Prod Info VYVANSE(TM) oral capsules, 2007).

3.3.12.A.9 Psychotic disorder

a) In multiple short term, placebo-controlled studies, psychotic episodes have been reported in 0.1% of
with recommended doses of methylphenidate or amphetamines compared with no patients receiving pla
2008).
b) Psychotic or manic symptoms may occur among patients without prior history of psychosis, or may w
(Prod Info VYVANSE(R) oral capsules, 2008).

3.3.12.A.10 Restlessness

a) Incidence: adult patients, 3% (Prod Info VYVANSE(R) oral capsules, 2008)
b) Restlessness was reported in 3% of adult patients who received lisdexamfetamine in final doses of 3
0% of patients who received placebo (n=62) in a 4-week, double-blind, randomized, placebo-controlled,
diagnosed with ADHD (Prod Info VYVANSE(R) oral capsules, 2008).

3.3.12.A.11 Summary

a) The use of stimulants may result in new-onset or worsening of existing psychotic disorders, even in p
aggressive behavior and evaluating the patient for bipolar disorder prior to stimulant use is recommende

3.3.14 Reproductive Effects

3.3.14.A Lisdexamfetamine Dimesylate

3.3.14.A.1 Impotence

a) Impotence has been reported following administration of amphetamines (Prod Info VYVANSE(R) oral

3.3.15 Respiratory Effects

3.3.15.A Lisdexamfetamine Dimesylate

3.3.15.A.1 Dyspnea

a) Incidence: adult patients, 2% (Prod Info VYVANSE(R) oral capsules, 2008)
b) Dyspnea was reported in 2% of adult patients who received lisdexamfetamine in final doses of 30 mg
patients who received placebo (n=62) in a 4-week, double-blind, randomized, placebo-controlled, paralle
ADHD. This led to a 1% discontinuation rate of lisdexamfetamine therapy (Prod Info VYVANSE(R) oral c

3.3.16 Other

3.3.16.A Lisdexamfetamine Dimesylate

3.3.16.A.1 Fever

a) Incidence: pediatric patients, 2% (Prod Info VYVANSE(R) oral capsules, 2008)

b) During a 4-week, double-blind, randomized, placebo-controlled, parallel-group clinical trial of pediatric (n=290), pyrexia was reported in 2% of pediatric patients receiving lisdexamfetamine (n=218) compared Info VYVANSE(TM) oral capsules, 2007).
c) Further, in a retrospective review of poison center databases in 8 states during the initial 10 months c 28) of patients between 4 and 44 years of age (median, 8 years) experiencing adverse events with lisdex reliably determined as concomitant drugs or conditions were not evaluated (Spiller et al, 2008).

3.4 Teratogenicity/Effects in Pregnancy/Breastfeeding

A) Teratogenicity/Effects in Pregnancy
1) U.S. Food and Drug Administration's Pregnancy Category: Category C (Prod Info VYVANSE(TM) oral capsule
a) Either studies in animals have revealed adverse effects on the fetus (teratogenic or embryocidal or other) studies in women and animals are not available. Drugs should be given only if the potential benefit justifies th
See Drug Consult reference: PREGNANCY RISK CATEGORIES
2) Crosses Placenta: Unknown
3) Clinical Management
a) There are no adequate and well-controlled studies with lisdexamfetamine in humans or animals. Studies v animals have shown adverse maternal and fetal effects. Until further data are available, it is recommended th only if the potential benefit justifies the potential risk to the fetus (Prod Info VYVANSE(TM) oral capsules, 200
4) Literature Reports
a) Reproduction studies with lisdexamfetamine (prodrug of dextroamphetamine) have not been conducted in of premature delivery and low birth weight in infants born to mothers dependent on amphetamine. Additionall agitation, and significant lassitude, may be present in such infants (Prod Info VYVANSE(TM) oral capsules, 2
b) In pregnant rats and rabbits, orally administered amphetamine (D to L enantiomer ratio of 3:1) at doses up not affect embryofetal development or survival. However, parenteral administration of dextroamphetamine at mice resulted in severe maternal toxicity and fetal malformations and death. Additionally, in several studies in clinically relevant amphetamine doses led to long-term neurochemical and behavioral effects, such as learnin activity, and changes in sexual function (Prod Info VYVANSE(TM) oral capsules, 2007).

B) Breastfeeding
1) Thomson Lactation Rating: Infant risk cannot be ruled out.
a) Available evidence and/or expert consensus is inconclusive or is inadequate for determining infant risk wh potential benefits of drug treatment against potential risks before prescribing this drug during breastfeeding.
2) Clinical Management
a) As amphetamines are excreted in human milk, breast-feeding women receiving lisdexamfetamine should VYVANSE(TM) oral capsules, 2007).

3.5 Drug Interactions

3.5.1 Drug-Drug Combinations

Amitriptyline

Amoxapine

Clomipramine

Clorgyline

Desipramine

Dothiepin

Doxepin

Furazolidone

Imipramine

Iproniazid

Isocarboxazid

Lofepramine

Moclobemide

Nialamide

Nortriptyline

Opipramol

Pargyline

Phenelzine

Procarbazine

Protriptyline

Rasagiline

Selegiline

Toloxatone

Tranylcypromine

Trimipramine

3.5.1.A Amitriptyline

1) Interaction Effect: hypertension, other cardiac effects, and CNS stimulation

2) Summary: Concomitant tricyclic antidepressant (TCA) and amphetamine administration has been reporte from the release of norepinephrine (Beaumont, 1973; Raisfeld, 1972). A similar reaction might also occur wit Acute elevations in blood pressure have been noted (Flemenbaum, 1971a). Some amphetamine-like drugs m most combinations have not been studied. When amphetamine analogs are being used to treat obesity, it sh moderate weight gain (Russ & Ackerman, 1988). False positive urine tests for amphetamines have been repo & Browning, 1993). Caution is advised when concurrent administration of amphetamine-like agents and TCA monitored for increased cardiovascular effects (hypertension and dysrhythmias).

3) Severity: moderate

4) Onset: delayed

5) Substantiation: theoretical

6) Clinical Management: Coadministration of amphetamines and tricyclic antidepressants or other sympatho increased cardiovascular effects, or CNS stimulation (Prod Info VYVANSE(TM) oral capsules, 2007; Prod Inf capsules, oral tablets, 2006; Prod Info ADDERALL(R) oral tablets, 2006; Flemenbaum, 1972). Use caution if closely for hypertension and dysrhythmias.

7) Probable Mechanism: synergistic effects on noradrenergic neurotransmission

8) Literature Reports

a) Amphetamines may increase the activity of tricyclic antidepressants (TCA) or sympathomimetic agen amphetamine with TCAs such as desipramine or protriptyline results in sustained increases in d-amphet VYVANSE(TM) oral capsules, 2007; Prod Info DEXEDRINE(R) sustained-release oral capsules, oral tab 2006).

b) Human pharmacologic studies have demonstrated that methylphenidate may inhibit the metabolism o imipramine, clomipramine, or desipramine (Prod Info DAYTRANA(TM) transdermal system, 2006).

c) Concomitant administration of tricyclic antidepressants and methylphenidate can result in increases i effects induced by TCAs may lead to blood pressures as high as 170/120 mmHg within one day of comb methylphenidate usually results in the blood pressure returning to normotensive levels; reinstitution of th pressure elevation (Flemenbaum, 1971; Flemenbaum, 1972).

d) Fifteen patients with DSM-III major depression, who failed to respond to treatment with desipramine g fenfluramine 40 mg to 120 mg daily for two weeks but did not result in any transient or sustained clinical doubled steady-state plasma levels of desipramine (Price et al, 1990).

e) There have been claims based on uncontrolled studies that a better antidepressant response may oc 1969). However, a systemic review of stimulants in the treatment of depression concluded that although ten placebo-controlled studies of stimulant drugs in primary depression, with one exception, indicated litt appear to be as effective as the conventional antidepressants in primary depression (Satel & Nelson, 19

3.5.1.B Amoxapine

1) Interaction Effect: hypertension, other cardiac effects, and CNS stimulation

2) Summary: Concomitant tricyclic antidepressant (TCA) and amphetamine administration has been reporte from the release of norepinephrine (Beaumont, 1973; Raisfeld, 1972). A similar reaction might also occur wit Acute elevations in blood pressure have been noted (Flemenbaum, 1971a). Some amphetamine-like drugs m most combinations have not been studied. When amphetamine analogs are being used to treat obesity, it sh moderate weight gain (Russ & Ackerman, 1988). False positive urine tests for amphetamines have been repo & Browning, 1993). Caution is advised when concurrent administration of amphetamine-like agents and TCAs monitored for increased cardiovascular effects (hypertension and dysrhythmias).

3) Severity: moderate

4) Onset: delayed

5) Substantiation: theoretical

6) Clinical Management: Coadministration of amphetamines and tricyclic antidepressants or other sympatho increased cardiovascular effects, or CNS stimulation (Prod Info VYVANSE(TM) oral capsules, 2007; Prod Inf capsules, oral tablets, 2006; Prod Info ADDERALL(R) oral tablets, 2006; Flemenbaum, 1972). Use caution if closely for hypertension and dysrhythmias.

7) Probable Mechanism: synergistic effects on noradrenergic neurotransmission

8) Literature Reports

a) Amphetamines may increase the activity of tricyclic antidepressants (TCA) or sympathomimetic agen amphetamine with TCAs such as desipramine or protriptyline results in sustained increases in d-amphet VYVANSE(TM) oral capsules, 2007; Prod Info DEXEDRINE(R) sustained-release oral capsules, oral tab 2006).

b) Human pharmacologic studies have demonstrated that methylphenidate may inhibit the metabolism o imipramine, clomipramine, or desipramine (Prod Info DAYTRANA(TM) transdermal system, 2006).

c) Concomitant administration of tricyclic antidepressants and methylphenidate can result in increases i effects induced by TCAs may lead to blood pressures as high as 170/120 mmHg within one day of comb methylphenidate usually results in the blood pressure returning to normotensive levels; reinstitution of th pressure elevation (Flemenbaum, 1971; Flemenbaum, 1972).

d) Fifteen patients with DSM-III major depression, who failed to respond to treatment with desipramine g fenfluramine 40 mg to 120 mg daily for two weeks but did not result in any transient or sustained clinical doubled steady-state plasma levels of desipramine (Price et al, 1990).

e) There have been claims based on uncontrolled studies that a better antidepressant response may oc 1969). However, a systemic review of stimulants in the treatment of depression concluded that although ten placebo-controlled studies of stimulant drugs in primary depression, with one exception, indicated litt appear to be as effective as the conventional antidepressants in primary depression (Satel & Nelson, 19

3.5.1.C Clomipramine

1) Interaction Effect: hypertension, other cardiac effects, and CNS stimulation

2) Summary: Concomitant tricyclic antidepressant (TCA) and amphetamine administration has been reporte from the release of norepinephrine (Beaumont, 1973; Raisfeld, 1972). A similar reaction might also occur wit Acute elevations in blood pressure have been noted (Flemenbaum, 1971a). Some amphetamine-like drugs m most combinations have not been studied. When amphetamine analogs are being used to treat obesity, it sh moderate weight gain (Russ & Ackerman, 1988). False positive urine tests for amphetamines have been repo & Browning, 1993). Caution is advised when concurrent administration of amphetamine-like agents and TCAs monitored for increased cardiovascular effects (hypertension and dysrhythmias).

3) Severity: moderate

4) Onset: delayed

5) Substantiation: theoretical

6) Clinical Management: Coadministration of amphetamines and tricyclic antidepressants or other sympatho increased cardiovascular effects, or CNS stimulation (Prod Info VYVANSE(TM) oral capsules, 2007; Prod Inf capsules, oral tablets, 2006; Prod Info ADDERALL(R) oral tablets, 2006; Flemenbaum, 1972). Use caution if closely for hypertension and dysrhythmias.

7) Probable Mechanism: synergistic effects on noradrenergic neurotransmission

8) Literature Reports

a) Amphetamines may increase the activity of tricyclic antidepressants (TCA) or sympathomimetic agen amphetamine with TCAs such as desipramine or protriptyline results in sustained increases in d-amphet VYVANSE(TM) oral capsules, 2007; Prod Info DEXEDRINE(R) sustained-release oral capsules, oral tab 2006).

b) Human pharmacologic studies have demonstrated that methylphenidate may inhibit the metabolism o imipramine, clomipramine, or desipramine (Prod Info DAYTRANA(TM) transdermal system, 2006).

c) Concomitant administration of tricyclic antidepressants and methylphenidate can result in increases i effects induced by TCAs may lead to blood pressures as high as 170/120 mmHg within one day of comb methylphenidate usually results in the blood pressure returning to normotensive levels; reinstitution of th pressure elevation (Flemenbaum, 1971; Flemenbaum, 1972).

d) Fifteen patients with DSM-III major depression, who failed to respond to treatment with desipramine g fenfluramine 40 mg to 120 mg daily for two weeks but did not result in any transient or sustained clinical doubled steady-state plasma levels of desipramine (Price et al, 1990).

e) There have been claims based on uncontrolled studies that a better antidepressant response may oc
1969). However, a systemic review of stimulants in the treatment of depression concluded that although
ten placebo-controlled studies of stimulant drugs in primary depression, with one exception, indicated litt
appear to be as effective as the conventional antidepressants in primary depression (Satel & Nelson, 19

3.5.1.D Clorgyline

1) Interaction Effect: hypertensive crisis (headache, hyperpyrexia, hypertension)
2) Summary: Use of lisdexamfetamine during or within 14 days following the administration of a monoamine
Amphetamines stimulate the release of norepinephrine, and the use of MAOIs slows down amphetamine met
norepinephrine and other monoamines from adrenergic nerve ending. This could result in hypertensive crisis,
hyperpyrexia (Prod Info VYVANSE(TM) oral capsules, 2007).
3) Severity: contraindicated
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Lisdexamfetamine use during or within 14 days following the administration of a mo
hypertensive crises may occur (Prod Info VYVANSE(TM) oral capsules, 2007).
7) Probable Mechanism: increased norepinephrine availability

3.5.1.E Desipramine

1) Interaction Effect: hypertension, other cardiac effects, and CNS stimulation
2) Summary: Concomitant tricyclic antidepressant (TCA) and amphetamine administration has been reporte
from the release of norepinephrine (Beaumont, 1973; Raisfeld, 1972). A similar reaction might also occur with
Acute elevations in blood pressure have been noted (Flemenbaum, 1971a). Some amphetamine-like drugs m
most combinations have not been studied. When amphetamine analogs are being used to treat obesity, it sho
moderate weight gain (Russ & Ackerman, 1988). False positive urine tests for amphetamines have been repo
& Browning, 1993). Caution is advised when concurrent administration of amphetamine-like agents and TCAs
monitored for increased cardiovascular effects (hypertension and dysrhythmias).
3) Severity: moderate
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: Coadministration of amphetamines and tricyclic antidepressants or other sympatho
increased cardiovascular effects, or CNS stimulation (Prod Info VYVANSE(TM) oral capsules, 2007; Prod Inf
capsules, oral tablets, 2006; Prod Info ADDERALL(R) oral tablets, 2006; Flemenbaum, 1972). Use caution if
closely for hypertension and dysrhythmias.
7) Probable Mechanism: synergistic effects on noradrenergic neurotransmission
8) Literature Reports

a) Amphetamines may increase the activity of tricyclic antidepressants (TCA) or sympathomimetic agen
amphetamine with TCAs such as desipramine or protriptyline results in sustained increases in d-amphet
VYVANSE(TM) oral capsules, 2007; Prod Info DEXEDRINE(R) sustained-release oral capsules, oral tab
2006).

b) Human pharmacologic studies have demonstrated that methylphenidate may inhibit the metabolism o
imipramine, clomipramine, or desipramine (Prod Info DAYTRANA(TM) transdermal system, 2006).

c) Concomitant administration of tricyclic antidepressants and methylphenidate can result in increases in
effects induced by TCAs may lead to blood pressures as high as 170/120 mmHg within one day of comb
methylphenidate usually results in the blood pressure returning to normotensive levels; reinstitution of th
pressure elevation (Flemenbaum, 1971; Flemenbaum, 1972).

d) Fifteen patients with DSM-III major depression, who failed to respond to treatment with desipramine g
fenfluramine 40 mg to 120 mg daily for two weeks but did not result in any transient or sustained clinical
doubled steady-state plasma levels of desipramine (Price et al, 1990).

e) There have been claims based on uncontrolled studies that a better antidepressant response may oc
1969). However, a systemic review of stimulants in the treatment of depression concluded that although
ten placebo-controlled studies of stimulant drugs in primary depression, with one exception, indicated litt
appear to be as effective as the conventional antidepressants in primary depression (Satel & Nelson, 19

3.5.1.F Dothiepin

1) Interaction Effect: hypertension, other cardiac effects, and CNS stimulation
2) Summary: Concomitant tricyclic antidepressant (TCA) and amphetamine administration has been reporte
from the release of norepinephrine (Beaumont, 1973; Raisfeld, 1972). A similar reaction might also occur with
Acute elevations in blood pressure have been noted (Flemenbaum, 1971a). Some amphetamine-like drugs m
most combinations have not been studied. When amphetamine analogs are being used to treat obesity, it sho
moderate weight gain (Russ & Ackerman, 1988). False positive urine tests for amphetamines have been repo
& Browning, 1993). Caution is advised when concurrent administration of amphetamine-like agents and TCAs
monitored for increased cardiovascular effects (hypertension and dysrhythmias).
3) Severity: moderate
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: Coadministration of amphetamines and tricyclic antidepressants or other sympatho
increased cardiovascular effects, or CNS stimulation (Prod Info VYVANSE(TM) oral capsules, 2007; Prod Inf

capsules, oral tablets, 2006; Prod Info ADDERALL(R) oral tablets, 2006; Flemenbaum, 1972). Use caution if closely for hypertension and dysrhythmias.
7) Probable Mechanism: synergistic effects on noradrenergic neurotransmission
8) Literature Reports
a) Amphetamines may increase the activity of tricyclic antidepressants (TCA) or sympathomimetic agen amphetamine with TCAs such as desipramine or protriptyline results in sustained increases in d-amphet VYVANSE(TM) oral capsules, 2007; Prod Info DEXEDRINE(R) sustained-release oral capsules, oral tab 2006).
b) Human pharmacologic studies have demonstrated that methylphenidate may inhibit the metabolism c imipramine, clomipramine, or desipramine (Prod Info DAYTRANA(TM) transdermal system, 2006).
c) Concomitant administration of tricyclic antidepressants and methylphenidate can result in increases i effects induced by TCAs may lead to blood pressures as high as 170/120 mmHg within one day of comb methylphenidate usually results in the blood pressure returning to normotensive levels; reinstitution of th pressure elevation (Flemenbaum, 1971; Flemenbaum, 1972).
d) Fifteen patients with DSM-III major depression, who failed to respond to treatment with desipramine g fenfluramine 40 mg to 120 mg daily for two weeks but did not result in any transient or sustained clinical doubled steady-state plasma levels of desipramine (Price et al, 1990).
e) There have been claims based on uncontrolled studies that a better antidepressant response may oc 1969). However, a systemic review of stimulants in the treatment of depression concluded that although ten placebo-controlled studies of stimulant drugs in primary depression, with one exception, indicated litt appear to be as effective as the conventional antidepressants in primary depression (Satel & Nelson, 19

3.5.1.G Doxepin

1) Interaction Effect: hypertension, other cardiac effects, and CNS stimulation
2) Summary: Concomitant tricyclic antidepressant (TCA) and amphetamine administration has been reporte from the release of norepinephrine (Beaumont, 1973; Raisfeld, 1972). A similar reaction might also occur wit Acute elevations in blood pressure have been noted (Flemenbaum, 1971a). Some amphetamine-like drugs m most combinations have not been studied. When amphetamine analogs are being used to treat obesity, it sh moderate weight gain (Russ & Ackerman, 1988). False positive urine tests for amphetamines have been repo & Browning, 1993). Caution is advised when concurrent administration of amphetamine-like agents and TCAs monitored for increased cardiovascular effects (hypertension and dysrhythmias).
3) Severity: moderate
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: Coadministration of amphetamines and tricyclic antidepressants or other sympatho increased cardiovascular effects, or CNS stimulation (Prod Info VYVANSE(TM) oral capsules, 2007; Prod Inf capsules, oral tablets, 2006; Prod Info ADDERALL(R) oral tablets, 2006; Flemenbaum, 1972). Use caution if closely for hypertension and dysrhythmias.
7) Probable Mechanism: synergistic effects on noradrenergic neurotransmission
8) Literature Reports
a) Amphetamines may increase the activity of tricyclic antidepressants (TCA) or sympathomimetic agen amphetamine with TCAs such as desipramine or protriptyline results in sustained increases in d-amphet VYVANSE(TM) oral capsules, 2007; Prod Info DEXEDRINE(R) sustained-release oral capsules, oral tab 2006).
b) Human pharmacologic studies have demonstrated that methylphenidate may inhibit the metabolism c imipramine, clomipramine, or desipramine (Prod Info DAYTRANA(TM) transdermal system, 2006).
c) Concomitant administration of tricyclic antidepressants and methylphenidate can result in increases i effects induced by TCAs may lead to blood pressures as high as 170/120 mmHg within one day of comb methylphenidate usually results in the blood pressure returning to normotensive levels; reinstitution of th pressure elevation (Flemenbaum, 1971; Flemenbaum, 1972).
d) Fifteen patients with DSM-III major depression, who failed to respond to treatment with desipramine g fenfluramine 40 mg to 120 mg daily for two weeks but did not result in any transient or sustained clinical doubled steady-state plasma levels of desipramine (Price et al, 1990).
e) There have been claims based on uncontrolled studies that a better antidepressant response may oc 1969). However, a systemic review of stimulants in the treatment of depression concluded that although ten placebo-controlled studies of stimulant drugs in primary depression, with one exception, indicated litt appear to be as effective as the conventional antidepressants in primary depression (Satel & Nelson, 19

3.5.1.H Furazolidone

1) Interaction Effect: hypertensive crisis (headache, hyperpyrexia, hypertension)
2) Summary: Use of lisdexamfetamine during or within 14 days following the administration of a monoamine Amphetamines stimulate the release of norepinephrine, and the use of MAOIs slows down amphetamine me norepinephrine and other monoamines from adrenergic nerve ending. This could result in hypertensive crisis, hyperpyrexia (Prod Info VYVANSE(TM) oral capsules, 2007). Furazolidone has significant MAOI activity (Pet Therefore, concurrent use of furazolidone with lisdexamfetamine should be avoided.
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical

6) Clinical Management: Lisdexamfetamine use during or within 14 days following the administration of a mo contraindicated as hypertensive crises may occur (Prod Info VYVANSE(TM) oral capsules, 2007). As furazoli concurrent use with lisdexamfetamine.
7) Probable Mechanism: increased norepinephrine availability

3.5.1.I Imipramine
1) Interaction Effect: hypertension, other cardiac effects, and CNS stimulation
2) Summary: Concomitant tricyclic antidepressant (TCA) and amphetamine administration has been reporte from the release of norepinephrine (Beaumont, 1973; Raisfeld, 1972). A similar reaction might also occur wit Acute elevations in blood pressure have been noted (Flemenbaum, 1971a). Some amphetamine-like drugs n most combinations have not been studied. When amphetamine analogs are being used to treat obesity, it sh moderate weight gain (Russ & Ackerman, 1988). False positive urine tests for amphetamines have been repo & Browning, 1993). Caution is advised when concurrent administration of amphetamine-like agents and TCA monitored for increased cardiovascular effects (hypertension and dysrhythmias).
3) Severity: moderate
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: Coadministration of amphetamines and tricyclic antidepressants or other sympatho increased cardiovascular effects, or CNS stimulation (Prod Info VYVANSE(TM) oral capsules, 2007; Prod Inf capsules, oral tablets, 2006; Prod Info ADDERALL(R) oral tablets, 2006; Flemenbaum, 1972). Use caution if closely for hypertension and dysrhythmias.
7) Probable Mechanism: synergistic effects on noradrenergic neurotransmission
8) Literature Reports
a) Amphetamines may increase the activity of tricyclic antidepressants (TCA) or sympathomimetic agen amphetamine with TCAs such as desipramine or protriptyline results in sustained increases in d-amphet VYVANSE(TM) oral capsules, 2007; Prod Info DEXEDRINE(R) sustained-release oral capsules, oral tab 2006).
b) Human pharmacologic studies have demonstrated that methylphenidate may inhibit the metabolism imipramine, clomipramine, or desipramine (Prod Info DAYTRANA(TM) transdermal system, 2006).
c) Concomitant administration of tricyclic antidepressants and methylphenidate can result in increases i effects induced by TCAs may lead to blood pressures as high as 170/120 mmHg within one day of comb methylphenidate usually results in the blood pressure returning to normotensive levels; reinstitution of th pressure elevation (Flemenbaum, 1971; Flemenbaum, 1972).
d) Fifteen patients with DSM-III major depression, who failed to respond to treatment with desipramine fenfluramine 40 mg to 120 mg daily for two weeks but did not result in any transient or sustained clinical doubled steady-state plasma levels of desipramine (Price et al, 1990).
e) There have been claims based on uncontrolled studies that a better antidepressant response may oc 1969). However, a systemic review of stimulants in the treatment of depression concluded that although ten placebo-controlled studies of stimulant drugs in primary depression, with one exception, indicated litt appear to be as effective as the conventional antidepressants in primary depression (Satel & Nelson, 19

3.5.1.J Iproniazid
1) Interaction Effect: hypertensive crisis (headache, hyperpyrexia, hypertension)
2) Summary: Use of lisdexamfetamine during or within 14 days following the administration of a monoamine Amphetamines stimulate the release of norepinephrine, and the use of MAOIs slows down amphetamine me norepinephrine and other monoamines from adrenergic nerve ending. This could result in hypertensive crisis hyperpyrexia (Prod Info VYVANSE(TM) oral capsules, 2007).
3) Severity: contraindicated
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Lisdexamfetamine use during or within 14 days following the administration of a mo hypertensive crises may occur (Prod Info VYVANSE(TM) oral capsules, 2007).
7) Probable Mechanism: increased norepinephrine availability

3.5.1.K Isocarboxazid
1) Interaction Effect: hypertensive crisis (headache, hyperpyrexia, hypertension)
2) Summary: Use of lisdexamfetamine during or within 14 days following the administration of a monoamine Amphetamines stimulate the release of norepinephrine, and the use of MAOIs slows down amphetamine me norepinephrine and other monoamines from adrenergic nerve ending. This could result in hypertensive crisis hyperpyrexia (Prod Info VYVANSE(TM) oral capsules, 2007).
3) Severity: contraindicated
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Lisdexamfetamine use during or within 14 days following the administration of a mo hypertensive crises may occur (Prod Info VYVANSE(TM) oral capsules, 2007).
7) Probable Mechanism: increased norepinephrine availability

3.5.1.L Lofepramine

1) Interaction Effect: hypertension, other cardiac effects, and CNS stimulation
2) Summary: Concomitant tricyclic antidepressant (TCA) and amphetamine administration has been reporte
from the release of norepinephrine (Beaumont, 1973; Raisfeld, 1972). A similar reaction might also occur wit
Acute elevations in blood pressure have been noted (Flemenbaum, 1971a). Some amphetamine-like drugs n
most combinations have not been studied. When amphetamine analogs are being used to treat obesity, it sh
moderate weight gain (Russ & Ackerman, 1988). False positive urine tests for amphetamines have been repo
& Browning, 1993). Caution is advised when concurrent administration of amphetamine-like agents and TCAs
monitored for increased cardiovascular effects (hypertension and dysrhythmias).
3) Severity: moderate
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: Coadministration of amphetamines and tricyclic antidepressants or other sympatho
increased cardiovascular effects, or CNS stimulation (Prod Info VYVANSE(TM) oral capsules, 2007; Prod Inf
capsules, oral tablets, 2006; Prod Info ADDERALL(R) oral tablets, 2006; Flemenbaum, 1972). Use caution if
closely for hypertension and dysrhythmias.
7) Probable Mechanism: synergistic effects on noradrenergic neurotransmission
8) Literature Reports
a) Amphetamines may increase the activity of tricyclic antidepressants (TCA) or sympathomimetic agen
amphetamine with TCAs such as desipramine or protriptyline results in sustained increases in d-amphet
VYVANSE(TM) oral capsules, 2007; Prod Info DEXEDRINE(R) sustained-release oral capsules, oral tab
2006).
b) Human pharmacologic studies have demonstrated that methylphenidate may inhibit the metabolism o
imipramine, clomipramine, or desipramine (Prod Info DAYTRANA(TM) transdermal system, 2006).
c) Concomitant administration of tricyclic antidepressants and methylphenidate can result in increases i
effects induced by TCAs may lead to blood pressures as high as 170/120 mmHg within one day of comb
methylphenidate usually results in the blood pressure returning to normotensive levels; reinstitution of th
pressure elevation (Flemenbaum, 1971; Flemenbaum, 1972).
d) Fifteen patients with DSM-III major depression, who failed to respond to treatment with desipramine g
fenfluramine 40 mg to 120 mg daily for two weeks but did not result in any transient or sustained clinical
doubled steady-state plasma levels of desipramine (Price et al, 1990).
e) There have been claims based on uncontrolled studies that a better antidepressant response may oc
1969). However, a systemic review of stimulants in the treatment of depression concluded that although
ten placebo-controlled studies of stimulant drugs in primary depression, with one exception, indicated litt
appear to be as effective as the conventional antidepressants in primary depression (Satel & Nelson, 19

3.5.1.M Moclobemide
1) Interaction Effect: hypertensive crisis (headache, hyperpyrexia, hypertension)
2) Summary: Use of lisdexamfetamine during or within 14 days following the administration of a monoamine
Amphetamines stimulate the release of norepinephrine, and the use of MAOIs slows down amphetamine me
norepinephrine and other monoamines from adrenergic nerve ending. This could result in hypertensive crisis
hyperpyrexia (Prod Info VYVANSE(TM) oral capsules, 2007).
3) Severity: contraindicated
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Lisdexamfetamine use during or within 14 days following the administration of a mo
hypertensive crises may occur (Prod Info VYVANSE(TM) oral capsules, 2007).
7) Probable Mechanism: increased norepinephrine availability

3.5.1.N Nialamide
1) Interaction Effect: hypertensive crisis (headache, hyperpyrexia, hypertension)
2) Summary: Use of lisdexamfetamine during or within 14 days following the administration of a monoamine
Amphetamines stimulate the release of norepinephrine, and the use of MAOIs slows down amphetamine me
norepinephrine and other monoamines from adrenergic nerve ending. This could result in hypertensive crisis
hyperpyrexia (Prod Info VYVANSE(TM) oral capsules, 2007).
3) Severity: contraindicated
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Lisdexamfetamine use during or within 14 days following the administration of a mo
hypertensive crises may occur (Prod Info VYVANSE(TM) oral capsules, 2007).
7) Probable Mechanism: increased norepinephrine availability

3.5.1.O Nortriptyline
1) Interaction Effect: hypertension, other cardiac effects, and CNS stimulation
2) Summary: Concomitant tricyclic antidepressant (TCA) and amphetamine administration has been reporte
from the release of norepinephrine (Beaumont, 1973; Raisfeld, 1972). A similar reaction might also occur wit
Acute elevations in blood pressure have been noted (Flemenbaum, 1971a). Some amphetamine-like drugs n
most combinations have not been studied. When amphetamine analogs are being used to treat obesity, it sh
moderate weight gain (Russ & Ackerman, 1988). False positive urine tests for amphetamines have been repo

& Browning, 1993). Caution is advised when concurrent administration of amphetamine-like agents and TCAs monitored for increased cardiovascular effects (hypertension and dysrhythmias).
3) Severity: moderate
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: Coadministration of amphetamines and tricyclic antidepressants or other sympatho increased cardiovascular effects, or CNS stimulation (Prod Info VYVANSE(TM) oral capsules, 2007; Prod Inf capsules, oral tablets, 2006; Prod Info ADDERALL(R) oral tablets, 2006; Flemenbaum, 1972). Use caution if closely for hypertension and dysrhythmias.
7) Probable Mechanism: synergistic effects on noradrenergic neurotransmission
8) Literature Reports
a) Amphetamines may increase the activity of tricyclic antidepressants (TCA) or sympathomimetic agen amphetamine with TCAs such as desipramine or protriptyline results in sustained increases in d-amphet VYVANSE(TM) oral capsules, 2007; Prod Info DEXEDRINE(R) sustained-release oral capsules, oral tab 2006).
b) Human pharmacologic studies have demonstrated that methylphenidate may inhibit the metabolism c imipramine, clomipramine, or desipramine (Prod Info DAYTRANA(TM) transdermal system, 2006).
c) Concomitant administration of tricyclic antidepressants and methylphenidate can result in increases i effects induced by TCAs may lead to blood pressures as high as 170/120 mmHg within one day of comb methylphenidate usually results in the blood pressure returning to normotensive levels; reinstitution of th pressure elevation (Flemenbaum, 1971; Flemenbaum, 1972).
d) Fifteen patients with DSM-III major depression, who failed to respond to treatment with desipramine g fenfluramine 40 mg to 120 mg daily for two weeks but did not result in any transient or sustained clinical doubled steady-state plasma levels of desipramine (Price et al, 1990).
e) There have been claims based on uncontrolled studies that a better antidepressant response may oc 1969). However, a systemic review of stimulants in the treatment of depression concluded that although ten placebo-controlled studies of stimulant drugs in primary depression, with one exception, indicated litt appear to be as effective as the conventional antidepressants in primary depression (Satel & Nelson, 19

3.5.1.P Opipramol
1) Interaction Effect: hypertension, other cardiac effects, and CNS stimulation
2) Summary: Concomitant tricyclic antidepressant (TCA) and amphetamine administration has been reporte from the release of norepinephrine (Beaumont, 1973; Raisfeld, 1972). A similar reaction might also occur with Acute elevations in blood pressure have been noted (Flemenbaum, 1971a). Some amphetamine-like drugs m most combinations have not been studied. When amphetamine analogs are being used to treat obesity, it sh moderate weight gain (Russ & Ackerman, 1988). False positive urine tests for amphetamines have been repo & Browning, 1993). Caution is advised when concurrent administration of amphetamine-like agents and TCAs monitored for increased cardiovascular effects (hypertension and dysrhythmias).
3) Severity: moderate
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: Coadministration of amphetamines and tricyclic antidepressants or other sympatho increased cardiovascular effects, or CNS stimulation (Prod Info VYVANSE(TM) oral capsules, 2007; Prod Inf capsules, oral tablets, 2006; Prod Info ADDERALL(R) oral tablets, 2006; Flemenbaum, 1972). Use caution if closely for hypertension and dysrhythmias.
7) Probable Mechanism: synergistic effects on noradrenergic neurotransmission
8) Literature Reports
a) Amphetamines may increase the activity of tricyclic antidepressants (TCA) or sympathomimetic agen amphetamine with TCAs such as desipramine or protriptyline results in sustained increases in d-amphet VYVANSE(TM) oral capsules, 2007; Prod Info DEXEDRINE(R) sustained-release oral capsules, oral tab 2006).
b) Human pharmacologic studies have demonstrated that methylphenidate may inhibit the metabolism c imipramine, clomipramine, or desipramine (Prod Info DAYTRANA(TM) transdermal system, 2006).
c) Concomitant administration of tricyclic antidepressants and methylphenidate can result in increases i effects induced by TCAs may lead to blood pressures as high as 170/120 mmHg within one day of comb methylphenidate usually results in the blood pressure returning to normotensive levels; reinstitution of th pressure elevation (Flemenbaum, 1971; Flemenbaum, 1972).
d) Fifteen patients with DSM-III major depression, who failed to respond to treatment with desipramine g fenfluramine 40 mg to 120 mg daily for two weeks but did not result in any transient or sustained clinical doubled steady-state plasma levels of desipramine (Price et al, 1990).
e) There have been claims based on uncontrolled studies that a better antidepressant response may oc 1969). However, a systemic review of stimulants in the treatment of depression concluded that although ten placebo-controlled studies of stimulant drugs in primary depression, with one exception, indicated litt appear to be as effective as the conventional antidepressants in primary depression (Satel & Nelson, 19

3.5.1.Q Pargyline
1) Interaction Effect: hypertensive crisis (headache, hyperpyrexia, hypertension)
2) Summary: Use of lisdexamfetamine during or within 14 days following the administration of a monoamine

Amphetamines stimulate the release of norepinephrine, and the use of MAOIs slows down amphetamine met
norepinephrine and other monoamines from adrenergic nerve ending. This could result in hypertensive crisis.
hyperpyrexia (Prod Info VYVANSE(TM) oral capsules, 2007).
3) Severity: contraindicated
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Lisdexamfetamine use during or within 14 days following the administration of a mo
hypertensive crises may occur (Prod Info VYVANSE(TM) oral capsules, 2007).
7) Probable Mechanism: increased norepinephrine availability

3.5.1.R Phenelzine
1) Interaction Effect: hypertensive crisis (headache, hyperpyrexia, hypertension)
2) Summary: Use of lisdexamfetamine during or within 14 days following the administration of a monoamine
Amphetamines stimulate the release of norepinephrine, and the use of MAOIs slows down amphetamine met
norepinephrine and other monoamines from adrenergic nerve ending. This could result in hypertensive crisis.
hyperpyrexia (Prod Info VYVANSE(TM) oral capsules, 2007).
3) Severity: contraindicated
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Lisdexamfetamine use during or within 14 days following the administration of a mo
hypertensive crises may occur (Prod Info VYVANSE(TM) oral capsules, 2007).
7) Probable Mechanism: increased norepinephrine availability

3.5.1.S Procarbazine
1) Interaction Effect: hypertensive crisis (headache, hyperpyrexia, hypertension)
2) Summary: Use of lisdexamfetamine during or within 14 days following the administration of a monoamine
Amphetamines stimulate the release of norepinephrine, and the use of MAOIs slows down amphetamine met
norepinephrine and other monoamines from adrenergic nerve ending. This could result in hypertensive crisis.
hyperpyrexia (Prod Info VYVANSE(TM) oral capsules, 2007).
3) Severity: contraindicated
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Lisdexamfetamine use during or within 14 days following the administration of a mo
hypertensive crises may occur (Prod Info VYVANSE(TM) oral capsules, 2007).
7) Probable Mechanism: increased norepinephrine availability

3.5.1.T Protriptyline
1) Interaction Effect: hypertension, other cardiac effects, and CNS stimulation
2) Summary: Concomitant tricyclic antidepressant (TCA) and amphetamine administration has been reported
from the release of norepinephrine (Beaumont, 1973; Raisfeld, 1972). A similar reaction might also occur with
Acute elevations in blood pressure have been noted (Flemenbaum, 1971a). Some amphetamine-like drugs m
most combinations have not been studied. When amphetamine analogs are being used to treat obesity, it sh
moderate weight gain (Russ & Ackerman, 1988). False positive urine tests for amphetamines have been repo
& Browning, 1993). Caution is advised when concurrent administration of amphetamine-like agents and TCAs
monitored for increased cardiovascular effects (hypertension and dysrhythmias).
3) Severity: moderate
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: Coadministration of amphetamines and tricyclic antidepressants or other sympatho
increased cardiovascular effects, or CNS stimulation (Prod Info VYVANSE(TM) oral capsules, 2007; Prod Inf
capsules, oral tablets, 2006; Prod Info ADDERALL(R) oral tablets, 2006; Flemenbaum, 1972). Use caution if
closely for hypertension and dysrhythmias.
7) Probable Mechanism: synergistic effects on noradrenergic neurotransmission
8) Literature Reports
a) Amphetamines may increase the activity of tricyclic antidepressants (TCA) or sympathomimetic agen
amphetamine with TCAs such as desipramine or protriptyline results in sustained increases in d-amphet
VYVANSE(TM) oral capsules, 2007; Prod Info DEXEDRINE(R) sustained-release oral capsules, oral tab
2006).
b) Human pharmacologic studies have demonstrated that methylphenidate may inhibit the metabolism o
imipramine, clomipramine, or desipramine (Prod Info DAYTRANA(TM) transdermal system, 2006).
c) Concomitant administration of tricyclic antidepressants and methylphenidate can result in increases in
effects induced by TCAs may lead to blood pressures as high as 170/120 mmHg within one day of comb
methylphenidate usually results in the blood pressure returning to normotensive levels; reinstitution of th
pressure elevation (Flemenbaum, 1971; Flemenbaum, 1972).
d) Fifteen patients with DSM-III major depression, who failed to respond to treatment with desipramine g
fenfluramine 40 mg to 120 mg daily for two weeks but did not result in any transient or sustained clinical
doubled steady-state plasma levels of desipramine (Price et al, 1990).
e) There have been claims based on uncontrolled studies that a better antidepressant response may oc

1969). However, a systemic review of stimulants in the treatment of depression concluded that although ten placebo-controlled studies of stimulant drugs in primary depression, with one exception, indicated litt appear to be as effective as the conventional antidepressants in primary depression (Satel & Nelson, 19

3.5.1.U Rasagiline

1) Interaction Effect: hypertensive crisis (headache, hyperpyrexia, hypertension)
2) Summary: Use of lisdexamfetamine during or within 14 days following the administration of a monoamine Amphetamines stimulate the release of norepinephrine, and the use of MAOIs slows down amphetamine me norepinephrine and other monoamines from adrenergic nerve ending. This could result in hypertensive crisis, hyperpyrexia (Prod Info VYVANSE(TM) oral capsules, 2007).
3) Severity: contraindicated
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Lisdexamfetamine use during or within 14 days following the administration of a mo hypertensive crises may occur (Prod Info VYVANSE(TM) oral capsules, 2007).
7) Probable Mechanism: increased norepinephrine availability

3.5.1.V Selegiline

1) Interaction Effect: hypertensive crisis (headache, hyperpyrexia, hypertension)
2) Summary: Use of lisdexamfetamine during or within 14 days following the administration of a monoamine Amphetamines stimulate the release of norepinephrine, and the use of MAOIs slows down amphetamine me norepinephrine and other monoamines from adrenergic nerve ending. This could result in hypertensive crisis, hyperpyrexia (Prod Info VYVANSE(TM) oral capsules, 2007).
3) Severity: contraindicated
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Lisdexamfetamine use during or within 14 days following the administration of a mo hypertensive crises may occur (Prod Info VYVANSE(TM) oral capsules, 2007).
7) Probable Mechanism: increased norepinephrine availability

3.5.1.W Toloxatone

1) Interaction Effect: hypertensive crisis (headache, hyperpyrexia, hypertension)
2) Summary: Use of lisdexamfetamine during or within 14 days following the administration of a monoamine Amphetamines stimulate the release of norepinephrine, and the use of MAOIs slows down amphetamine me norepinephrine and other monoamines from adrenergic nerve ending. This could result in hypertensive crisis, hyperpyrexia (Prod Info VYVANSE(TM) oral capsules, 2007).
3) Severity: contraindicated
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Lisdexamfetamine use during or within 14 days following the administration of a mo hypertensive crises may occur (Prod Info VYVANSE(TM) oral capsules, 2007).
7) Probable Mechanism: increased norepinephrine availability

3.5.1.X Tranylcypromine

1) Interaction Effect: hypertensive crisis (headache, hyperpyrexia, hypertension)
2) Summary: Use of lisdexamfetamine during or within 14 days following the administration of a monoamine Amphetamines stimulate the release of norepinephrine, and the use of MAOIs slows down amphetamine me norepinephrine and other monoamines from adrenergic nerve ending. This could result in hypertensive crisis, hyperpyrexia (Prod Info VYVANSE(TM) oral capsules, 2007).
3) Severity: contraindicated
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Lisdexamfetamine use during or within 14 days following the administration of a mo hypertensive crises may occur (Prod Info VYVANSE(TM) oral capsules, 2007).
7) Probable Mechanism: increased norepinephrine availability

3.5.1.Y Trimipramine

1) Interaction Effect: hypertension, other cardiac effects, and CNS stimulation
2) Summary: Concomitant tricyclic antidepressant (TCA) and amphetamine administration has been reporte from the release of norepinephrine (Beaumont, 1973; Raisfeld, 1972). A similar reaction might also occur wit Acute elevations in blood pressure have been noted (Flemenbaum, 1971a). Some amphetamine-like drugs m most combinations have not been studied. When amphetamine analogs are being used to treat obesity, it sh moderate weight gain (Russ & Ackerman, 1988). False positive urine tests for amphetamines have been rep & Browning, 1993). Caution is advised when concurrent administration of amphetamine-like agents and TCA monitored for increased cardiovascular effects (hypertension and dysrhythmias).
3) Severity: moderate
4) Onset: delayed
5) Substantiation: theoretical

6) Clinical Management: Coadministration of amphetamines and tricyclic antidepressants or other sympatho increased cardiovascular effects, or CNS stimulation (Prod Info VYVANSE(TM) oral capsules, 2007; Prod Inf capsules, oral tablets, 2006; Prod Info ADDERALL(R) oral tablets, 2006; Flemenbaum, 1972). Use caution if closely for hypertension and dysrhythmias.
7) Probable Mechanism: synergistic effects on noradrenergic neurotransmission
8) Literature Reports
a) Amphetamines may increase the activity of tricyclic antidepressants (TCA) or sympathomimetic agen amphetamine with TCAs such as desipramine or protriptyline results in sustained increases in d-amphet VYVANSE(TM) oral capsules, 2007; Prod Info DEXEDRINE(R) sustained-release oral capsules, oral tab 2006).
b) Human pharmacologic studies have demonstrated that methylphenidate may inhibit the metabolism c imipramine, clomipramine, or desipramine (Prod Info DAYTRANA(TM) transdermal system, 2006).
c) Concomitant administration of tricyclic antidepressants and methylphenidate can result in increases i effects induced by TCAs may lead to blood pressures as high as 170/120 mmHg within one day of comb methylphenidate usually results in the blood pressure returning to normotensive levels; reinstitution of th pressure elevation (Flemenbaum, 1971; Flemenbaum, 1972).
d) Fifteen patients with DSM-III major depression, who failed to respond to treatment with desipramine g fenfluramine 40 mg to 120 mg daily for two weeks but did not result in any transient or sustained clinical doubled steady-state plasma levels of desipramine (Price et al, 1990).
e) There have been claims based on uncontrolled studies that a better antidepressant response may oc 1969). However, a systemic review of stimulants in the treatment of depression concluded that although ten placebo-controlled studies of stimulant drugs in primary depression, with one exception, indicated litt appear to be as effective as the conventional antidepressants in primary depression (Satel & Nelson, 19

4.0 Clinical Applications

Monitoring Parameters

Patient Instructions

Place In Therapy

Mechanism of Action / Pharmacology

Therapeutic Uses

4.1 Monitoring Parameters

A) Lisdexamfetamine Dimesylate
1) Therapeutic
a) Improvement in mental and behavioral symptoms of attention deficit hyperactivity disorder (ADHD), includ hyperactivity, and cognitive performance.
2) Toxic
a) Physical Findings
1) The American Academy of Pediatrics (AAP) does not recommend the routine use of electrocardiogra evaluations (which were previously recommended by the American Heart Association (AHA) scientific st place the child at risk for sudden cardiac death) before initiating stimulant therapy to treat attention-defici The APA cited specific reasons for changing the recommendation including: lack of evidence establishin treat ADHD and sudden cardiac death (SCD), the frequency of sudden unexpected deaths among patier in the general population of children, and lack of cost-effective analysis to support ECG screening or spe al, 2008).
2) Based on the American Academy of Pediatrics (AAP) and the American Heart Association (AHA) con monitoring recommendations have been established to assist clinicians in the evaluation of children treat lisdexamfetamine, for ADHD (Perrin et al, 2008; Vetter et al, 2008):
- Conduct a thorough examination prior to initiating lisdexamfetamine therapy for a diagnosis of ADH symptoms indicative of a cardiac condition, including palpitations, near syncope, or syncope.
- Obtain a complete family and patient history for conditions associated with SCD, and determine cu counter medications.
- Conduct a complete physical evaluation of the patient for hypertension, cardiac murmurs, physical signs of irregular cardiac rhythms.
- Perform further evaluation if family history, patient history or physical exam is suggestive of cardiac and if indicated, consult pediatric cardiologist .
- Continue to assess the patient for cardiac symptoms and any changes in family history at follow up
- Blood pressure and heart rate should be evaluated at baseline, during routine follow-up within 1 to months. Increases in blood pressure and heart rate have been reported with stimulant use.

b) It is not conclusive whether chronic use of stimulants in children may be associated with suppression of g during treatment (Prod Info VYVANSE(TM) oral capsules, 2007).

4.2 Patient Instructions

A) Lisdexamfetamine Dimesylate (By mouth)

Lisdexamfetamine Dimesylate

Treats attention deficit hyperactivity disorder (ADHD). This medicine is a stimulant.

When This Medicine Should Not Be Used:

You should not use this medicine if you or your child have had an allergic reaction to lisdexamfetamine dimesylate glaucoma, an overactive thyroid, high blood pressure, heart disease, or blood vessel problems. Do not use this m you are very nervous, tense, or agitated most of the time. You should not use this medicine if you have used a dru (MAOI), such as Eldepryl®, Marplan®, Nardil®, or Parnate®, in the past 14 days. Do not give this medicine to a c

How to Use This Medicine:

Capsule

Your doctor will tell you how much of this medicine to use and how often. Your dose may need to be changed best for you. Do not use more medicine or use it more often than your doctor tells you to.

This medicine should come with a Medication Guide. Read and follow these instructions carefully. Ask your d Ask your pharmacist for the Medication Guide if you do not have one. Your doctor might ask you to sign some information.

You may take this medicine with or without food.

It is best to take this medicine in the morning. Taking this medicine in the afternoon or evening could make it

If you cannot swallow the capsule whole, you may open it and pour the medicine into a glass of water. Stir thi

This medicine is part of an ADHD treatment program that may also include counseling or special education. C all treatment measures.

If a Dose is Missed:

If you miss a dose or forget to use your medicine, use it as soon as you can. If it is almost time for your next d the missed dose. Do not use extra medicine to make up for a missed dose.

How to Store and Dispose of This Medicine:

Store the medicine in a closed container at room temperature, away from heat, moisture, and direct light.

Ask your pharmacist, doctor, or health caregiver about the best way to dispose of any leftover medicine after need to throw away old medicine after the expiration date has passed.

Keep all medicine away from children and never share your medicine with anyone.

Drugs and Foods to Avoid:

Ask your doctor or pharmacist before using any other medicine, including over-the-counter medicines, vitamins, a

Make sure your doctor knows if you are also using blood pressure medicines (such as atenolol, lisinopril, met medicines (such as meperidine, propoxyphene, Demerol®, or Darvon®), chlorpromazine (Thorazine®), cold haloperidol (Haldol®), lithium carbonate (Lithobid®), certain medicines for depression (such as amitriptyline, methenamine (Hiprex, Urex®), phenobarbital, or phenytoin (Dilantin®).

Warnings While Using This Medicine:

Make sure your doctor knows if you are pregnant or breastfeeding, or if you or your child have heart problems

Tell your doctor if you or your child have muscle tics or Tourette's syndrome, a condition that causes you to h not able to control.

Your doctor should know if you or your child have epilepsy, or a history of seizures, depression, or mental illn problems. Also tell your doctor if you or anyone in your family has tried to commit suicide.

This medicine may be habit-forming. If you feel that the medicine is not working as well, do not use more than instructions.

This medicine may cause slow growth. If your child is using this medicine, the doctor will need to keep track o your child is growing properly.

This medicine may cause blurred vision or make you drowsy or dizzy. If any of these occur, do not drive, use dangerous if you are not alert or not able to see well.

Your doctor will need to check your progress at regular visits while you are using this medicine. Be sure to ke

Possible Side Effects While Using This Medicine:

Call your doctor right away if you notice any of these side effects:

Allergic reaction: Itching or hives, swelling in your face or hands, swelling or tingling in your mouth or throat, o

Blistering, peeling, red skin rash.

Blurred vision or trouble seeing.

Chest pain, shortness of breath, or fainting.

Fast, pounding, or irregular heartbeat.

Mood or mental changes, or unusual or disturbing thoughts.

Numbness or weakness in your arm or leg, or on one side of your body.

Seeing, hearing, or feeling things that are not there.
Seizures.
Tremors or shaking.
Uncontrollable muscle movements or twitching.

If you notice these less serious side effects, talk with your doctor:
Constipation, diarrhea, or upset stomach.
Dry mouth or bad taste in your mouth.
Feeling restless or nervous.
Headache or dizziness.
Loss of appetite or weight loss.
Nausea, vomiting, or stomach pain.
Problems having sex.
Trouble sleeping.

If you notice other side effects that you think are caused by this medicine, tell your doctor.

4.3 Place In Therapy

A) Lisdexamfetamine Dimesylate

1) Lisdexamfetamine dimesylate is a pro-drug of dextroamphetamine, approved for the treatment of Attention-De placebo-controlled trials, lisdexamfetamine dimesylate showed improvement in behavior in children aged 6 to 12 v combined type or hyperactive-impulsive type. The long-term (greater than 4 weeks) efficacy of lisdexamfetamine assessed in controlled trials (Prod Info VYVANSE(TM) oral capsules, 2007).

4.4 Mechanism of Action / Pharmacology

A) Lisdexamfetamine Dimesylate

1) After oral administration, lisdexamfetamine dimesylate is rapidly absorbed in the gastrointestinal tract and conv responsible for the drug's activity. The mechanism of action of dextroamphetamine in the treatment of attention-de Amphetamines may block the reuptake of norepinephrine and dopamine at the presynaptic neuron and thus increa dopamine into the extraneuronal space (Prod Info VYVANSE(TM) oral capsules, 2007).

4.5 Therapeutic Uses

4.5.A Lisdexamfetamine Dimesylate

4.5.A.1 Attention deficit hyperactivity disorder

FDA Labeled Indication

a) Overview

FDA Approval: Adult, yes; Pediatric, yes (age 6 to 12 years)
Efficacy: Adult, Evidence favors efficacy; Pediatric, Effective
Recommendation: Adult, Class IIb; Pediatric, Class IIa
Strength of Evidence: Adult, Category B; Pediatric, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:

Approved for the treatment of Attention-Deficit/Hyperactivity Disorder in children aged 6 to 12 and ac 2008)
In a 4-week, randomized, double-blind, placebo-controlled, parallel-group study (n=420), lisdexamfe in the treatment of adults meeting Diagnostic and Statistical Manual of Mental Disorders-Fourth Edit VYVANSE(R) oral capsules, 2008)
In a 4-week, multicenter, randomized, double-blind, fixed-dose study (n=290), lisdexamfetamine dim treatment of children aged 6 to 12 meeting Diagnostic and Statistical Manual of Mental Disorders-Fo or hyperactive-impulsive type ADHD (Biederman et al, 2007)

c) Adult:

1) Lisdexamfetamine mesylate was effective and well tolerated in the treatment of adult ADHD in a rand parallel-group study. Adults meeting the Diagnostic and Statistical Manual of Mental Disorders-Fourth Ed to receive fixed doses of either 30 milligrams (mg), 50 mg, or 70 mg of lisdexamfetamine (n=358) or plac Lisdexamfetamine was initiated at 30 mg and titrated in weekly increments of 20 mg to achieve the 50 ar ratings on the ADHD Rating Scale (ADHD-RS), significant improvements occurred for all lisdexamfetami Treatment-emergent adverse events occurring commonly and more frequently than placebo included dry nausea (7% vs 0%), decreased appetite (27% vs 3%), insomnia (27% vs 8%), and anxiety (6% vs 0%) (

d) Pediatric:

1) Lisdexamfetamine was effective and well tolerated for the treatment of children with combined type o Deficit/Hyperactivity Disorder (ADHD) in a multicenter, randomized, double-blind, fixed-dose study of 4 w 1.8 years) were included if their ADHD Rating Scale version IV (ADHD-RS-IV) was 28 or greater. Childre dimesylate 30 milligrams (mg) once in the morning for 4 weeks (n=71), 50 mg once in the morning (30 m to 4) for 4 weeks (n=74), 70 mg once in the morning (30 mg for 1 week, then titrated to 50 mg for week 2 (n=73), or placebo for 4 weeks (n=72). The primary efficacy endpoint was the mean change from baselir ADHD-RS-IV rated 18 symptoms on a scale of 0 (no symptoms) to 3 (severe symptoms) based on the in

and child. The majority of patients were male (69%), treatment-naive (59.2% to 69.9%), and diagnosed v
ADHD-RS-IV score improved 4- to 5-fold for each lisdexamfetamine dose group relative to the placebo (
improvement was demonstrated in the 70-mg dose group (-26.7 (standard deviation (SD), 1.54)) compar
0.001). Improvement was noticed for all dose groups during the first week with continued improvement th
Conners' Parent Rating Scale-Revised: Short Form (CPRS-R), a 27-question parent rating of the childs's
and ADHD index, at three times through the day (up to 6 PM). Compared with the placebo group, the CP
(morning, afternoon, and evening) improved significantly starting at week 1 through week 4 for all dose g
mg dose group experiencing the greatest improvement. Adverse events were primarily mild to moderate
mostly in the first week. The most common adverse events experienced in the lisdexamfetamine and pla
appetite (39% and 4%, p less than or equal to 0.05), insomnia (19% and 3%, p less than or equal to 0.05
significant), headache (12% and 10%, p = not significant), irritability (10% and 0%, p less than or equal t
significant), weight decrease (9% and 1%, p less than or equal to 0.05), and nausea (6% and 3%, p = no
demonstrated in mean ECG parameters (including QT intervals), laboratory values, or blood pressure fo
2007).

2) Treatment with lisdexamfetamine mesylate led to a significant difference in patient behavior compare
crossover design, analog classroom study in children aged 6 to 12 years (n=52) meeting the Diagnostic
Fourth Edition criteria for ADHD (combined type or hyperactive-impulsive type). Subsequent to a 3-week
amphetamine/dextroamphetamine (Adderall XR(R)) 10 to 30 milligrams (mg) daily, patients were randon
amphetamine/dextroamphetamine, lisdexamfetamine mesylate (30, 50, or 70 mg/day), or placebo once
lasted for 1 week. Efficacy was assessed as the mean of investigator ratings on the Swanson, Kotkin, Al
scores over 8 sessions of a 12 hour treatment day (Prod Info VYVANSE(R) oral capsules, 2008).

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Last Modified: June 18, 2009

DRUGDEX® Evaluations

SERTRALINE

0.0 Overview

1) Class
- **a)** This drug is a member of the following class(es):
  Antidepressant
  Central Nervous System Agent
  Serotonin Reuptake Inhibitor

2) Dosing Information
- **a)** Sertraline Hydrochloride
  - **1)** Adult
    - **a)** Major depressive disorder
      - **1)** 50 mg/day ORALLY as a single dose in the morning or the evening; dosage may be increased at inte
    - **b)** Obsessive-compulsive disorder
      - **1)** 50 mg/day ORALLY as a single dose in the morning or the evening; dosage may be increased at inte
    - **c)** Panic disorder
      - **1)** 25 mg/day ORALLY for 1 week, then increase to 50 mg/day; dosage may then be increased at interv
    - **d)** Posttraumatic stress disorder
      - **1)** 25 mg/day ORALLY for 1 week, then increase to 50 mg/day; dosage may then be increased at interv
    - **e)** Premenstrual dysphoric disorder
      - **1)** daily dosing, 50 mg/day ORALLY as a single dose in the morning or the evening throughout the mens
        150 mg/day (Prod Info Zoloft(R), 2002)
      - **2)** luteal phase dosing, 50 mg/day ORALLY only during the luteal phase; dosage may be increased to 1
        cycle should begin with 50 mg/day for 3 days before increasing the dosage to 100 mg/day (Prod Info Zol
    - **f)** Social phobia
      - **1)** 25 mg/day ORALLY for 1 week, then increase to 50 mg/day; dosage may then be increased at interv
  - **2)** Pediatric
    - **a)** Obsessive-compulsive disorder
      - **1)** children 6-12 yr, 25 mg/day ORALLY as a single dose in the morning or the evening; dosage may be
        (R), 2002)
      - **2)** children 13-17 yr, 50 mg/day ORALLY as a single dose in the morning or the evening; dosage may b
        Zoloft(R), 2002)

3) Contraindications
- **a)** Sertraline Hydrochloride
  - **1)** concomitant use of disulfiram (oral concentrate) (Prod Info ZOLOFT(R) concentrate, oral tablets, 2009)
  - **2)** concomitant use of monoamine oxidase inhibitors (MAOIs) or pimozide (Prod Info ZOLOFT(R) concentrate, or
  - **3)** hypersensitivity to sertraline or any other component of the product (Prod Info ZOLOFT(R) concentrate, oral ta

4) Serious Adverse Effects
- **a)** Sertraline Hydrochloride
  - **1)** Bleeding, Abnormal
  - **2)** Depression, exacerbation
  - **3)** Hypomania
  - **4)** Hyponatremia
  - **5)** Mania
  - **6)** Seizure
  - **7)** Serotonin syndrome
  - **8)** Suicidal thoughts
  - **9)** Suicide

5) Clinical Applications
- **a)** Sertraline Hydrochloride
  - **1)** FDA Approved Indications
    - **a)** Major depressive disorder
    - **b)** Obsessive-compulsive disorder
    - **c)** Panic disorder
    - **d)** Posttraumatic stress disorder
    - **e)** Premenstrual dysphoric disorder
    - **f)** Social phobia

1.0 Dosing Information

Drug Properties

Storage and Stability

Adult Dosage

Pediatric Dosage

1.1 Drug Properties

A) Information on specific products and dosage forms can be obtained by referring to the Tradename List (Product In

B) Synonyms

Sertraline
Sertraline HCl
Sertraline Hydrochloride

C) Physicochemical Properties

1) Molecular Weight

a) Sertraline hydrochloride: 342.7 (Fleeger, 1996)

2) Solubility

a) Systemic: Sertraline hydrochloride is slightly soluble in water and sparingly soluble in ethyl alcohol (Prod I

1.2 Storage and Stability

A) Sertraline Hydrochloride

1) Preparation

a) Oral route

1) The oral concentrate formulation of sertraline should be diluted in 4 ounces (½ cup) using only water, (Prod Info ZOLOFT(R) tablets and oral concentrate, 2005).

B) Oral route

1) Tablets and oral concentrate should be stored at a controlled room temperature of 25 degrees Celsius (77 deg are permitted (Prod Info Zoloft(R), 2002).

1.3 Adult Dosage

Normal Dosage

Dosage in Renal Failure

Dosage in Hepatic Insufficiency

Dosage in Geriatric Patients

1.3.1 Normal Dosage

1.3.1.A Sertraline Hydrochloride

1.3.1.A.1 Oral route

Dysthymia

Major depressive disorder

Obsessive-compulsive disorder

Panic disorder

Posttraumatic stress disorder

Premenstrual dysphoric disorder

Social phobia

1.3.1.A.1.a Dysthymia

1) A dose of sertraline 50 milligrams (mg) daily orally as a single dose in the morning or the evening controlled trial. Dose increases up to a maximum of 200 mg/day were allowed (Ravindran et al, 200

1.3.1.A.1.b Major depressive disorder

1) The initial recommended dosage is 50 milligrams daily as a single dose in the morning or the eve recommended dosage of 200 milligrams daily (Prod Info Zoloft(R), 2002).

2) Sertraline oral concentrate contains 20 milligrams/milliliter (mg/mL). Immediately before taking se lemon/lime soda, lemonade, or orange juice. After mixing, a slight haze may appear; this is normal. contains dry natural rubber (Prod Info Zoloft(R), 2002).

a) DURATION OF THERAPY

1) Clinical trials have suggested that depressed patients responding during the first 8 weel term studies of sertraline efficacy have not been completed, treatment of depression gener unknown whether the dose of sertraline required to maintain euthymia is the same as that r

1.3.1.A.1.c Obsessive-compulsive disorder

1) The initial dosage is 50 milligrams once daily in the morning or evening. If 50 milligrams does not daily at intervals of at least 1 week (Prod Info Zoloft(R), 2002).

2) Sertraline oral concentrate contains 20 milligrams/milliliter (mg/mL). Immediately before taking se lemon/lime soda, lemonade, or orange juice. After mixing, a slight haze may appear; this is normal. contains dry natural rubber (Prod Info Zoloft(R), 2002).

a) DURATION OF THERAPY

1) Efficacy of sertraline therapy in obsessive compulsive disorder has not been documente disorder, therapy should be continued for responding patients. Periodic determination of th provide the patient with the lowest effective dose (Prod Info Zoloft(R), 2002).

1.3.1.A.1.d Panic disorder

1) The initial recommended dosage is 25 milligrams (mg) once daily, taken in the morning or evenir still inadequate, the dosage may be increased at intervals of 1 week to a maximum of 200 mg/day (

2) Sertraline oral concentrate contains 20 milligrams/milliliter (mg/mL). Immediately before taking se lemon/lime soda, lemonade, or orange juice. After mixing, a slight haze may appear; this is normal. contains dry natural rubber (Prod Info Zoloft(R), 2002).

a) DURATION OF THERAPY

1) Efficacy of sertraline therapy in panic disorder has not been documented for longer thar therapy should be continued for responding patients. Periodic determination of the need fo patient with the lowest effective dose (Prod Info Zoloft(R), 2002).

1.3.1.A.1.e Posttraumatic stress disorder

1) The initial recommended dosage is 25 milligrams (mg) once daily, taken in the morning or evenir still inadequate, the dosage may be increased at intervals of 1 week to a maximum of 200 mg/day (

2) Sertraline oral concentrate contains 20 milligrams/milliliter (mg/mL). Immediately before taking se lemon/lime soda, lemonade, or orange juice. After mixing, a slight haze may appear; this is normal. contains dry natural rubber (Prod Info Zoloft(R), 2002).

1.3.1.A.1.f Premenstrual dysphoric disorder

1) CONTINUOUS DOSING

a) Premenstrual dysphoric disorder (PMDD) may be treated with sertraline either throughout th dosing). For continuous dosing, sertraline should be started at 50 milligrams (mg) per day (mor day. Dosage adjustments, if needed, should be made in 50 mg increments at the onset of each

2) LUTEAL PHASE DOSING

a) Premenstrual dysphoric disorder (PMDD) may be treated with sertraline either throughout th dosing). For luteal phase dosing, sertraline should be started at 50 milligrams (mg) per day (mo day. For doses higher than 50 mg, use a 50 mg/day titration step for three days at the beginnin

1.3.1.A.1.g Social phobia

1) The initial recommended dosage is 25 milligrams (mg) once daily, taken in the morning or evenir still inadequate, the dosage may be increased at intervals of 1 week to a maximum of 200 mg/day (

a) DURATION OF THERAPY

1) Sertraline in doses of 50 to 200 milligrams per day was effective in the treatment of adu trials. Dosages should be adjusted to the lowest effective dose and periodic determinations

1.3.1.A.2 MAXIMUM DOSE

a) Recommended maximum is 200 milligrams daily (Prod Info Zoloft(R), 2002).

1.3.2 Dosage in Renal Failure

A) Sertraline Hydrochloride

1) In patients with renal impairment, dosage adjustment is NOT necessary. Sertraline is extensively metabol Zoloft(R), 2002).

1.3.3 Dosage in Hepatic Insufficiency

A) Sertraline Hydrochloride

1) Sertraline is extensively metabolized in the liver. In patients with hepatic impairment or cirrhosis, a lower c

1.3.4 Dosage in Geriatric Patients

A) Sertraline Hydrochloride

1) Although no specific dosage adjustments have been recommended for sertraline use in geriatric patients, patients treated with a dose of 100 milligrams daily for 14 days. Steady-state clearance is achieved in 2-3 we but not in females (Prod Info Zoloft(R), 2002). Since steady state may take longer to achieve in elderly, dose

1.4 Pediatric Dosage

Normal Dosage

Dosage in Hepatic Insufficiency

1.4.1 Normal Dosage

1.4.1.A Sertraline Hydrochloride

1.4.1.A.1 Oral route

1.4.1.A.1.a Obsessive-compulsive disorder

1) The initial recommended dose is 25 milligrams (mg) once daily in children 6 to 12 years of age o 200 mg/day in clinical trials which established efficacy in the pediatric population; however, dosage may be administered in the morning or evening (Prod Info Zoloft(R), 2002).

2) Sertraline oral concentrate contains 20 milligrams/milliliter (mg/mL). Immediately before taking se lemon/lime soda, lemonade, or orange juice. After mixing, a slight haze may appear; this is normal. contains dry natural rubber (Prod Info Zoloft(R), 2002).

1.4.3 Dosage in Hepatic Insufficiency

A) Sertraline Hydrochloride

1) In patients with hepatic impairment, a lower or less frequent dosage interval should be used (Prod Info Zo

2.0 Pharmacokinetics

Onset and Duration

Drug Concentration Levels

ADME

2.1 Onset and Duration

A) Onset

1) Initial Response

a) Depression, regular release: 2 weeks (Reimherr et al, 1988).

2) Peak Response

a) Depression, regular release: 6 weeks (Amin et al, 1989a; Doogan & Caillard, 1988).

2.2 Drug Concentration Levels

A) Time to Peak Concentration

1) Oral, regular release: 4 to 8 hours (Prod Info Zoloft(R), 2002w; Doogan & Caillard, 1988; Saletu et al, 1986).

a) The Cmax after continuous administration of sertraline 200 mg/day was 165 ng/mL (children 6 to 12 years

b) A study of 22 young (less than 45 years) and elderly (greater than 65 years) healthy male and female volu and elderly groups after continuous administration of 200 mg for 21 days (Ronfeld et al, 1997).

c) The time of administration (morning versus evening) did NOT affect mean peak plasma sertraline concent single doses of 100 mg. Although no specific recommendation can be made, it appears that sertraline may b 1997a).

d) A mean peak plasma sertraline concentration of 54.5 ng/mL was observed 4 hours after a single 100-milli were 105.4 and 253.2 ng/mL, respectively, at 6 hours post-dosing (Saletu et al, 1986).

B) Area Under the Curve

1) 2296 to 3107 ng-hr/mL (Prod Info Zoloft(R), 2002w).

a) The AUC was 3107 ng-hr/mL (children 6 to 12 years), 2296 ng-hr/mL (adolescents 13 to 17 years), and 2

2002w).

2.3 ADME

Absorption

Distribution

Metabolism

Excretion

Elimination Half-life

Extracorporeal Elimination

2.3.1 Absorption

A) Bioavailability

1) Oral, regular release: complete (Prod Info Zoloft(R), 2002w; Doogan & Caillard, 1988).

a) Single dose bioavailability studies have shown that the tablets and oral solution are approximately eq

b) The time of day of administration (morning versus evening) did NOT affect the area under the curve (mean terminal elimination half-life, or mean elimination rate constant, in 22 healthy male volunteers who appears that sertraline may be administered in the morning or evening without bioavailability differences

B) Effects of Food

1) small (Prod Info Zoloft(R), 2002w).

a) For the tablet, food increased the mean peak plasma concentration by 25%, and it decreased the tim (Prod Info Zoloft(R), 2002w).

2.3.2 Distribution

A) Distribution Sites

1) Protein Binding

a) 99% (Doogan & Caillard, 1988).

B) Distribution Kinetics

1) Volume of Distribution

a) 20 L/kg (Doogan & Caillard, 1988).

2.3.3 Metabolism

A) Metabolism Sites and Kinetics

1) Liver, extensive (Prod Info Zoloft(R), 2002w).

a) Sertraline undergoes extensive first-pass metabolism (Prod Info Zoloft(R), 2002w).

b) Sertraline is primarily metabolized via N-demethylation to desmethylsertraline, which is weakly active hydroxylated. The alpha-hydroxy ketone metabolite is excreted in the urine and feces (Doogan & Caillard

B) Metabolites

1) Desmethylsertraline, weakly active (Doogan & Caillard, 1988).

2) Alcohol metabolites, inactive (Doogan & Caillard, 1988).

3) Oxime metabolites, inactive (Doogan & Caillard, 1988).

2.3.4 Excretion

A) Kidney

1) Renal Excretion (%)

a) 40% to 45% (Prod Info Zoloft(R), 2002w).

2) None of the dose is recovered as unchanged sertraline (Prod Info Zoloft(R), 2002w). The alpha-hydroxy k

B) Other

1) OTHER EXCRETION

a) Feces, 40% to 45% (Prod Info Zoloft(R), 2002w).

b) About 12-14% of sertaline is found unchanged in the feces along with the alpha-hydroxy ketone meta

2.3.5 Elimination Half-life

A) Parent Compound

1) ELIMINATION HALF-LIFE

a) 24 hours (Doogan & Caillard, 1988; Saletu et al, 1986).

1) The half-life after continuous administration of sertraline 200 mg/day was 26.2 hours (children 6 t 2002w).

2) A study of 22 young (less than 45 years) and elderly (greater than 65 years) healthy male and fe

exhibited a 50% shorter half-life (mean 22 hours) compared to the other groups (32 to 36 hours) (Rc
3) The time of day of administration (morning versus evening) did NOT affect mean terminal elimina
single doses of 100 mg (Ronfeld et al, 1997a).

B) Metabolites

1) Desmethylsertraline, 62 to 104 hours (Doogan & Caillard, 1988; Saletu et al, 1986; Prod Info Zoloft(R), 20

2.3.6 Extracorporeal Elimination

A) Hemodialysis

1) Dialyzable: No (Schwenk et al, 1995).

a) In 2 patients undergoing hemodialysis with a Baxter CA-110 hollow fiber dialysis filter, no sertraline w
the dialysis time was 4 and 3.63 hours for patient 1 and 2, respectively (Schwenk et al, 1995).

3.0 Cautions

Contraindications

Precautions

Adverse Reactions

Teratogenicity/Effects in Pregnancy/Breastfeeding

Drug Interactions

3.0.A Black Box WARNING

1) Sertraline Hydrochloride

a) Oral (Solution; Tablet)

Suicidality and Antidepressant Drugs
Antidepressants increased the risk compared to placebo of suicidal thinking and behavior (suicidality) in child
(MDD) and other psychiatric disorders. Anyone considering the use of sertraline hydrochloride or any other a
need. Short-term studies did not show an increase in the risk of suicidality with antidepressants compared to
compared to placebo in adults aged 65 and older. Depression and certain other psychiatric disorders are ther
started on antidepressant therapy should be monitored appropriately and observed closely for clinical worser
advised of the need for close observation and communication with the prescriber. Sertraline hydrochloride is
disorder (OCD) (Prod Info ZOLOFT(R) concentrate, oral tablets, 2009).

3.1 Contraindications

A) Sertraline Hydrochloride

1) concomitant use of disulfiram (oral concentrate) (Prod Info ZOLOFT(R) concentrate, oral tablets, 2009)
2) concomitant use of monoamine oxidase inhibitors (MAOIs) or pimozide (Prod Info ZOLOFT(R) concentrate, or
3) hypersensitivity to sertraline or any other component of the product (Prod Info ZOLOFT(R) concentrate, oral ta

3.2 Precautions

A) Sertraline Hydrochloride

1) suicidal ideation and behavior or worsening depression; increased risk, particularly in children, adolescents, ar
(Prod Info ZOLOFT(R) concentrate, oral tablets, 2009)
2) abnormal bleeding has been reported, including life-threatening hemorrhages (Prod Info ZOLOFT(R) concentr
3) abrupt withdrawal; serious discontinuation symptoms have been reported (Prod Info ZOLOFT(R) concentrate,
4) bipolar disorder; increased risk of precipitation of a mixed/manic episode (Prod Info ZOLOFT(R) concentrate, c
5) Concomitant use of NSAIDs, aspirin, warfarin, or other drugs that affect coagulation; monitoring recommended
tablets, 2009)
6) concomitant use of serotonergic drugs (serotonin precursors (tryptophan), SSRIs, serotonin-norepinephrine re
tablets, 2009)
7) conditions or diseases that may affect metabolism or hemodynamic response (Prod Info ZOLOFT(R) concentr
8) latex allergy; oral concentrate dropper dispenser contains dry natural rubber (Prod Info ZOLOFT(R) concentra
9) liver disease or impairment; risk of drug toxicity; lower or less frequent dose may be required (Prod Info ZOLO
10) mania, history; risk of activation of mania/hypomania (Prod Info ZOLOFT(R) concentrate, oral tablets, 2009)
11) seizures, history (Prod Info ZOLOFT(R) concentrate, oral tablets, 2009)
12) serotonin syndrome has been reported, including cases that are life-threatening or that resemble neuroleptic
tablets, 2009)
13) use of sertraline within 14 days of MAOI discontinuation (Prod Info ZOLOFT(R) concentrate, oral tablets, 200
14) use of MAOIs within 14 days after sertraline discontinuation (Prod Info ZOLOFT(R) concentrate, oral tablets,
15) volume-depleted, elderly, or concurrent diuretic therapy; hyponatremia, syndrome of inappropriate antidiuretic
concentrate, oral tablets, 2009)

3.3 Adverse Reactions

Cardiovascular Effects

Dermatologic Effects

Endocrine/Metabolic Effects

Gastrointestinal Effects

Hematologic Effects

Hepatic Effects

Immunologic Effects

Musculoskeletal Effects

Neurologic Effects

Ophthalmic Effects

Psychiatric Effects

Renal Effects

Reproductive Effects

Respiratory Effects

Other

3.3.1 Cardiovascular Effects

3.3.1.A Sertraline Hydrochloride

Angina

Cardiac dysrhythmia

Cardiovascular finding

EKG finding

Syncope

3.3.1.A.1 Angina

a) Summary

1) CASE REPORT - A case report notes the occurrence angina along with shortness of breath and were severe enough to warrant hospitalization and withdrawal of treatment. Authors postulate that ir vasoconstriction. This results from the inability of the endothelium to produce sufficient endothelium- al, 1997).

b) LITERATURE REPORTS

1) An 81-year-old woman developed nausea and severe, crushing, retrosternal chest pain with sho milligrams. The pain worsened over the subsequent 2 hours and required hospitalization. The cardio were also normal. The electrocardiogram revealed normal sinus rhythm with nonspecific ST-T wave

acetylsalicylic acid, intravenous (IV) heparin, IV nitroglycerin, and diltiazem; sertraline was stopped. coronary artery and circumflex artery, respectively. Although it is difficult to attribute angina to sertra atherosclerotic coronary arteries causes vasoconstriction. This results from the inability of the endot vasoconstriction caused by serotonin (Sunderji et al, 1997).

3.3.1.A.2 Cardiac dysrhythmia

a) Summary

1) In postmarketing evaluation, AV BLOCK and VENTRICULAR TACHYCARDIA, including TORSA sertraline (Prod Info Zoloft(R), 2002).

3.3.1.A.3 Cardiovascular finding

a) Summary

1) Sertraline has been associated with PALPITATIONS, CHEST PAIN, HYPERTENSION, HYPOTE

b) Arrhythmias, palpitations, electrocardiogram changes, chest pain, hypertension, hypotension, edema

c) In a large cohort study including 481,744 persons and 1487 cases of SUDDEN CARDIAC DEATH oc associated with an increased risk of sudden cardiac death (rate ratio, 0.95; 95% CI, 0.42 to 2.15). In con equivalent) had a 41% increased rate of sudden cardiac death (rate ratio, 1.41; 95% CI, 1.02 to 1.95) (R

3.3.1.A.4 EKG finding

a) Summary

1) Electrocardiographic abnormalities were noted in 2 of 8 patients taking sertraline, 200 milligrams clinically significant Q-T INTERVAL PROLONGATION. Additional data are necessary to establish a

3.3.1.A.5 Syncope

a) Three patients with neurally mediated syncope, which was exacerbated following the use of sertraline

3.3.2 Dermatologic Effects

3.3.2.A Sertraline Hydrochloride

Dermatological finding

Night sweats

Stevens-Johnson syndrome

3.3.2.A.1 Dermatological finding

a) Summary

1) Infrequently, RASH, ACNE, PRURITUS, ALOPECIA, DERMATITIS, and PHOTOSENSITIVITY F

b) Infrequently, rash, acne, pruritus, alopecia, dermatitis, and photosensitivity reaction have been assoc have also been noted.

3.3.2.A.2 Night sweats

a) Summary

1) CASE REPORT - Progressively worse night sweats developed in a young woman treated with se with progressive worsening of night sweats. The patient stopped sertraline abruptly and noted resolu noted mild daytime sweating. After switching sertraline to fluoxetine, she had no further episodes of

3.3.2.A.3 Stevens-Johnson syndrome

a) Summary

1) CASE REPORT - A 96-year-old woman developed cutaneous and mucosal eruptions 3 weeks a atypical flat lesions were found on the face, trunk, and proximal limbs. Painful, oral erosions and cor days after sertraline and arginine chlorhydrate were stopped, the skin lesions disappeared. The auth distribution, atypical flat appearance, and total necrolysis of the epidermis. Other medications or dis

3.3.3 Endocrine/Metabolic Effects

3.3.3.A Sertraline Hydrochloride

Decreased uric acid level

Disorder of fluid AND/OR electrolyte

Endocrine finding

Galactorrhea

Gynecomastia

Hyperglycemia

Hyponatremia

Hypothyroidism

Metabolic finding

Syndrome of inappropriate antidiuretic hormone secretion

3.3.3.A.1 Decreased uric acid level

a) Summary

1) A small decrease in serum uric acid (7%) has been occasionally associated with sertraline therap

3.3.3.A.2 Disorder of fluid AND/OR electrolyte

a) Hyponatremia, which in some cases may be related to syndrome of inappropriate antidiuretic hormon

3.3.3.A.3 Endocrine finding

a) A small decrease in serum uric acid has been occasionally associated with therapeutic sertraline use reported. Syndrome of inappropriate antidiuretic hormone (SIADH) has also been reported in patients of

3.3.3.A.4 Galactorrhea

a) Summary

1) Sertraline therapy has been associated with galactorrhea. The probable mechanism for SSRI-inc stimulation of postsynaptic serotonin receptors in the hypothalamus or presynaptic serotonin recepto

b) LITERATURE REPORTS

1) Galactorrhea associated with sertraline was reported in a 37-year-old woman with a 1-year histo intolerable nausea developed, she was switched to sertraline 50 mg daily. After 2 weeks, the dosag beginning treatment. Sertraline was discontinued, and lactation ceased 21 days later. She was rece Stahl, 1993). Sixteen anecdotal cases of galactorrhea associated with sertraline have been reported have been reported in approximately 36 patients (Pers Comm, 1994).

3.3.3.A.5 Gynecomastia

a) Summary

1) Gynecomastia has been reported with sertraline use (Prod Info Zoloft(R), 2002). BREAST PAIN,

3.3.3.A.6 Hyperglycemia

a) Summary

1) Hyperglycemia was reported following the administration of sertraline for the treatment of depres Following the initiation of sertraline (12.5 milligrams (mg)/day, titrated weekly to 50 mg/day), the wor 116.3 mg/deciliter (dL) to 180.3 mg/dL. Laboratory studies revealed an increase in fasting serum glu treatment. During sertraline therapy, the patient lost 4 pounds and reported a reduction in carbohydr

3.3.3.A.7 Hyponatremia

a) Summary

1) The use of sertraline by elderly patients has been associated with cases of clinically significant h antidiuretic hormone secretion (SIADH) has also been reported following therapy. This effect has be frequently in patients over 65 years of age (Pecora et al, 1997)(Jackson et al, 1995; Leung & Remic Resch, 1995).

b) Incidence: rare

3.3.3.A.8 Hypothyroidism

a) Summary

1) Patients with thyroid disease who are also receiving treatment for depression should have thyroi levels and small increases in serum thyrotropin levels after starting treatment with sertraline and oth

3.3.3.A.9 Metabolic finding

a) Summary

1) HYPOGLYCEMIA, or HYPERCHOLESTEROLEMIA, and HYPERTRIGLYCERIDEMIA have bee DECREASED WEIGHT was also reported in at least 2% of pediatric patients during clinical trials of

b) Weight loss, hypoglycemia, hypercholesterolemia, hyperglycemia, and hypertriglyceridemia has occu

3.3.3.A.10 Syndrome of inappropriate antidiuretic hormone secretion

a) Summary

1) Sertraline has been associated with syndrome of inappropriate antidiuretic hormone secretion (S occurs between 3 days and 4 month after beginning therapy (Woo & Smythe, 1997; Bradley et al, 1

b) LITERATURE REPORTS

1) Of the 25 case reports of selective serotonin reuptake inhibitor (SSRI)-induced SYNDROME OF published, the majority occurred in patients over 70 years of age. Based on published reports, the o included confusion, lethargy, dizziness, fatigue, anorexia, delirium, and abdominal pain. Abnormal la (milliosmole/liter) mOsm/L; range 214 to 272 mOsm/L), decreased serum sodium concentration (me (median 392.5 mOsm/L; 229 to 613 mOsm/L). In all but 1 case, the selective serotonin reuptake inh patient was also treated with sodium chloride 3%. Patients in their fifties generally recovered in 2 to the 6 patients rechallenged with an SSRI, 3 developed a decrease in serum sodium consistent with adequately report symptoms, laboratory results, and exclusion of other causes making it difficult to a

2) Three days after starting sertraline 50 milligrams daily, a 78-year-old woman was diagnosed with encephalopathic and had myoclonus. Her serum sodium decreased from 136 milliequivalents/liter (n 125 mEq/L and 474 milliosmoles/kilogram (mOsm/kg), respectively, compared to a plasma osmolali mL of sodium chloride 3%, (3) restricting fluid intake to 1000 mL/day, and (4) initiating demeclocyclin sodium returned to 138 mEq/L within 3 days. Other drugs and medical conditions were considered u reported although symptoms occurred later, after 5 days and 4 months; discontinuation of sertraline 1996).

3.3.4 Gastrointestinal Effects

3.3.4.A Sertraline Hydrochloride

Gastrointestinal hemorrhage

Gastrointestinal tract finding

Grinding teeth

Nausea and vomiting

Pancreatitis

Xerostomia

3.3.4.A.1 Gastrointestinal hemorrhage

See Drug Consult reference: CONCOMITANT USE OF SSRIs AND NSAIDs - INCREASED RISK OF GA

3.3.4.A.2 Gastrointestinal tract finding

a) Summary

1) During placebo-controlled clinical trials, the following were reported in adults at an incidence grea FLATULENCE (Prod Info Zoloft(R), 2002). Infrequently, sertraline has been reported to cause INDIG

b) Infrequently, sertraline has been reported to cause diarrhea, indigestion, dry mouth, abdominal pain, flatulence, nausea and vomiting have occurred more frequently. Minimal weight loss (mean 1-2 pounds)

3.3.4.A.3 Grinding teeth

a) Sertraline-induced bruxism has occurred after exposure to daily doses ranging from 6.25 to 150 mg, v Stanziani, 1993). Dose reduction from 25 mg/day to 6.25 mg/day failed to relieve symptoms in one 36-ye with longstanding anxiety disorder and depression had her 100 mg/day sertraline discontinued, with an 1 patient's mood deteriorated. Replacement of paroxetine with fluvoxamine (dosage not reported) resulted failed to alleviate her bruxism (Fitzgerald & Healy, 1995).

3.3.4.A.4 Nausea and vomiting

a) Summary

1) During placebo-controlled clinical trials, nausea, and vomiting were reported in adults with sertral vomiting were noted 4 to 6 hours after single doses of 100 milligrams in one study, and were reporte

b) LITERATURE REPORTS

1) The selective serotonin reuptake inhibitors (SSRIs) produce nausea and vomiting in 20% to 25% decreases or resolves over approximately 3 weeks. However, in others, reduction of the dose or dis for a few weeks may facilitate continued treatment with the SSRI. Limited data suggest that ondanse

with careful monitoring for arrhythmias may be more cost effective than ondansetron. The proposed the chemoreceptor trigger zone and area postrema in the brainstem, the primary areas within the br

3.3.4.A.5 Pancreatitis

a) Summary

1) Pancreatitis has been temporally associated with the use of sertraline (Prod Info Zoloft(R), 2002)

3.3.4.A.6 Xerostomia

a) Summary

1) Several studies have reported XEROSTOMIA as an occasional adverse effect of sertraline in the

3.3.5 Hematologic Effects

3.3.5.A Sertraline Hydrochloride

Disorder of hemostatic system

Hematology finding

3.3.5.A.1 Disorder of hemostatic system

a) Summary

1) Rare occurrences (incidence less than 0.1%) of BRUISING, ECCHYMOSES, EPISTAXIS, PROL therapy. The majority of cases have been reported in patients taking fluoxetine but case reports are

b) LITERATURE REPORTS

1) INCIDENCE

a) Rare (incidence less than 0.1%). The majority of cases have been reported in patients takin (Berk & Jacobson, 1998).

2) OUTCOME

a) Mild (treatment continued with/without other management) (Berk & Jacobson, 1998).

3) ASSOCIATED SYMPTOMS

a) Symptoms include: bruising, ecchymoses, epistaxis, prolonged bleeding time, rectal bleedin

4) CLINICAL MANAGEMENT

a) PHARMACOLOGIC - For minor bleeding diatheses (ie, bruising), treatment is usually unnec clinically significant, occurs with other underlying medical illnesses, or fails to improve with time

5) PREDISPOSING RISK FACTORS

a) DOSE-RELATED

1) Yes. Many cases have occurred in patients taking doses at the higher end of the dose r

b) DISEASE STATES

1) Yes. More common in patients with underlying diseases; 1 case occurred in a patient w

6) PROBABLE MECHANISM

a) PHARMACOLOGIC (extension of the expected effects of the drug). Selective serotonin reup storage of serotonin is observed. Serotonin-mediated platelet aggregation may be decreased (E

7) DOCUMENTATION QUALITY

a) Fair

8) CASE REPORT

a) A case of prolonged bleeding time associated with ecchymoses and normal prothrombin and resolved spontaneously with drug cessation (Calhoun & Calhoun, 1996a).

3.3.5.A.2 Hematology finding

a) Summary

1) AGRANULOCYTOSIS, APLASTIC ANEMIA, and THROMBOCYTOPENIA have been reported a

b) Sertraline therapy has been associated with bruising, ecchymoses, epistaxis, prolonged bleeding tim thrombocytopenia. Rare cases of impaired platelet aggregation have been reported.

c) Purpura has been reported in at least 2% of pediatric patients treated with sertraline (Prod Info Zoloft

3.3.6 Hepatic Effects

3.3.6.A Sertraline Hydrochloride

Increased liver enzymes

Liver failure

Liver finding

3.3.6.A.1 Increased liver enzymes

a) Summary

1) Asymptomatic elevations in serum transaminases have been reported within the first 9 weeks of (Prod Info Zoloft(R), 2002).

3.3.6.A.2 Liver failure

a) Summary

1) Liver failure has been temporally associated with the use of sertraline (Prod Info Zoloft(R), 2002)

3.3.6.A.3 Liver finding

a) Elevated liver enzymes and liver failure have been noted occasionally with therapeutic sertraline use.

3.3.7 Immunologic Effects

3.3.7.A Sertraline Hydrochloride

3.3.7.A.1 Anaphylaxis

a) Summary

1) In postmarketing surveillance, ANAPHYLACTOID REACTIONS have been associated with use c

3.3.8 Musculoskeletal Effects

3.3.8.A Sertraline Hydrochloride

Arthralgia

Fracture of bone

Fracture of bone, Nonvertebral

Muscle weakness

Myalgia

Summary

3.3.8.A.1 Arthralgia

a) Incidence: 0.1% to 1% (Prod Info ZOLOFT(R) concentrate, oral tablets, 2009)

b) Arthralgia was reported in 0.1 to 1% of over 4000 adult patients exposed to multiple doses of sertralir concentrate, oral tablets, 2009).

3.3.8.A.2 Fracture of bone

a) In a case-control study including fracture cases (n=124,655) during the year 2000 and age- and gend participants who were using an average standard daily dose of sertraline (adjusted odds ratio (OR), 1.25 use was associated with an increased risk of hip fracture (adjusted OR, 1.76; 95% CI, 1.52 to 2.03), fore 1.74; CI, 1.26 to 2.41) (Vestergaard et al, 2008)

b) In a population-based, randomly selected, prospective cohort study adjusted for potential covariates, years of age and older who used daily SSRIs (n=137; mean age of 65.1 years), including sertraline, com use was associated with a significant 2.1-fold increased risk of fragility fracture (95% confidence interval fragility fracture (95% CI, 1.1 to 2.1). Daily SSRI users who were recurrent (ie, treated with SSRIs at bas (95% CI, 1.1 to 4.0). Fractures were reported at the following sites: forearm (40%), ankle and foot (21%), or fingers (Richards et al, 2007).

3.3.8.A.3 Fracture of bone, Nonvertebral

a) In a prospective, population-based, cohort study (n=7983) with a mean follow-up of 8.4 years, there w age (mean age of 77.5 years) who were currently using an SSRI (citalopram, escitalopram, fluoxetine, flu antidepressants. Current SSRI use was associated with an increased risk of nonvertebral fracture (adjus antidepressant use. Current SSRI use was also associated with an increased risk of nonvertebral fractur (n=1217). In addition, duration of SSRI use showed a 9% increase in fracture risk per extra month on an humerus, and pelvis were reported (Ziere et al, 2008).

3.3.8.A.4 Muscle weakness

a) Incidence: 0.1% to 1% (Prod Info ZOLOFT(R) concentrate, oral tablets, 2009)

b) Muscle weakness was reported in 0.1 to 1% of over 4000 adult patients exposed to multiple doses of (R) concentrate, oral tablets, 2009).

3.3.8.A.5 Myalgia

a) Incidence: 1% or greater (Prod Info ZOLOFT(R) concentrate, oral tablets, 2009)

b) Myalgia was reported in at least 1% of over 4000 adult patients exposed to multiple doses of sertralin concentrate, oral tablets, 2009).

3.3.8.A.6 Summary

a) Sertraline has been frequently associated with myalgia, and infrequently associated with arthralgia ar was associated with an increased risk of hip, forearm, and spine fracture in a case-controlled study (Ves prospective cohort study of SSRIs, including sertraline (Richards et al, 2007). An increased risk of nonve paroxetine, in adult participants older than 55 years of age (Ziere et al, 2008).

3.3.9 Neurologic Effects

Sertraline

Sertraline Hydrochloride

3.3.9.A Sertraline

3.3.9.A.1 Seizure

See Drug Consult reference: COMPARATIVE INCIDENCE OF SEIZURES FROM ANTIDEPRESSANTS

3.3.9.B Sertraline Hydrochloride

Agitation

Cognitive function finding

Dizziness

Dystonia

Dystonia, Mandibular

Extrapyramidal sign

Headache

Hyperactive behavior

Impaired psychomotor performance

Insomnia

Parkinsonism

Restless legs syndrome

Seizure

Sleep walking disorder

Somnolence

Summary

Tic

Tremor

3.3.9.B.1 Agitation

a) Agitation is one of the most frequently reported adverse effects of sertraline (incidence greater than 5

3.3.9.B.2 Cognitive function finding

a) Summary

1) Increases in objective measurements of alertness were observed with sertraline in doses of 50, 7 (critical flicker fusion and choice reaction time tests) were performed on 10 patients after single dose 7.5 hours post-dosing. However, subjective drowsiness was reported with these doses (Hindmarch

3.3.9.B.3 Dizziness

a) Dizziness is one the most frequently reported adverse effects of sertraline (incidence greater than 5%

3.3.9.B.4 Dystonia

a) Incidence: rare (Prod Info Zoloft(R), 2002)

b) Sertraline has been infrequently associated with muscle dystonia (Prod Info Zoloft(R), 2002).

3.3.9.B.5 Dystonia, Mandibular

a) Summary

1) Mandibular dystonia has been noted in several case reports during therapeutic sertraline use. W abatement. Patients on multiple drug therapies should be carefully monitored for interactions or pote 1996b).

b) LITERATURE REPORTS

1) "Sneering" movements developed in the upper mouth area 7.5 months after sertraline was initiat painful pulling sensation of the upper lip. Other dyskinesias or tics were not identified. Symptoms re reappearance of the sneering movement 24 hours later. Two days after stopping sertraline, the abn after identification of this movement disorder (Stanislav & Childs, 1999).

2) A case of mandibular dystonia was reported two days after the addition of metoclopramide 10 mi months with sertraline 100 mg/day (Wilks, 1998b).

3) In a case report, DYSTONIA was reported in a 24-year-old man treated for posttraumatic stress then this dose was increased to 50 mg. Three days after starting the higher dosages, he presented jaw stiffness and feeling as if his face was "frozen." The symptoms were relieved by administration was noted over a year later after he began treatment with sertraline 25 mg, which was increased to common to both drugs, possibly associated with enhancement of serotonergic neurotransmission th

4) A 22-year-old woman developed mandibular dystonia characterized by periauricular pain, jaw tig (mg) daily. Symptoms were relieved by diphenhydramine 50 mg. A third dose of sertraline was admi taking metoclopramide 15 mg four times daily for gastroesophageal reflux which had caused no adv effect of sertraline and metoclopramide resulting in dystonia. This case is intended to alert clinicians (Christensen & Byerly, 1996b).

5) TORTICOLLIS and JAW STIFFNESS responsive to treatment with diphenhydramine, and akathi

3.3.9.B.6 Extrapyramidal sign

a) Summary

1) Extrapyramidal reactions (EPRs) including acute DYSTONIC REACTIONS, NEUROLEPTIC MA selective serotonin reuptake inhibitors (SSRI). The majority of case reports involve fluoxetine; howe

b) LITERATURE REPORTS

1) Extrapyramidal reactions occurred more frequently in women (about 75%) possibly due to more reports, the dose of the SSRI was increased to the maximum recommended dose within 7 days or during the second to fourth week of treatment. Possible mechanisms by which SSRIs cause Extrapy activity resulting in clinically significant effects; and (2) Concurrent use of an SSRI and antipsychotic combination of the two (Caley, 1997).

2) TREATMENT - The majority of extrapyramidal reactions (EPRs) occur within the first few days to during the first 4 weeks of treatment with selective serotonin reuptake inhibitors (SSRIs) and periodi stopping the SSRI (Caley, 1997; Gill et al, 1997). In a limited number of case reports, propranolol a to 90 milligrams (mg) daily, and the dose of clonazepam was 1.5 mg daily (Gill et al, 1997). In single trihexyphenidyl or diphenhydramine 50 mg. Parkinsonism characterized by increasing rigidity and tr a neuroleptic agent. In all cases, symptoms disappeared after reducing the dose or stopping the SS spontaneously over days to weeks after the SSRI is stopped (Gill et al, 1997).

3.3.9.B.7 Headache

a) Headache is one of the most frequently reported adverse effects of sertraline (incidence greater than

3.3.9.B.8 Hyperactive behavior

a) Hyperkinesia has been reported in at least 2% of pediatric patients treated with sertraline (Prod Info Z

3.3.9.B.9 Impaired psychomotor performance

a) Summary

1) Subjective drowsiness was reported with sertraline in a study testing psychomotor function, but t
chart review, nursing home patients treated with fluoxetine and other selective serotonin-reuptake in
risk of falls compared to patients who are not on antidepressants (Thapa et al, 1998).

b) LITERATURE REPORTS

1) A retrospective chart review of 2428 nursing home residents treated with antidepressants assess
were then compared to those not treated (n=847). Antidepressant treatment included tricyclic antide
treated patients was higher than that for patients who were not treated, both before and after the init
or related conditions are at a greater risk of falls than those without such conditions. Patients on TC
(CI), 1.8 to 2.2). The SSRIs had a adjusted rate ratio of 1.8 (1.6 to 2, p=0.001) and trazodone had a
among medications of the same class. It was, however, noted that patients receiving a dose of 20 m
significant increase in the incidence of falls than those receiving lower doses (Thapa et al, 1998).

2) The acute effects of single doses of sertraline 100 milligrams (mg), amitriptyline 50 mg, and plac
double-blind, placebo-controlled crossover study. While performance was clearly impaired by amitri
objective measures of alertness. Although subjective DROWSINESS was reported with both drugs,

3.3.9.B.10 Insomnia

a) Insomnia is one of the most frequently reported adverse effects of sertraline (incidence greater than 5

3.3.9.B.11 Parkinsonism

a) Summary

1) CASE REPORT - A case report notes the development of parkinsonism with symptoms of pill-rol
two weeks after his sertraline dose was increased. A rapid decrease of the dose resolved symptoms
Parkinsonism; therefore, the authors attribute the reaction to sertraline although no rechallenge at a

b) LITERATURE REPORTS

1) Two weeks after the dose of sertraline was increased to 150 milligram (mg) daily, a 90-year-old r
bradykinesia, and festinating gait; he fell twice. The dose of sertraline was rapidly tapered to 50 mg/
sertraline, mental and neurologic examination was normal. The only other medical conditions were s
treated with furosemide and enalapril. In this case, other medical conditions and medications were r
sertraline although rechallenge with the higher dose was not performed (Schechter & Nunes, 1997).

3.3.9.B.12 Restless legs syndrome

a) In a prospective, naturalistic study of patients (median age, 46 years; range, 18 to 87 years) treated v
syndrome (RLS) or worsening of preexisting RLS as a side effect related to treatment. Antidepressants i
duloxetine, reboxetine, and mirtazapine. Mirtazapine led to a marked decline of RLS in 28% of subjects
symptoms (newly occurred or deteriorated) at the rate of 5% to 10%. Subjects stated symptoms occurre

3.3.9.B.13 Seizure

a) Summary

1) CASE REPORT - A 34-year-old woman had a severe TONIC-CLONIC SEIZURE when her sertra
depression. Initial computerized tomography (CT) head scan and electroencephalogram (EEG) were
consistent with a postictal disturbance rather than epilepsy. Sertraline was switched to citalopram, a
predisposing risk factors for seizures such as previous seizures or sedative or alcohol abuse. For m
patient (Saraf & Schrader, 1999).

b) Incidence: rare

3.3.9.B.14 Sleep walking disorder

a) Summary

1) CASE REPORT - A 34-year-old HIV-positive woman developed somnambulism while being treat
milligram (mg) daily dose of paroxetine was gradually increased over 2 weeks to 20 mg daily. Three
according to witnesses. The somnambulism disappeared completely 1 week after the daily dose wa
increasing the dose to 20 mg/day, the sleepwalking reappeared. Paroxetine was discontinued and s
100 mg/day, she again began to sleepwalk. Her symptoms of depression and anxiety improved at th
(Alao et al, 1999).

3.3.9.B.15 Somnolence

a) Somnolence is one of the most frequently reported adverse effects of sertraline (incidence greater tha

3.3.9.B.16 Summary

a) Some of the most frequently reported adverse effects of sertraline are insomnia, headache, dizziness
in 0.4% of patients during clinical studies. Extrapyramidal reactions (EPRs) including acute dystonic reac
been associated with therapeutic use. Nursing home patients have an increased risk of falls compared to

3.3.9.B.17 Tic

a) Exacerbation of TICS in a patient with Tourette's Syndrome that responded to cessation of sertraline

3.3.9.B.18 Tremor

a) Tremor is one of the most frequently reported adverse effects of sertraline (incidence greater than 5%

3.3.10 Ophthalmic Effects

3.3.10.A Sertraline Hydrochloride

Eye / vision finding

Oculogyric crisis

3.3.10.A.1 Eye / vision finding

a) Summary

1) XEROPHTHALMIA, or DIPLOPIA, PHOTOPHOBIA, accommodation changes and CONJUNCTI evaluation, OPTIC NEURITIS and CATARACTS have been temporally associated with use of sertra

b) Rare reports of xerophthalmia, diplopia, photophobia, anterior chamber eye hemorrhage, accommod neuritis and cataracts have also been reported.

3.3.10.A.2 Oculogyric crisis

a) Summary

1) In postmarketing evaluation, oculogyric crisis has been temporally associated with use of sertrali

3.3.12 Psychiatric Effects

3.3.12.A Sertraline Hydrochloride

Depression, exacerbation

Hypomania

Psychiatric sign or symptom

Suicidal thoughts

3.3.12.A.1 Depression, exacerbation

a) Incidence: rare

b) Adult and pediatric patients who experience symptoms of anxiety, agitation, panic attacks, insomnia, hypomania, or mania may be at risk of worsening of their depression. This same concern applies to treat observed, therapy should be reevaluated and it may be necessary to discontinue medications when sym (Anon, 2004).

3.3.12.A.2 Hypomania

a) Summary

1) Two cases of hypomania were reported; one occurred after 5 weeks of sertraline 200 milligrams discontinuation of sertraline and treatment with short-term clonazepam or lithium (Laporta et al, 198

b) Incidence: rare

3.3.12.A.3 Psychiatric sign or symptom

a) Summary

1) Abnormal dreams, AGGRESSIVE BEHAVIOR, delusions, HALLUCINATIONS, EMOTIONAL LAI Info Zoloft(R), 2002; Reimherr et al, 1988b).

2) Aggressive reactions have been reported in at least 2% of pediatric patients treated with sertralir

b) Abnormal dreams, agitation, aggressive behavior, delusions, hallucinations, emotional lability, paranc associated with sertraline therapy.

c) LITERATURE REPORTS

1) Complex, colorful visual hallucinations have been reported less than 3 weeks after initiation of se seconds after awakening and resolved following discontinuation of sertraline (Bourgeois et al, 1998)

3.3.12.A.4 Suicidal thoughts

a) Summary

1) Adult and pediatric patients being treated with antidepressants for major depressive disorder wh

(aggressiveness), impulsivity, akathisia (psychomotor restlessness), hypomania, or mania may be a treating patients with other psychiatric and nonpsychiatric disorders. If these symptoms are observe when symptoms are severe, sudden in onset, or were not part of the patient's initial symptoms. Patie this drug (Anon, 2004; Anon, 2004).

2) A causal role for antidepressants in inducing suicidality has been established in pediatric patients this risk with the clinical need. In pooled analyses of 24 short-term, placebo-controlled trials of nine a mirtazapine, nefazodone, and venlafaxine extended-release) including over 4400 pediatric patients disorders, a greater risk of suicidal behavior or ideation during the first few months of therapy was d respectively). The risk of suicidality was most consistently observed in the trials that included patient psychiatric indications, such as obsessive compulsive disorder and social anxiety disorder. No suici several months) in pediatric patients is not known. It is also unknown whether this risk extends to ad

b) Incidence: rare

3.3.13 Renal Effects

3.3.13.A Sertraline Hydrochloride

Renal failure

Urinary incontinence

Urinary tract infectious disease

Urogenital finding

3.3.13.A.1 Renal failure

a) Summary

1) Acute renal failure has been reported in temporal association with use of sertraline (Prod Info Zo

3.3.13.A.2 Urinary incontinence

a) Urinary incontinence has been reported in at least 2% of pediatric patients treated with sertraline (Pro

3.3.13.A.3 Urinary tract infectious disease

a) Summary

1) In placebo-controlled clinical trials with geriatric patients, the incidence of urinary tract infections placebo (Anon, 2001).

3.3.13.A.4 Urogenital finding

a) Infrequent reports of dysmenorrhea, intermenstrual bleeding, amenorrhea, leukorrhea, and atrophic v failure have occasionally been associated with sertraline therapy. Male sexual dysfunction and priapism

3.3.14 Reproductive Effects

Sertraline

Sertraline Hydrochloride

3.3.14.A Sertraline

3.3.14.A.1 Sexual dysfunction

See Drug Consult reference: DRUG-INDUCED SEXUAL DYSFUNCTION

See Drug Consult reference: SELECTIVE SEROTONIN REUPTAKE INHIBITOR-INDUCED SEXUAL D

3.3.14.B Sertraline Hydrochloride

Disorder of menstruation

Priapism

Sexual dysfunction

3.3.14.B.1 Disorder of menstruation

a) Summary

1) Sertraline may cause infrequent DYSMENORRHEA, INTERMENSTRUAL BLEEDING, AMENOF

3.3.14.B.2 Priapism

a) Summary

1) Therapeutic use of sertraline has resulted in rare case occurrence of priapism. The Adverse Eve 46 reports of priapism associated with sertraline (Rand, 1998) One case report noted a 47-year-old resolution occurred after tapering the patient off sertraline. The patient was started on nefazodone t

b) LITERATURE REPORTS

1) INCIDENCE

a) Rare (incidence less than 0.1%). The Adverse Events Reporting System maintained by the sertraline (Rand, 1998).

2) OUTCOME

a) Severe (hospitalization required for treatment) (Rand, 1998).

3) ASSOCIATED SYMPTOMS

a) Pain.

4) ONSET/DURATION

a) DURATION OF SYMPTOMS (with treatment)

1) Several weeks (1 case) (Rand, 1998).

5) CLINICAL MANAGEMENT

a) PHARMACOLOGIC

1) Initial treatment consisted of repeated intracorporeal injection of methoxamine which wa cavernosa and a Winter's shunt procedure which was partially effective. After several week (Rand, 1998).

6) PROBABLE MECHANISM

a) Pharmacologic (extension of the expected effects of a drug).

1) The proposed mechanism for this adverse effect is alpha- 1-adrenergic blockade. Amor alpha-1-adrenergic activity (Rand, 1998).

7) DOCUMENTATION QUALITY

a) Poor.

8) CASE REPORT

a) A 47-year-old man treated with sertraline 200 milligram (mg)/day and dextroamphetamine 1(several brief episodes over the past month. He came to the emergency department (ED) due to injection of methoxamine appeared effective; however, he returned to the ED and was admitted with injection of dilute epinephrine and a Winter's shunt procedure. At follow-up, several weeks was started on nefazodone (Rand, 1998).

3.3.14.B.3 Sexual dysfunction

a) Summary

1) During clinical trials, DELAYED EJACULATION (14%) and DECREASED LIBIDO (6%) were rep & Caillard, 1988c).

2) .FMI DC9691

3.3.15 Respiratory Effects

3.3.15.A Sertraline Hydrochloride

Pulmonary hypertension

Respiratory finding

3.3.15.A.1 Pulmonary hypertension

a) Summary

1) Pulmonary hypertension has been temporally associated with the use of sertraline (Prod Info Zol

3.3.15.A.2 Respiratory finding

a) Summary

1) BRONCHOSPASM, DYSPNEA, and COUGH have occasionally been associated with sertraline

b) Occasional bronchospasm, dyspnea, and cough have been noted with sertraline therapy. Temporary

c) Sinusitis and epistaxis have been reported in at least 2% of pediatric patients treated with sertraline (

3.3.16 Other

Sertraline

Sertraline Hydrochloride

3.3.16.A Sertraline

3.3.16.A.1 Drug withdrawal
See Drug Consult reference: WITHDRAWAL SYNDROME OF SELECTIVE SEROTONIN REUPTAKE I

3.3.16.B Sertraline Hydrochloride

Drug dependence

Drug withdrawal

Fatigue

Fever

Serotonin syndrome

3.3.16.B.1 Drug dependence
a) Summary
1) In a placebo-controlled study designed to assess abuse potential, patients treated with sertraline

3.3.16.B.2 Drug withdrawal
a) Summary
1) Premarketing studies did not report withdrawal reaction to sertraline (Prod Info Zoloft(R), 2002). I
sertraline therapy. Symptoms have included: fatigue, nausea, abdominal cramps, diarrhea, shortnes
tinnitus, ataxia, abnormal sensations ("electric shocks", skin tingling sensations, and involuntary mo
reinstatement of sertraline therapy (Wolfe, 1997; Zajecka et al, 1997; Leiter et al, 1995; Louie et al,
b) LITERATURE REPORTS
1) PEDIATRIC
a) On the fourth day, following the abrupt discontinuation of sertraline (200 milligrams (mg) per
tremor, irritability, and insomnia. The patient was treated with paroxetine 20 mg/day (sertraline
resolved within 30 hours (Diler & Avci, 2002).
b) Withdrawal symptoms in a neonate after maternal sertraline therapy has been reported. Sym
enhanced startle reaction. The child had been well until one day postpartum and symptoms res
Laidlaw, 1995).

3.3.16.B.3 Fatigue
a) Fatigue is one of the most frequently reported adverse effects of sertraline (incidence greater than 5%

3.3.16.B.4 Fever
a) Fever has been reported in at least 2% of pediatric patients treated with sertraline (Prod Info Zoloft(R

3.3.16.B.5 Serotonin syndrome
a) Serotonin syndrome, including life-threatening cases, or neuroleptic malignant syndrome (NMS)-like
serotonin syndrome include mental status changes (eg, agitation, hallucination, coma), autonomic instab
hyperreflexia, incoordination) and/or gastrointestinal symptoms (eg, nausea, vomiting, diarrhea). Severe
rigidity, autonomic instability with possible rapid fluctuation of vital signs, and mental status changes. Se
including triptans, with drugs that impair metabolism of serotonin, including MAOIs, or with antipsychotics
b) Sertraline, a selective serotonin reuptake inhibitor, is capable, as other drugs in this class, of inducing
more drugs capable of enhancing CNS (central nervous system) serotonin activity. Often, patients with s
(Horowitz & Mullins, 1999; Lane & Baldwin, 1997).
c) A 43-year-old woman with severe mental retardation experienced serotonin syndrome (palpitations, c
hypertonicity of the lower limbs, diffuse hyperreflexia, hyperthermia, and leukocytosis) after taking 2 sub-
recovery for hospital discharge on the second day (Bhanji, 2000).

3.4 Teratogenicity/Effects in Pregnancy/Breastfeeding
A) Teratogenicity/Effects in Pregnancy
1) U.S. Food and Drug Administration's Pregnancy Category: Category C (Prod Info Zoloft(R), 2003a) (All Trimes

a) Either studies in animals have revealed adverse effects on the fetus (teratogenic or embryocidal or other) available. Drugs should be given only if the potential benefit justifies the potential risk to the fetus.

2) Australian Drug Evaluation Committee's (ADEC) Category: C(Australian Drug Evaluation Committee, 1999)

a) Drugs which, owing to their pharmacological effects, have caused or may be suspected of causing harmfu be reversible. Accompanying texts should be consulted for further details.

See Drug Consult reference: PREGNANCY RISK CATEGORIES

3) Crosses Placenta: Yes

4) Clinical Management

a) A population-based study found no increased risk of malformations, but the exposed infants were more lik SSRIs, including sertraline, after 20 weeks of gestation has been associated with an increased risk of persist significant association between the use of SSRIs in early pregnancy and the risks of birth defects, including c al, 2007). Sertraline is generally well tolerated in pregnancy and does not appear to pose an unusually high ri and in each case, these dangers must be weighed against the potential for teratogenic effects (Lamberg, 199

5) Literature Reports

a) Data from the case-controlled National Birth Defects Prevention Study (NBDPS), which included data from (defined as treatment with any SSRI from 1 month before to 3 months after conception) to SSRIs was associ confidence interval (CI), 1.1 to 5.1; P=0.02), craniosynostosis in 24 exposed infants out of 432 (adjusted OR 181 (adjusted OR 2.8; 95% CI, 1.3 to 5.7; P=0.005). However, early exposure did not significantly increase th SSRIs reported by control mothers were sertraline, fluoxetine, paroxetine, and citalopram (Alwan et al, 2007)

b) A case-control study found that the use of selective serotonin reuptake inhibitors (SSRIs) after 20 weeks o the newborn (PPHN). Fluoxetine, paroxetine, and sertraline were the specific SSRIs studied to carry this incr and their infants. Assessment of exposure was determined by telephone interview within 6 months of birth. A with an odds ratio of 6.1 (95% CI 2.2 to 16.8; p=0.001) of delivering an infant with PPHN relative to no use du antidepressants use at any gestation time was not associated with increased risk of PPHN development. The study, infants exposed to SSRIs after 20 weeks of gestation have a PPHN incidence of 0.6 to1.2% (Chamber

c) A population-based study of 1782 pregnant women exposed to selective serotonin reuptake inhibitors (SS neonatal intensive or special care unit, particularly with third trimester exposure. Using 1996-2001 data derive who had at least one purchase (a 3-months' supply) of an SSRI during the period of one month before pregn drug purchases during the same peripartum period. The mean age of both cohorts was 30 years (+/- 7). Ther artificial reproductive techniques in the SSRI group compared to controls (p less than 0.001), and mean lengt Malformations, however, were not more common in the SSRI group (p = 0.4). Purchases of SSRIs (citoprar trimester than later in pregnancy, with 118 women purchasing sertraline during the first trimester, 31 during th first trimester exposure, treatment in a special or intensive care unit was more common for the infants expose adjusting for confounding variables, this difference remained statistically significant (OR 1.6; 95% CI 1.1 to 2.

d) In a prospective, multicenter, controlled cohort study of 267 pregnant women taking 3 different SSRIs, 14 group (267 pregnant women exposed only to nonteratogens) no differences between the two groups were re stillbirth, prematurity, birth weight, and gestational age (Kulin et al, 1998).

e) A prospective study through the California Teratogen Information Service compared the outcomes of 112 teratogens. The rate of major anomalies in the two groups was similar (3.8% and 1.9%, respectively). Wome (16.3%) and their infants were more often admitted to the special care nursery (Chambers et al, 1999).

B) Breastfeeding

1) American Academy of Pediatrics Rating: Drugs for which the effect on nursing infants is unknown but may be

2) Thomson Lactation Rating: Infant risk is minimal.

a) The weight of an adequate body of evidence and/or expert consensus suggests this drug poses minimal r

3) Clinical Management

a) The selective serotonin-reuptake inhibitors, including sertraline, are lipid soluble and therefore excreted in manufacturer recommends that sertraline not be used by women while breastfeeding (Prod Info Zoloft(R), 20 should be monitored for anorexia, weight loss, irritability and insomnia.

4) Literature Reports

a) Low or undetectable levels of sertraline in human breast milk have been reported. A study of 3 nursing inf sertraline and the metabolite norsertraline were reported (Mammen et al, 1997). No adverse effects in the inf sertraline; neither drug was detectable in the infant serum (Altshuler et al, 1996).

b) One study involved 12 nursing infants whose mothers used sertraline while breastfeeding (Llewellyn & St adverse effects were noted. Similarly, sertraline was not detectable in the serum of 6 nursing infants whose m as reported by the mothers. The authors suggest that breastfeeding should generally not be discouraged in m

c) Although the clinical data suggest that the absolute dose of sertraline and the metabolite N-desmethylsert adverse outcomes, the effects of perinatal infant exposure to sertraline on long-term cognitive development o

d) Non-quantifiable (0 ng/mL to 2 ng/mL) concentrations of sertraline were detected in 7 of 9 nursing infants; ng/mL. The infant with a sertraline concentration of 64 ng/mL had an N-desmethylsertraline concentration of The infant did not experience any adverse events related to the high concentrations. Two infants had non-qua ng/mL to 6 ng/mL), and one infant had a level of 24 ng/mL, despite a low serum sertraline level. Because N-d Researchers could not conclude why the 1 infant had such high concentrations. Maternal doses of sertraline

e) Three and 6 infants had detectable serum concentrations of sertraline and desmethylsertraline, respective sertraline and desmethylsertraline were highest 7 to 8 hours and 5 to 11 hours, respectively, after the dose. C breast milk 7 to 8 hours after the maternal dose for an infant feeding every 3 hours. Breast milk concentration higher with higher maternal doses. This study was conducted in 12 mother-infant pairs; exposure to sertraline 150 mg daily (Stowe et al, 1997).

5) Drug Levels in Breastmilk

a) Parent Drug
1) Milk to Maternal Plasma Ratio
a) 1.0-3.6 (Buist & A, 2001)
b) Active Metabolites
1) Desmethylsertraline (Stowe et al, 1997)

3.5 Drug Interactions

Drug-Drug Combinations

Drug-Food Combinations

3.5.1 Drug-Drug Combinations

Abciximab

Aceclofenac

Acemetacin

Acenocoumarol

Alclofenac

Almotriptan

Alprazolam

Amitriptyline

Amoxapine

Anagrelide

Ancrod

Anisindione

Antithrombin III Human

Ardeparin

Aspirin

Astemizole

Benoxaprofen

Bivalirudin

Bromfenac

Bufexamac

Bupropion

Cannabis

Carbamazepine

Carprofen

Celecoxib

Certoparin

Cilostazol

Cimetidine

Clomipramine

Clonixin

Clopidogrel

Clorgyline

Clozapine

Dalteparin

Danaparoid

Darunavir

Defibrotide

Dehydroepiandrosterone

Dermatan Sulfate

Desipramine

Desirudin

Desvenlafaxine

Dexfenfluramine

Dexketoprofen

Diclofenac

Dicumarol

Diflunisal

Dipyridamole

Dipyrone

Dothiepin

Doxepin

Droperidol

Droxicam

Duloxetine

Efavirenz

Eletriptan

Enoxaparin

Epoprostenol

Eptifibatide

Erythromycin

Etodolac

Etofenamate

Etoricoxib

Felbinac

Fenbufen

Fenfluramine

Fenoprofen

Fentiazac

Flecainide

Floctafenine

Flufenamic Acid

Fluphenazine

Flurbiprofen

Fondaparinux

Fosphenytoin

Frovatriptan

Furazolidone

Ginkgo

Heparin

Hydroxytryptophan

Ibuprofen

Iloprost

Imipramine

Indomethacin

Indoprofen

Iproniazid

Isocarboxazid

Isoxicam

Ketoprofen

Ketorolac

Lamifiban

Lamotrigine

Levomethadyl

Lexipafant

Linezolid

Lithium

Lofepramine

Lornoxicam

Meclofenamate

Mefenamic Acid

Meloxicam

Methadone

Methylphenidate

Metoclopramide

Milnacipran

Moclobemide

Morniflumate

Nabumetone

Nadroparin

Naproxen

Naratriptan

Nialamide

Niflumic Acid

Nimesulide

Nortriptyline

Oxaprozin

Oxycodone

Parecoxib

Pargyline

Parnaparin

Pentosan Polysulfate Sodium

Phenelzine

Phenindione

Phenprocoumon

Phenylbutazone

Phenytoin

Pimozide

Pirazolac

Piroxicam

Pirprofen

Procarbazine

Propafenone

Propranolol

Propyphenazone

Proquazone

Protriptyline

Rasagiline

Reviparin

Rifampin

Rizatriptan

Rofecoxib

Selegiline

Sibrafiban

Sibutramine

St John's Wort

Sulfinpyrazone

Sulindac

Sulodexide

Sumatriptan

Suprofen

Tapentadol

Tenidap

Tenoxicam

Terfenadine

Tiaprofenic Acid

Ticlopidine

Tinzaparin

Tipranavir

Tirofiban

Tolmetin

Toloxatone

Tramadol

Tranylcypromine

Triazolam

Trimipramine

Valdecoxib

Warfarin

Xemilofiban

Zolmitriptan

Zolpidem

Zomepirac

3.5.1.A Abciximab

1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and
been associated with an increased risk of bleeding. Bleeding events reported have included epistaxis, ecchy
tablets, suspension, 2008; Prod Info PROZAC(R) oral capsules, delayed-release capsules, solution, 2008).
3) Severity: major
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When an SSRI and an antiplatelet agent are given concurrently, monitor patient for
PROZAC(R) oral capsules, delayed-release capsules, solution, 2008)
7) Probable Mechanism: unknown

3.5.1.B Aceclofenac

1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and
associated with an increased risk of bleeding. Bleeding events have included epistaxis, ecchymosis, hemator
suspension, 2008) (Prod Info Lexapro(TM), 2003; Dalton et al, 2003a; Prod Info CELEXA (R) oral tablet, solu
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When an SSRI and an NSAID are given concurrently, monitor patient for signs of in
7) Probable Mechanism: unknown
8) Literature Reports
a) SSRIs increase the risk of upper gastrointestinal bleeding and this effect is potentiated by concurrent
were searched among 26,005 users of antidepressant medications and compared with the number of ho
amount of upper GI bleeding episodes was 3.6 times more than expected (95% confidence interval, 2.7 t
12.2 (95% confidence interval, 7.1 to 19.5) and 5.2 (95% confidence interval, 3.2 to 8), respectively. The
SSRIs. Combined use of SSRIs and NSAIDs or low-dose aspirin increased the risk even further (Dalton
b) Coadministration of ketorolac with psychoactive drugs (such as fluoxetine) has been associated with

3.5.1.C Acemetacin

1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and
associated with an increased risk of bleeding. Bleeding events have included epistaxis, ecchymosis, hemator
suspension, 2008) (Prod Info Lexapro(TM), 2003; Dalton et al, 2003a; Prod Info CELEXA (R) oral tablet, solu
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When an SSRI and an NSAID are given concurrently, monitor patient for signs of in
7) Probable Mechanism: unknown
8) Literature Reports
a) SSRIs increase the risk of upper gastrointestinal bleeding and this effect is potentiated by concurrent

were searched among 26,005 users of antidepressant medications and compared with the number of ho
amount of upper GI bleeding episodes was 3.6 times more than expected (95% confidence interval, 2.7 t
12.2 (95% confidence interval, 7.1 to 19.5) and 5.2 (95% confidence interval, 3.2 to 8), respectively. The
SSRIs. Combined use of SSRIs and NSAIDs or low-dose aspirin increased the risk even further (Dalton
b) Coadministration of ketorolac with psychoactive drugs (such as fluoxetine) has been associated with

3.5.1.D Acenocoumarol

1) Interaction Effect: an increased risk of bleeding

2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and
anticoagulants has been associated with an increased risk of bleeding (Wallerstedt et al, 2009; Schalekamp e
reported have included epistaxis, ecchymosis, hematoma, petechiae, and life-threatening hemorrhages. Alter
coadministration of SSRIs with warfarin (Prod Info ZOLOFT(R) oral tablets, concentrate, 2008). Prothrombin
1997a).

3) Severity: major

4) Onset: delayed

5) Substantiation: probable

6) Clinical Management: When sertraline and an anticoagulant are given concurrently, monitor patient for sig
closely for altered anticoagulant effects, including increased bleeding, when sertraline therapy is initiated or d

7) Probable Mechanism: unknown

8) Literature Reports

a) According to a retrospective cohort study (n=234), there was an increased risk of clinically relevant bl
fibrillation during concomitant SSRI therapy or within 2 weeks following SSRI therapy termination. Patien
with randomly selected patients who received warfarin only (n=117). SSRI included fluoxetine, citalopram
bleeding episodes during 213.9 treatment years in the warfarin plus SSRI group, and 10 patients experie
corresponding total incidences of bleedings were 51.4 and 23.9 per 1000 treatment years, respectively. T
(95% CI; 1.37 to 8.91, p=0.009) compared with warfarin only. The SSRI implicated in patients experienci
addition of an SSRI was not associated with a change in warfarin dose or INR (p=0.48 and p=0.31 respe
patient adherence, and exclusion of clopidogrel, dipyridamol, corticosteroids and anticoagulants other tha

b) A population-based, case-controlled study of new coumarin users (acenocoumarol and phenprocoum
increased risk of hospitalization due to nongastrointestinal bleeding. Using national pharmacy and hospit
for abnormal bleeding and compared them with 5818 control subjects who were also taking a coumarin.
on SSRIs showed greater risk for hospitalization for nongastrointestinal bleeding (adjusted odds ratio (OI
bleeding (adjusted OR 0.8, 95% CI, 0.4 to 1.5) was not significantly different (Schalekamp et al, 2008).

c) Sertraline 50 mg to 200 mg daily for 21 days produced an 8% increase in prothrombin time in subject
given prior to sertraline; this compared with a 1% decrease with placebo. Normalization of the prothromb
findings is unknown (Prod Info ZOLOFT(R) oral tablets, concentrate, 2008).

d) In a non-blinded, randomized, placebo-controlled trial involving 12 healthy volunteers, the effect of se
study, all participants received warfarin 0.75 mg/kg. Beginning on day 11, each volunteer was randomize
mg/day to 200 mg/day. Prothrombin time was measured prior to each dose of warfarin and periodically th
enhanced by sertraline to a clinically significant degree, despite the fact that sertraline was given in a hig

3.5.1.E Alclofenac

1) Interaction Effect: an increased risk of bleeding

2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and
associated with an increased risk of bleeding. Bleeding events have included epistaxis, ecchymosis, hematon
suspension, 2008) (Prod Info Lexapro(TM), 2003; Dalton et al, 2003a; Prod Info CELEXA (R) oral tablet, solu

3) Severity: moderate

4) Onset: unspecified

5) Substantiation: probable

6) Clinical Management: When an SSRI and an NSAID are given concurrently, monitor patient for signs of in

7) Probable Mechanism: unknown

8) Literature Reports

a) SSRIs increase the risk of upper gastrointestinal bleeding and this effect is potentiated by concurrent
were searched among 26,005 users of antidepressant medications and compared with the number of ho
amount of upper GI bleeding episodes was 3.6 times more than expected (95% confidence interval, 2.7 t
12.2 (95% confidence interval, 7.1 to 19.5) and 5.2 (95% confidence interval, 3.2 to 8), respectively. The
SSRIs. Combined use of SSRIs and NSAIDs or low-dose aspirin increased the risk even further (Dalton

b) Coadministration of ketorolac with psychoactive drugs (such as fluoxetine) has been associated with

3.5.1.F Almotriptan

1) Interaction Effect: an increased risk of serotonin syndrome

2) Summary: Concomitant use of almotriptan and selective serotonin reuptake inhibitors (SSRI's) has been r
Concurrent use of a triptan and an SSRI may result in serotonin syndrome which may be life-threatening. Sy
coordination, fast heart beat, rapid changes in blood pressure, increased body temperature, overreactive refl
commonly used intermittently and that either the triptan or the SSRI may be prescribed by a different physicia
combination and monitor them closely for symptoms of serotonin syndrome (US Food and Drug Administratio

3) Severity: major

4) Onset: delayed

5) Substantiation: theoretical
6) Clinical Management: Coadministration of a triptan, such as almotriptan, and an SSRI may result in a life-
used intermittently and that either the triptan or the SSRI may be prescribed by a different physician. If these
monitor closely for symptoms of serotonin syndrome (restlessness, hyperthermia, hyperreflexia, incoordinatic
7) Probable Mechanism: additive pharmacologic effects resulting in excessive serotonergic stimulation
8) Literature Reports
a) Concomitant administration of fluoxetine and almotriptan is well tolerated and fluoxetine has only a m
pharmacokinetics are not significantly affected. A randomized, open-label, two-way crossover study invo
treatments with a minimum 3-week washout between periods: (1) three 20 mg fluoxetine capsules on da
on day 8 with no treatment on days 1 through 7. Peak almotriptan concentrations were 18% higher follov
This difference was statistically significant (p equal 0.023). Mean almotriptan area under the concentratic
treatment groups. Mean half-life was not statistically different between the treatment groups. During fluo
almotriptan may have been increased by fluoxetine. The author concludes that based on the results of th
and fluoxetine can be safely used concomitantly in migraine management (Fleishaker et al, 2001).

3.5.1.G Alprazolam

1) Interaction Effect: an increased risk of psychomotor impairment and sedation
2) Summary: To date, limited information is available related to the effects of coadministered alprazolam and
metabolism (Von Moltke et al, 1994). It is theoretically possible that an interaction might occur because alpra
inhibit one or more P450 isoenzymes (DeVane, 1994). Current evidence indicates that alprazolam is metabol
inhibiting the CYP3A4 isoenzyme. However, a study involving ten healthy volunteers failed to show an alterat
sertraline (Hassan et al, 2000a).
3) Severity: moderate
4) Onset: rapid
5) Substantiation: probable
6) Clinical Management: Caution is warranted if alprazolam and sertraline are to be coadministered. Monitor
may need to be reduced.
7) Probable Mechanism: inhibition of cytochrome P450 3A-mediated alprazolam metabolism
8) Literature Reports
a) Ten healthy white volunteers (eight women and two men) participated in a randomized, double-blind,
potential to impair alprazolam metabolism and to assess whether any potential impairment is dependent
sertraline 50 mg, 100 mg, or 150 mg daily. The alprazolam maximum concentration (Cmax), time to max
were not clinically significantly altered in the presence of sertraline. No pharmacodynamic interactions, a
recall, were detected between sertraline and alprazolam at any dose of sertraline. These in vivo findings
via cytochrome P450 3A4 enzymes (Hassan et al, 2000).

3.5.1.H Amitriptyline

1) Interaction Effect: elevated amitriptyline serum levels or possible serotonin syndrome (hypertension, hype
2) Summary: There is limited evidence suggesting that sertraline may inhibit tricyclic antidepressant (TCA) m
P450 2D6 enzyme activity and may increase the plasma concentrations of coadministered drugs that are me
2002o; Preskorn et al, 1994s; Lydiard et al, 1993i). There have been several reports of serotonin syndrome d
antidepressants, including one case report due to sertraline and amitriptyline coadministration (George & Goo
rare but potentially fatal condition of serotonergic hyperstimulation characterized by changes in mental status
1991k). Further clinical studies or case reports are necessary to determine the incidence and implications of s
3) Severity: major
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: The combined use of tricyclic antidepressants (TCAs) and selective serotonin reupt
serotonin syndrome have also been reported with concurrent TCA and SSRI therapy. Caution should be obse
7) Probable Mechanism: inhibition of amitriptyline metabolism
8) Literature Reports
a) A 40-year old woman was admitted to the hospital after developing symptoms of serotonin syndrome
amitriptyline 75 mg was added to a regimen of sertraline 40 mg twice daily. Other medications at time of
examination, the patient had a fever of 38.0 degrees Celsius, was diaphoretic and showed signs of hype
resolved rapidly (Alderman & Lee, 1996).
b) Desipramine pharmacokinetics were studied in 18 healthy male volunteers. Study subjects received c
mg daily) for 21 days. When sertraline was added to desipramine therapy, the mean maximum concentra
increased by 26%. Trough concentrations of desipramine were close to baseline one week after sertralin
interaction may not be clinically significant (Preskorn et al, 1994r).

3.5.1.I Amoxapine

1) Interaction Effect: modest elevation in amoxapine serum levels or possible serotonin syndrome (hypertens
2) Summary: There is limited evidence suggesting that sertraline may inhibit tricyclic antidepressant (TCA) m
P450 2D6 enzyme activity and may increase the plasma concentrations of coadministered drugs that are me
2002p; Preskorn et al, 1994u; Lydiard et al, 1993j). Effects of the interaction may have little or no clinical impa
were modest compared with those found when fluoxetine (another selective serotonin reuptake inhibitor) was
sertraline therapy for TCA toxicity (dry mouth, urinary retention, CNS depression). Amoxapine doses may nee
3) Severity: major

4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: The combined use of tricyclic antidepressants (TCAs) and selective serotonin reupt serotonin syndrome have also been reported with concurrent TCA and SSRI therapy. Caution should be obs
7) Probable Mechanism: inhibition of amoxapine metabolism
8) Literature Reports
a) The pharmacokinetics of desipramine have been studied in 18 healthy male volunteers. Study subjec sertraline (50 mg daily) for 21 days. When sertraline was added to desipramine therapy, the mean maxi concentration-time curve increased by 26%. Trough concentrations of desipramine were close to baseli were modest and the interaction may not be clinically significant (Preskorn et al, 1994t).

3.5.1.J Anagrelide

1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control an been associated with an increased risk of bleeding. Bleeding events reported have included epistaxis, ecchy tablets, suspension, 2008; Prod Info PROZAC(R) oral capsules, delayed-release capsules, solution, 2008).
3) Severity: major
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When an SSRI and an antiplatelet agent are given concurrently, monitor patient for PROZAC(R) oral capsules, delayed-release capsules, solution, 2008)
7) Probable Mechanism: unknown

3.5.1.K Ancrod

1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control an anticoagulants has been associated with an increased risk of bleeding (Wallerstedt et al, 2009; Schalekamp reported have included epistaxis, ecchymosis, hematoma, petechiae, and life-threatening hemorrhages. Alte coadministration of SSRIs with warfarin (Prod Info ZOLOFT(R) oral tablets, concentrate, 2008). Prothrombin 1997a).
3) Severity: major
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: When sertraline and an anticoagulant are given concurrently, monitor patient for sig closely for altered anticoagulant effects, including increased bleeding, when sertraline therapy is initiated or d
7) Probable Mechanism: unknown
8) Literature Reports
a) According to a retrospective cohort study (n=234), there was an increased risk of clinically relevant bl fibrillation during concomitant SSRI therapy or within 2 weeks following SSRI therapy termination. Patie with randomly selected patients who received warfarin only (n=117). SSRI included fluoxetine, citalopra bleeding episodes during 213.9 treatment years in the warfarin plus SSRI group, and 10 patients experie corresponding total incidences of bleedings were 51.4 and 23.9 per 1000 treatment years, respectively. (95% CI; 1.37 to 8.91, p=0.009) compared with warfarin only. The SSRI implicated in patients experienci addition of an SSRI was not associated with a change in warfarin dose or INR (p=0.48 and p=0.31 respe patient adherence, and exclusion of clopidogrel, dipyridamol, corticosteroids and anticoagulants other th
b) A population-based, case-controlled study of new coumarin users (acenocoumarol and phenprocou increased risk of hospitalization due to nongastrointestinal bleeding. Using national pharmacy and hospi for abnormal bleeding and compared them with 5818 control subjects who were also taking a coumarin. on SSRIs showed greater risk for hospitalization for nongastrointestinal bleeding (adjusted odds ratio (O bleeding (adjusted OR 0.8, 95% CI, 0.4 to 1.5) was not significantly different (Schalekamp et al, 2008).
c) Sertraline 50 mg to 200 mg daily for 21 days produced an 8% increase in prothrombin time in subject given prior to sertraline; this compared with a 1% decrease with placebo. Normalization of the prothromb findings is unknown (Prod Info ZOLOFT(R) oral tablets, concentrate, 2008).
d) In a non-blinded, randomized, placebo-controlled trial involving 12 healthy volunteers, the effect of se study, all participants received warfarin 0.75 mg/kg. Beginning on day 11, each volunteer was randomize mg/day to 200 mg/day. Prothrombin time was measured prior to each dose of warfarin and periodically t enhanced by sertraline to a clinically significant degree, despite the fact that sertraline was given in a hig

3.5.1.L Anisindione

1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control an anticoagulants has been associated with an increased risk of bleeding (Wallerstedt et al, 2009; Schalekamp reported have included epistaxis, ecchymosis, hematoma, petechiae, and life-threatening hemorrhages. Alte coadministration of SSRIs with warfarin (Prod Info ZOLOFT(R) oral tablets, concentrate, 2008). Prothrombin 1997a).
3) Severity: major
4) Onset: delayed
5) Substantiation: probable

6) Clinical Management: When sertraline and an anticoagulant are given concurrently, monitor patient for sig closely for altered anticoagulant effects, including increased bleeding, when sertraline therapy is initiated or d
7) Probable Mechanism: unknown
8) Literature Reports
a) According to a retrospective cohort study (n=234), there was an increased risk of clinically relevant bl fibrillation during concomitant SSRI therapy or within 2 weeks following SSRI therapy termination. Patien with randomly selected patients who received warfarin only (n=117). SSRI included fluoxetine, citalopran bleeding episodes during 213.9 treatment years in the warfarin plus SSRI group, and 10 patients experie corresponding total incidences of bleedings were 51.4 and 23.9 per 1000 treatment years, respectively. T (95% CI; 1.37 to 8.91, p=0.009) compared with warfarin only. The SSRI implicated in patients experienci addition of an SSRI was not associated with a change in warfarin dose or INR (p=0.48 and p=0.31 respe patient adherence, and exclusion of clopidogrel, dipyridamol, corticosteroids and anticoagulants other th
b) A population-based, case-controlled study of new coumarin users (acenocoumarol and phenprocoum increased risk of hospitalization due to nongastrointestinal bleeding. Using national pharmacy and hospit for abnormal bleeding and compared them with 5818 control subjects who were also taking a coumarin. on SSRIs showed greater risk for hospitalization for nongastrointestinal bleeding (adjusted odds ratio (O bleeding (adjusted OR 0.8, 95% CI, 0.4 to 1.5) was not significantly different (Schalekamp et al, 2008).
c) Sertraline 50 mg to 200 mg daily for 21 days produced an 8% increase in prothrombin time in subject given prior to sertraline; this compared with a 1% decrease with placebo. Normalization of the prothromb findings is unknown (Prod Info ZOLOFT(R) oral tablets, concentrate, 2008).
d) In a non-blinded, randomized, placebo-controlled trial involving 12 healthy volunteers, the effect of se study, all participants received warfarin 0.75 mg/kg. Beginning on day 11, each volunteer was randomize mg/day to 200 mg/day. Prothrombin time was measured prior to each dose of warfarin and periodically th enhanced by sertraline to a clinically significant degree, despite the fact that sertraline was given in a hig

3.5.1.M Antithrombin III Human

1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and anticoagulants has been associated with an increased risk of bleeding (Wallerstedt et al, 2009; Schalekamp reported have included epistaxis, ecchymosis, hematoma, petechiae, and life-threatening hemorrhages. Alter coadministration of SSRIs with warfarin (Prod Info ZOLOFT(R) oral tablets, concentrate, 2008). Prothrombin 1997a).
3) Severity: major
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: When sertraline and an anticoagulant are given concurrently, monitor patient for sig closely for altered anticoagulant effects, including increased bleeding, when sertraline therapy is initiated or d
7) Probable Mechanism: unknown
8) Literature Reports
a) According to a retrospective cohort study (n=234), there was an increased risk of clinically relevant bl fibrillation during concomitant SSRI therapy or within 2 weeks following SSRI therapy termination. Patien with randomly selected patients who received warfarin only (n=117). SSRI included fluoxetine, citalopran bleeding episodes during 213.9 treatment years in the warfarin plus SSRI group, and 10 patients experie corresponding total incidences of bleedings were 51.4 and 23.9 per 1000 treatment years, respectively. T (95% CI; 1.37 to 8.91, p=0.009) compared with warfarin only. The SSRI implicated in patients experienci addition of an SSRI was not associated with a change in warfarin dose or INR (p=0.48 and p=0.31 respe patient adherence, and exclusion of clopidogrel, dipyridamol, corticosteroids and anticoagulants other th
b) A population-based, case-controlled study of new coumarin users (acenocoumarol and phenprocoum increased risk of hospitalization due to nongastrointestinal bleeding. Using national pharmacy and hospit for abnormal bleeding and compared them with 5818 control subjects who were also taking a coumarin. on SSRIs showed greater risk for hospitalization for nongastrointestinal bleeding (adjusted odds ratio (O bleeding (adjusted OR 0.8, 95% CI, 0.4 to 1.5) was not significantly different (Schalekamp et al, 2008).
c) Sertraline 50 mg to 200 mg daily for 21 days produced an 8% increase in prothrombin time in subject given prior to sertraline; this compared with a 1% decrease with placebo. Normalization of the prothromb findings is unknown (Prod Info ZOLOFT(R) oral tablets, concentrate, 2008).
d) In a non-blinded, randomized, placebo-controlled trial involving 12 healthy volunteers, the effect of se study, all participants received warfarin 0.75 mg/kg. Beginning on day 11, each volunteer was randomize mg/day to 200 mg/day. Prothrombin time was measured prior to each dose of warfarin and periodically th enhanced by sertraline to a clinically significant degree, despite the fact that sertraline was given in a hig

3.5.1.N Ardeparin

1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and anticoagulants has been associated with an increased risk of bleeding (Wallerstedt et al, 2009; Schalekamp reported have included epistaxis, ecchymosis, hematoma, petechiae, and life-threatening hemorrhages. Alter coadministration of SSRIs with warfarin (Prod Info ZOLOFT(R) oral tablets, concentrate, 2008). Prothrombin 1997a).
3) Severity: major

4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: When sertraline and an anticoagulant are given concurrently, monitor patient for sig closely for altered anticoagulant effects, including increased bleeding, when sertraline therapy is initiated or d
7) Probable Mechanism: unknown
8) Literature Reports
a) According to a retrospective cohort study (n=234), there was an increased risk of clinically relevant bl fibrillation during concomitant SSRI therapy or within 2 weeks following SSRI therapy termination. Patien with randomly selected patients who received warfarin only (n=117). SSRI included fluoxetine, citalopram bleeding episodes during 213.9 treatment years in the warfarin plus SSRI group, and 10 patients experie corresponding total incidences of bleedings were 51.4 and 23.9 per 1000 treatment years, respectively. (95% CI; 1.37 to 8.91, p=0.009) compared with warfarin only. The SSRI implicated in patients experienci addition of an SSRI was not associated with a change in warfarin dose or INR (p=0.48 and p=0.31 respe patient adherence, and exclusion of clopidogrel, dipyridamol, corticosteroids and anticoagulants other th
b) A population-based, case-controlled study of new coumarin users (acenocoumarol and phenprocoum increased risk of hospitalization due to nongastrointestinal bleeding. Using national pharmacy and hospit for abnormal bleeding and compared them with 5818 control subjects who were also taking a coumarin. on SSRIs showed greater risk for hospitalization for nongastrointestinal bleeding (adjusted odds ratio (O bleeding (adjusted OR 0.8, 95% CI, 0.4 to 1.5) was not significantly different (Schalekamp et al, 2008).
c) Sertraline 50 mg to 200 mg daily for 21 days produced an 8% increase in prothrombin time in subject given prior to sertraline; this compared with a 1% decrease with placebo. Normalization of the prothromb findings is unknown (Prod Info ZOLOFT(R) oral tablets, concentrate, 2008).
d) In a non-blinded, randomized, placebo-controlled trial involving 12 healthy volunteers, the effect of se study, all participants received warfarin 0.75 mg/kg. Beginning on day 11, each volunteer was randomize mg/day to 200 mg/day. Prothrombin time was measured prior to each dose of warfarin and periodically th enhanced by sertraline to a clinically significant degree, despite the fact that sertraline was given in a hig

3.5.1.O Aspirin
1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and been associated with an increased risk of bleeding. Bleeding events reported have included epistaxis, ecchy tablets, suspension, 2008; Prod Info PROZAC(R) oral capsules, delayed-release capsules, solution, 2008).
3) Severity: major
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When an SSRI and an antiplatelet agent are given concurrently, monitor patient for PROZAC(R) oral capsules, delayed-release capsules, solution, 2008)
7) Probable Mechanism: unknown

3.5.1.P Astemizole
1) Interaction Effect: cardiotoxicity (QT interval prolongation, torsades de pointes, cardiac arrest)
2) Summary: Coadministered sertraline may inhibit astemizole metabolism, thereby leading to increased ast administration of astemizole and sertraline should be avoided (Prod Info Hismanal(R), 1998).
3) Severity: major
4) Onset: rapid
5) Substantiation: probable
6) Clinical Management: Concomitant use of astemizole and sertraline is not recommended.
7) Probable Mechanism: inhibition of cytochrome P450-mediated metabolism of astemizole

3.5.1.Q Benoxaprofen
1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and associated with an increased risk of bleeding. Bleeding events have included epistaxis, ecchymosis, hematom suspension, 2008) (Prod Info Lexapro(TM), 2003; Dalton et al, 2003a; Prod Info CELEXA (R) oral tablet, solu
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When an SSRI and an NSAID are given concurrently, monitor patient for signs of in
7) Probable Mechanism: unknown
8) Literature Reports
a) SSRIs increase the risk of upper gastrointestinal bleeding and this effect is potentiated by concurrent were searched among 26,005 users of antidepressant medications and compared with the number of ho amount of upper GI bleeding episodes was 3.6 times more than expected (95% confidence interval, 2.7 12.2 (95% confidence interval, 7.1 to 19.5) and 5.2 (95% confidence interval, 3.2 to 8), respectively. The SSRIs. Combined use of SSRIs and NSAIDs or low-dose aspirin increased the risk even further (Dalton
b) Coadministration of ketorolac with psychoactive drugs (such as fluoxetine) has been associated with

3.5.1.R Bivalirudin

1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and anticoagulants has been associated with an increased risk of bleeding (Wallerstedt et al, 2009; Schalekamp reported have included epistaxis, ecchymosis, hematoma, petechiae, and life-threatening hemorrhages. Alter coadministration of SSRIs with warfarin (Prod Info ZOLOFT(R) oral tablets, concentrate, 2008). Prothrombin 1997a).
3) Severity: major
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: When sertraline and an anticoagulant are given concurrently, monitor patient for sig closely for altered anticoagulant effects, including increased bleeding, when sertraline therapy is initiated or d
7) Probable Mechanism: unknown
8) Literature Reports
a) According to a retrospective cohort study (n=234), there was an increased risk of clinically relevant bl fibrillation during concomitant SSRI therapy or within 2 weeks following SSRI therapy termination. Patien with randomly selected patients who received warfarin only (n=117). SSRI included fluoxetine, citalopram bleeding episodes during 213.9 treatment years in the warfarin plus SSRI group, and 10 patients experie corresponding total incidences of bleedings were 51.4 and 23.9 per 1000 treatment years, respectively. (95% CI; 1.37 to 8.91, p=0.009) compared with warfarin only. The SSRI implicated in patients experienci addition of an SSRI was not associated with a change in warfarin dose or INR (p=0.48 and p=0.31 respe patient adherence, and exclusion of clopidogrel, dipyridamol, corticosteroids and anticoagulants other th
b) A population-based, case-controlled study of new coumarin users (acenocoumarol and phenprocoum increased risk of hospitalization due to nongastrointestinal bleeding. Using national pharmacy and hospit for abnormal bleeding and compared them with 5818 control subjects who were also taking a coumarin. on SSRIs showed greater risk for hospitalization for nongastrointestinal bleeding (adjusted odds ratio (O bleeding (adjusted OR 0.8, 95% CI, 0.4 to 1.5) was not significantly different (Schalekamp et al, 2008).
c) Sertraline 50 mg to 200 mg daily for 21 days produced an 8% increase in prothrombin time in subject given prior to sertraline; this compared with a 1% decrease with placebo. Normalization of the prothromb findings is unknown (Prod Info ZOLOFT(R) oral tablets, concentrate, 2008).
d) In a non-blinded, randomized, placebo-controlled trial involving 12 healthy volunteers, the effect of se study, all participants received warfarin 0.75 mg/kg. Beginning on day 11, each volunteer was randomize mg/day to 200 mg/day. Prothrombin time was measured prior to each dose of warfarin and periodically t enhanced by sertraline to a clinically significant degree, despite the fact that sertraline was given in a hig

3.5.1.S Bromfenac

1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and associated with an increased risk of bleeding. Bleeding events have included epistaxis, ecchymosis, hemator suspension, 2008) (Prod Info Lexapro(TM), 2003; Dalton et al, 2003a; Prod Info CELEXA (R) oral tablet, solu
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When an SSRI and an NSAID are given concurrently, monitor patient for signs of in
7) Probable Mechanism: unknown
8) Literature Reports
a) SSRIs increase the risk of upper gastrointestinal bleeding and this effect is potentiated by concurrent were searched among 26,005 users of antidepressant medications and compared with the number of ho amount of upper GI bleeding episodes was 3.6 times more than expected (95% confidence interval, 2.7 12.2 (95% confidence interval, 7.1 to 19.5) and 5.2 (95% confidence interval, 3.2 to 8), respectively. The SSRIs. Combined use of SSRIs and NSAIDs or low-dose aspirin increased the risk even further (Dalton
b) Coadministration of ketorolac with psychoactive drugs (such as fluoxetine) has been associated with

3.5.1.T Bufexamac

1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and associated with an increased risk of bleeding. Bleeding events have included epistaxis, ecchymosis, hemator suspension, 2008) (Prod Info Lexapro(TM), 2003; Dalton et al, 2003a; Prod Info CELEXA (R) oral tablet, solu
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When an SSRI and an NSAID are given concurrently, monitor patient for signs of in
7) Probable Mechanism: unknown
8) Literature Reports
a) SSRIs increase the risk of upper gastrointestinal bleeding and this effect is potentiated by concurrent were searched among 26,005 users of antidepressant medications and compared with the number of ho amount of upper GI bleeding episodes was 3.6 times more than expected (95% confidence interval, 2.7 12.2 (95% confidence interval, 7.1 to 19.5) and 5.2 (95% confidence interval, 3.2 to 8), respectively. The SSRIs. Combined use of SSRIs and NSAIDs or low-dose aspirin increased the risk even further (Dalton

b) Coadministration of ketorolac with psychoactive drugs (such as fluoxetine) has been associated with

3.5.1.U Bupropion

1) Interaction Effect: increased plasma levels of sertraline

2) Summary: It is recommended that sertraline, an antidepressant metabolized by the cytochrome P450 2D6 concomitantly with bupropion (Prod Info Wellbutrin XL(TM), 2003; Prod Info Zyban(R), 2000).

3) Severity: moderate

4) Onset: delayed

5) Substantiation: probable

6) Clinical Management: Coadministration of bupropion and sertraline should be approached with caution an to the treatment regimen of a patient already receiving sertraline, consider decreasing the dose of sertraline.

7) Probable Mechanism: inhibition of cytochrome P450 2D6-mediated sertraline metabolism

3.5.1.V Cannabis

1) Interaction Effect: manic symptoms

2) Summary: One case of mania following use of marijuana with fluoxetine therapy has been reported (Stoll symptoms could have resulted from the fluoxetine or marijuana alone. Caution is advised for patients using m

3) Severity: moderate

4) Onset: rapid

5) Substantiation: theoretical

6) Clinical Management: Caution patients taking selective serotonin reuptake inhibitors to avoid concomitant

7) Probable Mechanism: additive serotonergic stimulation

8) Literature Reports

a) A 21-year-old female presented with mania, agitation, and grandiose delusions following use of mariju reported smoking 2 "joints" during a 36-hour period. Over the next 24 hours, she developed increased en perphenazine were given for agitation and excitement which gradually resolved over 4 days. She remain prior to discharge. One week after discharge, she discontinued fluoxetine due to insomnia and feeling "h rapid switch to mania after smoking marijuana with fluoxetine, the manic symptoms were associated with from either fluoxetine or marijuana alone (Stoll et al, 1991).

3.5.1.W Carbamazepine

1) Interaction Effect: an increased risk of carbamazepine toxicity (ataxia, nystagmus, diplopia, headache, vo

2) Summary: Coadministration of sertraline and carbamazepine may cause reduced carbamazepine clearan possibly blood dyscrasias (Joblin & Ghose, 1994a). Similar interactions have been reported between carbam fluvoxamine (Pearson, 1990; Fritze et al, 1991). However, in two separate in vivo studies, coadministration of concentrations of carbamazepine (Prod Info Zoloft(R), 2002j). Two case reports of coadministration of carbar sertraline (Khan et al, 2000).

3) Severity: moderate

4) Onset: delayed

5) Substantiation: probable

6) Clinical Management: Due to the potential for elevated carbamazepine levels, patients should be closely f Consider measuring carbamazepine serum concentrations within two to three weeks of adding or discontinui metabolism of sertraline, sertraline levels may be lower than expected, which may result in lack of efficacy of

7) Probable Mechanism: inhibition of carbamazepine metabolism, increase in sertraline CYP3A4-mediated m

8) Literature Reports

a) A 24-year-old woman received maintenance carbamazepine 600 mg daily and flecainide 100 mg dail increased from 4.7 to 8.5 mg/L (normal range, 4 to 10 mg/L), and her blood counts were normal. Two mo white blood cell counts were abnormally low. Postoperatively her blood counts remained low, despite blo had missed one or more doses. On bone marrow examination, erythroid hyperplasia with megaloblastic counts began to improve five days after withdrawal of sertraline and carbamazepine; she was not rechall to inhibition of cytochrome P450 isoenzymes and carbamazepine protein binding displacement (Joblin &

b) Sertraline is suspected of inhibiting cytochrome P450IIIA4 (CYP3A4) enzyme activity (DeVane, 1994 have a potentially significant interaction with sertraline. Conversely, carbamazepine is also a known pote decreased sertraline concentrations (Spina et al, 1996).

c) Two cases have been reported in which concomitant use of sertraline and carbamazepine resulted in schizoaffective disorder who had been successfully treated with haloperidol and carbamazepine for 3 ye mg/day. A plasma level for carbamazepine and sertraline was obtained after sertraline initiation. Sertralin male diagnosed with posttraumatic stress disorder who had been successfully treated with carbamazepi disorder. Plasma levels were obtained for sertraline and carbamazepine during therapy. Sertraline levels mg/day (Kahn et al, 2000).

3.5.1.X Carprofen

1) Interaction Effect: an increased risk of bleeding

2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and associated with an increased risk of bleeding. Bleeding events have included epistaxis, ecchymosis, hemator suspension, 2008) (Prod Info Lexapro(TM), 2003; Dalton et al, 2003a; Prod Info CELEXA (R) oral tablet, solu

3) Severity: moderate

4) Onset: unspecified

5) Substantiation: probable
6) Clinical Management: When an SSRI and an NSAID are given concurrently, monitor patient for signs of in
7) Probable Mechanism: unknown
8) Literature Reports
a) SSRIs increase the risk of upper gastrointestinal bleeding and this effect is potentiated by concurrent were searched among 26,005 users of antidepressant medications and compared with the number of ho amount of upper GI bleeding episodes was 3.6 times more than expected (95% confidence interval, 2.7 t 12.2 (95% confidence interval, 7.1 to 19.5) and 5.2 (95% confidence interval, 3.2 to 8), respectively. The SSRIs. Combined use of SSRIs and NSAIDs or low-dose aspirin increased the risk even further (Dalton
b) Coadministration of ketorolac with psychoactive drugs (such as fluoxetine) has been associated with

3.5.1.Y Celecoxib
1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and associated with an increased risk of bleeding. Bleeding events have included epistaxis, ecchymosis, hemator suspension, 2008) (Prod Info Lexapro(TM), 2003; Dalton et al, 2003a; Prod Info CELEXA (R) oral tablet, solu
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When an SSRI and an NSAID are given concurrently, monitor patient for signs of in
7) Probable Mechanism: unknown
8) Literature Reports
a) SSRIs increase the risk of upper gastrointestinal bleeding and this effect is potentiated by concurrent were searched among 26,005 users of antidepressant medications and compared with the number of ho amount of upper GI bleeding episodes was 3.6 times more than expected (95% confidence interval, 2.7 t 12.2 (95% confidence interval, 7.1 to 19.5) and 5.2 (95% confidence interval, 3.2 to 8), respectively. The SSRIs. Combined use of SSRIs and NSAIDs or low-dose aspirin increased the risk even further (Dalton
b) Coadministration of ketorolac with psychoactive drugs (such as fluoxetine) has been associated with

3.5.1.Z Certoparin
1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and anticoagulants has been associated with an increased risk of bleeding (Wallerstedt et al, 2009; Schalekamp e reported have included epistaxis, ecchymosis, hematoma, petechiae, and life-threatening hemorrhages. Alter coadministration of SSRIs with warfarin (Prod Info ZOLOFT(R) oral tablets, concentrate, 2008). Prothrombin 1997a).
3) Severity: major
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: When sertraline and an anticoagulant are given concurrently, monitor patient for sig closely for altered anticoagulant effects, including increased bleeding, when sertraline therapy is initiated or d
7) Probable Mechanism: unknown
8) Literature Reports
a) According to a retrospective cohort study (n=234), there was an increased risk of clinically relevant bl fibrillation during concomitant SSRI therapy or within 2 weeks following SSRI therapy termination. Patien with randomly selected patients who received warfarin only (n=117). SSRI included fluoxetine, citalopram bleeding episodes during 213.9 treatment years in the warfarin plus SSRI group, and 10 patients experie corresponding total incidences of bleedings were 51.4 and 23.9 per 1000 treatment years, respectively. T (95% CI; 1.37 to 8.91, p=0.009) compared with warfarin only. The SSRI implicated in patients experienci addition of an SSRI was not associated with a change in warfarin dose or INR (p=0.48 and p=0.31 respe patient adherence, and exclusion of clopidogrel, dipyridamol, corticosteroids and anticoagulants other th
b) A population-based, case-controlled study of new coumarin users (acenocoumarol and phenprocoum increased risk of hospitalization due to nongastrointestinal bleeding. Using national pharmacy and hospit for abnormal bleeding and compared them with 5818 control subjects who were also taking a coumarin. on SSRIs showed greater risk for hospitalization for nongastrointestinal bleeding (adjusted odds ratio (OI bleeding (adjusted OR 0.8, 95% CI, 0.4 to 1.5) was not significantly different (Schalekamp et al, 2008).
c) Sertraline 50 mg to 200 mg daily for 21 days produced an 8% increase in prothrombin time in subject given prior to sertraline; this compared with a 1% decrease with placebo. Normalization of the prothromb findings is unknown (Prod Info ZOLOFT(R) oral tablets, concentrate, 2008).
d) In a non-blinded, randomized, placebo-controlled trial involving 12 healthy volunteers, the effect of se study, all participants received warfarin 0.75 mg/kg. Beginning on day 11, each volunteer was randomize mg/day to 200 mg/day. Prothrombin time was measured prior to each dose of warfarin and periodically tl enhanced by sertraline to a clinically significant degree, despite the fact that sertraline was given in a hig

3.5.1.AA Cilostazol
1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and been associated with an increased risk of bleeding. Bleeding events reported have included epistaxis, ecchyr

tablets, suspension, 2008; Prod Info PROZAC(R) oral capsules, delayed-release capsules, solution, 2008).
3) Severity: major
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When an SSRI and an antiplatelet agent are given concurrently, monitor patient for
PROZAC(R) oral capsules, delayed-release capsules, solution, 2008)
7) Probable Mechanism: unknown

3.5.1.AB Cimetidine
1) Interaction Effect: elevated sertraline serum concentrations and increased risk of adverse side effects
2) Summary: Coadministration of cimetidine with sertraline may result in inhibition of sertraline metabolism, l
clinical significance of this effect is as yet undefined. Adjustments in sertraline doses may be required when c
3) Severity: moderate
4) Onset: rapid
5) Substantiation: probable
6) Clinical Management: Closely follow patients for signs of sertraline toxicity (nausea, diarrhea, tremor, dizz
cimetidine.
7) Probable Mechanism: inhibited cytochrome P450 metabolism of sertraline
8) Literature Reports
a) When sertraline 100 mg was given on the second day of an 8-day regimen of cimetidine 800 mg daily
curve (AUC), a 24% in the maximum concentration (Cmax), and a 26% increased in the half-life as comp
interaction is unknown.

3.5.1.AC Clomipramine
1) Interaction Effect: modest elevations of clomipramine serum levels or possible serotonin syndrome (hyper
2) Summary: There is limited evidence suggesting that sertraline may inhibit tricyclic antidepressant (TCA) m
P450 2D6 enzyme activity and may increase the plasma concentrations of coadministered drugs that are me
2002h; Preskorn et al, 1994k; Lydiard et al, 1993e). Effects of the interaction may have little or no clinical imp
were modest compared with those found when fluoxetine (another selective serotonin reuptake inhibitor) was
sertraline therapy for TCA toxicity (dry mouth, urinary retention, CNS depression). Clomipramine doses may
3) Severity: major
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: The combined use of tricyclic antidepressants (TCAs) and selective serotonin reupt
serotonin syndrome have also been reported with concurrent TCA and SSRI therapy. Caution should be obse
7) Probable Mechanism: inhibition of clomipramine metabolism
8) Literature Reports
a) The pharmacokinetics of desipramine were studied in 18 healthy male volunteers. Study subjects rec
sertraline (50 mg daily) for 21 days. When sertraline was added to desipramine therapy, the mean maxin
concentration-time curve increased by 26%. Trough concentrations of desipramine were close to baselin
were modest and the interaction may not be clinically significant (Preskorn et al, 1994j).

3.5.1.AD Clonixin
1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and
associated with an increased risk of bleeding. Bleeding events have included epistaxis, ecchymosis, hemator
suspension, 2008) (Prod Info Lexapro(TM), 2003; Dalton et al, 2003a; Prod Info CELEXA (R) oral tablet, solu
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When an SSRI and an NSAID are given concurrently, monitor patient for signs of in
7) Probable Mechanism: unknown
8) Literature Reports
a) SSRIs increase the risk of upper gastrointestinal bleeding and this effect is potentiated by concurrent
were searched among 26,005 users of antidepressant medications and compared with the number of ho
amount of upper GI bleeding episodes was 3.6 times more than expected (95% confidence interval, 2.7 t
12.2 (95% confidence interval, 7.1 to 19.5) and 5.2 (95% confidence interval, 3.2 to 8), respectively. The
SSRIs. Combined use of SSRIs and NSAIDs or low-dose aspirin increased the risk even further (Dalton
b) Coadministration of ketorolac with psychoactive drugs (such as fluoxetine) has been associated with

3.5.1.AE Clopidogrel
1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and
been associated with an increased risk of bleeding. Bleeding events reported have included epistaxis, ecchyr
tablets, suspension, 2008; Prod Info PROZAC(R) oral capsules, delayed-release capsules, solution, 2008).
3) Severity: major
4) Onset: unspecified
5) Substantiation: probable

6) Clinical Management: When an SSRI and an antiplatelet agent are given concurrently, monitor patient for
PROZAC(R) oral capsules, delayed-release capsules, solution, 2008)
7) Probable Mechanism: unknown

3.5.1.AF Clorgyline

1) Interaction Effect: CNS toxicity or serotonin syndrome (hypertension, hyperthermia, myoclonus, mental sta
2) Summary: Concurrent administration or overlapping therapy with sertraline and a monoamine oxidase (MA
characterized by symptoms such as restlessness, myoclonus, changes in mental status, hyperreflexia, diaph
Zoloft(R), 2002g; Lappin & Auchincloss, 1994e; Graber et al, 1994e; Bhatara & Bandettini, 1993b; Suchowers
3) Severity: contraindicated
4) Onset: rapid
5) Substantiation: probable
6) Clinical Management: Concurrent use of sertraline and a MAO inhibitor is contraindicated. Wait at least 14
least 14 days after discontinuing sertraline before initiating therapy with a MAO inhibitor.
7) Probable Mechanism: inhibition of serotonin metabolism by monoamine oxidase
8) Literature Reports

a) Concomitant use of serotonin specific reuptake inhibitors and monoamine oxidase inhibitors can prod
syndrome is a condition of serotonergic hyperstimulation and manifests as restlessness, myoclonus, cha
not recognized and correctly treated, death can result.

b) A 26-year old woman who had been taking isocarboxazid for eight weeks stopped taking the drug for
the patient became restless and developed leg twitches. The patients was later admitted to the emergen
disturbances. The patient did not improve after treatment with diazepam and propranolol. The patient wa
in symptoms after the second dose (Lappin & Auchincloss, 1994d).

c) A drug interaction was reported in a 61-year old woman in which sertraline 100 mg twice daily was ac
taking the first sertraline dose, the patient was found in a semicomatose state, with elevated body tempe
mmHg. After transportation to the hospital, the patient was misdiagnosed as having neuroleptic malignar
between sertraline and phenelzine. The authors suggest that MAO inhibitor therapy should be discontinu
inhibitor (SSRI) and that before starting a MAOI, SSRI therapy should be discontinued for at least 5 half-

d) Two cases reports suggested a possible interaction between fluoxetine and selegiline (Suchowersky
approximately one month after adding selegiline to fluoxetine therapy. The patient improved 2 months af
involved diaphoresis, vasoconstriction, and cyanosis of the hands which occurred in close temporal relat
quick resolution of symptoms. Rechallenge with fluoxetine alone occurred without incident.

3.5.1.AG Clozapine

1) Interaction Effect: an increased risk of clozapine toxicity (sedation, seizures, hypotension)
2) Summary: Coadministration of clozapine with sertraline has been reported to result in increased clozapine
Chong et al, 1997a; Centorrino et al, 1996a). Clozapine is metabolized by the cytochrome P450 2D6 isoenzy
addition to being metabolized by CYP2D6 itself (Prod Info Zoloft(R), 1999g; DeVane, 1994e). Cytochrome P4
CYP3A4 (Chong & Remington, 1998).
3) Severity: moderate
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: Monitor the therapeutic efficacy of clozapine and for any evidence of toxicity, partic
dosage may be required in some clinical situations.
7) Probable Mechanism: decreased clozapine metabolism
8) Literature Reports

a) Two case reports revealed the exacerbation of psychotic symptoms with the addition of a selective se
schizophrenia, had been taking clozapine 175 mg per day. Other medications included propranolol for ta
symptoms but continued compulsive behavior, sertraline 50 mg per day was added. Within four weeks, t
clozapine concentrations increased from 325 ng/mL before sertraline therapy to 695 ng/mL after sertralir
of clozapine 500 mg per day which was later increased to 600 mg per day. After fluvoxamine 50 mg per
ng/mL before fluvoxamine treatment to 2750 ng/mL after 28 days of fluvoxamine treatment. During this ti
worsened. The authors postulated that the worsening of psychotic symptoms could be due to SSRI inhib
serotonergic and dopaminergic blockade caused by coadministration of the two drugs (Chong et al, 1997

b) A study evaluated the serum concentrations of clozapine and norclozapine, the major metabolite, wh
paroxetine, and sertraline. Eighty outpatients receiving clozapine all had been diagnosed with schizophre
combination with clozapine. Of these 40 patients, 14 were receiving fluoxetine, 10 were receiving sertrali
serum concentrations of clozapine and norclozapine were 41.1% and 44.8% higher, respectively, than in
norclozapine concentration to dose was also 37.7% higher in patients receiving SSRIs, indicating clozap
study groups were too limited for an accurate statistical comparison between the individual SSRIs (Cento

3.5.1.AH Dalteparin

1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and
anticoagulants has been associated with an increased risk of bleeding (Wallerstedt et al, 2009; Schalekamp
reported have included epistaxis, ecchymosis, hematoma, petechiae, and life-threatening hemorrhages. Alter
coadministration of SSRIs with warfarin (Prod Info ZOLOFT(R) oral tablets, concentrate, 2008). Prothrombin
1997a).

3) Severity: major
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: When sertraline and an anticoagulant are given concurrently, monitor patient for sig closely for altered anticoagulant effects, including increased bleeding, when sertraline therapy is initiated or d
7) Probable Mechanism: unknown
8) Literature Reports
a) According to a retrospective cohort study (n=234), there was an increased risk of clinically relevant bl fibrillation during concomitant SSRI therapy or within 2 weeks following SSRI therapy termination. Patien with randomly selected patients who received warfarin only (n=117). SSRI included fluoxetine, citalopram bleeding episodes during 213.9 treatment years in the warfarin plus SSRI group, and 10 patients experie corresponding total incidences of bleedings were 51.4 and 23.9 per 1000 treatment years, respectively. T (95% CI; 1.37 to 8.91, p=0.009) compared with warfarin only. The SSRI implicated in patients experienci addition of an SSRI was not associated with a change in warfarin dose or INR (p=0.48 and p=0.31 respe patient adherence, and exclusion of clopidogrel, dipyridamol, corticosteroids and anticoagulants other th
b) A population-based, case-controlled study of new coumarin users (acenocoumarol and phenprocoum increased risk of hospitalization due to nongastrointestinal bleeding. Using national pharmacy and hospit for abnormal bleeding and compared them with 5818 control subjects who were also taking a coumarin. on SSRIs showed greater risk for hospitalization for nongastrointestinal bleeding (adjusted odds ratio (O bleeding (adjusted OR 0.8, 95% CI, 0.4 to 1.5) was not significantly different (Schalekamp et al, 2008).
c) Sertraline 50 mg to 200 mg daily for 21 days produced an 8% increase in prothrombin time in subject given prior to sertraline; this compared with a 1% decrease with placebo. Normalization of the prothromb findings is unknown (Prod Info ZOLOFT(R) oral tablets, concentrate, 2008).
d) In a non-blinded, randomized, placebo-controlled trial involving 12 healthy volunteers, the effect of se study, all participants received warfarin 0.75 mg/kg. Beginning on day 11, each volunteer was randomize mg/day to 200 mg/day. Prothrombin time was measured prior to each dose of warfarin and periodically th enhanced by sertraline to a clinically significant degree, despite the fact that sertraline was given in a hig

3.5.1.AI Danaparoid

1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and anticoagulants has been associated with an increased risk of bleeding (Wallerstedt et al, 2009; Schalekamp reported have included epistaxis, ecchymosis, hematoma, petechiae, and life-threatening hemorrhages. Alter coadministration of SSRIs with warfarin (Prod Info ZOLOFT(R) oral tablets, concentrate, 2008). Prothrombin 1997a).
3) Severity: major
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: When sertraline and an anticoagulant are given concurrently, monitor patient for sig closely for altered anticoagulant effects, including increased bleeding, when sertraline therapy is initiated or d
7) Probable Mechanism: unknown
8) Literature Reports
a) According to a retrospective cohort study (n=234), there was an increased risk of clinically relevant bl fibrillation during concomitant SSRI therapy or within 2 weeks following SSRI therapy termination. Patien with randomly selected patients who received warfarin only (n=117). SSRI included fluoxetine, citalopram bleeding episodes during 213.9 treatment years in the warfarin plus SSRI group, and 10 patients experie corresponding total incidences of bleedings were 51.4 and 23.9 per 1000 treatment years, respectively. T (95% CI; 1.37 to 8.91, p=0.009) compared with warfarin only. The SSRI implicated in patients experienci addition of an SSRI was not associated with a change in warfarin dose or INR (p=0.48 and p=0.31 respe patient adherence, and exclusion of clopidogrel, dipyridamol, corticosteroids and anticoagulants other th
b) A population-based, case-controlled study of new coumarin users (acenocoumarol and phenprocoum increased risk of hospitalization due to nongastrointestinal bleeding. Using national pharmacy and hospit for abnormal bleeding and compared them with 5818 control subjects who were also taking a coumarin. on SSRIs showed greater risk for hospitalization for nongastrointestinal bleeding (adjusted odds ratio (O bleeding (adjusted OR 0.8, 95% CI, 0.4 to 1.5) was not significantly different (Schalekamp et al, 2008).
c) Sertraline 50 mg to 200 mg daily for 21 days produced an 8% increase in prothrombin time in subject given prior to sertraline; this compared with a 1% decrease with placebo. Normalization of the prothromb findings is unknown (Prod Info ZOLOFT(R) oral tablets, concentrate, 2008).
d) In a non-blinded, randomized, placebo-controlled trial involving 12 healthy volunteers, the effect of se study, all participants received warfarin 0.75 mg/kg. Beginning on day 11, each volunteer was randomize mg/day to 200 mg/day. Prothrombin time was measured prior to each dose of warfarin and periodically th enhanced by sertraline to a clinically significant degree, despite the fact that sertraline was given in a hig

3.5.1.AJ Darunavir

1) Interaction Effect: decreased sertraline exposure and plasma concentrations
2) Summary: Coadministration of darunavir/ritonavir with sertraline has resulted in significantly decreased se sertraline dose should be carefully titrated based on clinical response. When darunavir/ritonavir is initiated in sertraline (Prod Info PREZISTA(TM) oral tablets, 2006).

3) Severity: moderate
4) Onset: unspecified
5) Substantiation: established
6) Clinical Management: Concurrent administration of sertraline with darunavir/ritonavir significantly decreas carefully titrate the sertraline dose based on clinical response. When darunavir/ritonavir is initiated in patients
7) Probable Mechanism: unknown
8) Literature Reports
a) In a pharmacokinetics study, concurrent administration of sertraline and darunavir/ritonavir significant administered sertraline 50 mg orally once daily concurrently with darunavir 400 mg/ritonavir 100 mg orall mean ratio % 0.56; 90% confidence interval (CI), 0.49 to 0.63), a 49% decreased in sertraline AUC (LS r mean ratio % 0.51; 90% CI, 0.45 to 0.57). Darunavir pharmacokinetics were not significantly altered (Pro

3.5.1.AK Defibrotide

1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and anticoagulants has been associated with an increased risk of bleeding (Wallerstedt et al, 2009; Schalekamp reported have included epistaxis, ecchymosis, hematoma, petechiae, and life-threatening hemorrhages. Alter coadministration of SSRIs with warfarin (Prod Info ZOLOFT(R) oral tablets, concentrate, 2008). Prothrombin 1997a).
3) Severity: major
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: When sertraline and an anticoagulant are given concurrently, monitor patient for sig closely for altered anticoagulant effects, including increased bleeding, when sertraline therapy is initiated or d
7) Probable Mechanism: unknown
8) Literature Reports
a) According to a retrospective cohort study (n=234), there was an increased risk of clinically relevant bl fibrillation during concomitant SSRI therapy or within 2 weeks following SSRI therapy termination. Patien with randomly selected patients who received warfarin only (n=117). SSRI included fluoxetine, citalopram bleeding episodes during 213.9 treatment years in the warfarin plus SSRI group, and 10 patients experie corresponding total incidences of bleedings were 51.4 and 23.9 per 1000 treatment years, respectively. (95% CI; 1.37 to 8.91, p=0.009) compared with warfarin only. The SSRI implicated in patients experienci addition of an SSRI was not associated with a change in warfarin dose or INR (p=0.48 and p=0.31 respe patient adherence, and exclusion of clopidogrel, dipyridamol, corticosteroids and anticoagulants other th
b) A population-based, case-controlled study of new coumarin users (acenocoumarol and phenprocoum increased risk of hospitalization due to nongastrointestinal bleeding. Using national pharmacy and hospit for abnormal bleeding and compared them with 5818 control subjects who were also taking a coumarin. on SSRIs showed greater risk for hospitalization for nongastrointestinal bleeding (adjusted odds ratio (O bleeding (adjusted OR 0.8, 95% CI, 0.4 to 1.5) was not significantly different (Schalekamp et al, 2008).
c) Sertraline 50 mg to 200 mg daily for 21 days produced an 8% increase in prothrombin time in subject given prior to sertraline; this compared with a 1% decrease with placebo. Normalization of the prothromb findings is unknown (Prod Info ZOLOFT(R) oral tablets, concentrate, 2008).
d) In a non-blinded, randomized, placebo-controlled trial involving 12 healthy volunteers, the effect of se study, all participants received warfarin 0.75 mg/kg. Beginning on day 11, each volunteer was randomize mg/day to 200 mg/day. Prothrombin time was measured prior to each dose of warfarin and periodically t enhanced by sertraline to a clinically significant degree, despite the fact that sertraline was given in a hig

3.5.1.AL Dehydroepiandrosterone

1) Interaction Effect: development of manic symptoms
2) Summary: A case has been reported in which concomitant dehydroepiandrosterone (DHEA) and sertralin disorder (Dean, 2000a). DHEA was also noted to cause mania in a patient with no previous personal or famil found in patients with mental disorders; DHEA suppression has lead to improvement in psychotic symptoms to manic episodes (Majewska, 1995). DHEA is a precursor to androgenic steroids, which in high doses may p patients with a personal and/or family history of bipolar disorder should not take DHEA until further data is av serotonin reuptake inhibitors (SSRIs) should be avoided due to the potential additive precipitation of mania.
3) Severity: moderate
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: Avoid concomitant use of dehydroepiandrosterone (DHEA) and selective serotonin irritability, aggressive behavior), determine if the patient is using DHEA and discontinue DHEA.
7) Probable Mechanism: serotonergic activity of dehydroepiandrosterone, possibly increased androgen level
8) Literature Reports
a) A 31-year-old male was admitted following threats to commit suicide and injure family members. He h depression. Sertraline had been prescribed 3 years prior when he was diagnosed with bipolar disorder, v 300 mg to 500 mg daily for the previous 2 months apparently for weight training. Following use of DHEA female friend and family members. He also drank alcohol occasionally and reportedly had difficulty contr valproic acid with the dose titrated to 500 mg twice daily. The combination of DHEA, sertraline, and alcoh

3.5.1.AM Dermatan Sulfate

1) Interaction Effect: an increased risk of bleeding

2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and anticoagulants has been associated with an increased risk of bleeding (Wallerstedt et al, 2009; Schalekamp reported have included epistaxis, ecchymosis, hematoma, petechiae, and life-threatening hemorrhages. Alter coadministration of SSRIs with warfarin (Prod Info ZOLOFT(R) oral tablets, concentrate, 2008). Prothrombin 1997a).

3) Severity: major

4) Onset: delayed

5) Substantiation: probable

6) Clinical Management: When sertraline and an anticoagulant are given concurrently, monitor patient for sig closely for altered anticoagulant effects, including increased bleeding, when sertraline therapy is initiated or d

7) Probable Mechanism: unknown

8) Literature Reports

a) According to a retrospective cohort study (n=234), there was an increased risk of clinically relevant bl fibrillation during concomitant SSRI therapy or within 2 weeks following SSRI therapy termination. Patien with randomly selected patients who received warfarin only (n=117). SSRI included fluoxetine, citalopram bleeding episodes during 213.9 treatment years in the warfarin plus SSRI group, and 10 patients experie corresponding total incidences of bleedings were 51.4 and 23.9 per 1000 treatment years, respectively. (95% CI; 1.37 to 8.91, p=0.009) compared with warfarin only. The SSRI implicated in patients experienci addition of an SSRI was not associated with a change in warfarin dose or INR (p=0.48 and p=0.31 respe patient adherence, and exclusion of clopidogrel, dipyridamol, corticosteroids and anticoagulants other th

b) A population-based, case-controlled study of new coumarin users (acenocoumarol and phenprocoum increased risk of hospitalization due to nongastrointestinal bleeding. Using national pharmacy and hospit for abnormal bleeding and compared them with 5818 control subjects who were also taking a coumarin. on SSRIs showed greater risk for hospitalization for nongastrointestinal bleeding (adjusted odds ratio (O bleeding (adjusted OR 0.8, 95% CI, 0.4 to 1.5) was not significantly different (Schalekamp et al, 2008).

c) Sertraline 50 mg to 200 mg daily for 21 days produced an 8% increase in prothrombin time in subject given prior to sertraline; this compared with a 1% decrease with placebo. Normalization of the prothromb findings is unknown (Prod Info ZOLOFT(R) oral tablets, concentrate, 2008).

d) In a non-blinded, randomized, placebo-controlled trial involving 12 healthy volunteers, the effect of se study, all participants received warfarin 0.75 mg/kg. Beginning on day 11, each volunteer was randomize mg/day to 200 mg/day. Prothrombin time was measured prior to each dose of warfarin and periodically th enhanced by sertraline to a clinically significant degree, despite the fact that sertraline was given in a hig

3.5.1.AN Desipramine

1) Interaction Effect: modest elevation of desipramine serum levels or possible serotonin syndrome (hyperte

2) Summary: There is limited evidence suggesting that sertraline may inhibit tricyclic antidepressant (TCA) m P450 2D6 enzyme activity and may increase the plasma concentrations of coadministered drugs that are me Lydiard et al, 1993d; Prod Info Zoloft(R), 1999c). Effects of the interaction may have little or no clinical impact were modest compared with those found when fluoxetine (another selective serotonin reuptake inhibitor) was

3) Severity: major

4) Onset: delayed

5) Substantiation: probable

6) Clinical Management: The combined use of tricyclic antidepressants (TCAs) and selective serotonin reupt serotonin syndrome have also been reported with concurrent TCA and SSRI therapy. Caution should be obse

7) Probable Mechanism: inhibition of desipramine metabolism

8) Literature Reports

a) Desipramine pharmacokinetics was studied in 18 healthy male volunteers. Study subjects received o mg daily) for 21 days. When sertraline was added to desipramine therapy, the mean maximum concentra increased by 26%. Trough concentrations of desipramine were close to baseline one week after sertralin interaction may not be clinically significant (Preskorn et al, 1994h).

3.5.1.AO Desirudin

1) Interaction Effect: an increased risk of bleeding

2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and anticoagulants has been associated with an increased risk of bleeding (Wallerstedt et al, 2009; Schalekamp reported have included epistaxis, ecchymosis, hematoma, petechiae, and life-threatening hemorrhages. Alter coadministration of SSRIs with warfarin (Prod Info ZOLOFT(R) oral tablets, concentrate, 2008). Prothrombin 1997a).

3) Severity: major

4) Onset: delayed

5) Substantiation: probable

6) Clinical Management: When sertraline and an anticoagulant are given concurrently, monitor patient for sig closely for altered anticoagulant effects, including increased bleeding, when sertraline therapy is initiated or d

7) Probable Mechanism: unknown

8) Literature Reports

a) According to a retrospective cohort study (n=234), there was an increased risk of clinically relevant bl

fibrillation during concomitant SSRI therapy or within 2 weeks following SSRI therapy termination. Patien with randomly selected patients who received warfarin only (n=117). SSRI included fluoxetine, citalopran bleeding episodes during 213.9 treatment years in the warfarin plus SSRI group, and 10 patients experie corresponding total incidences of bleedings were 51.4 and 23.9 per 1000 treatment years, respectively. T (95% CI; 1.37 to 8.91, p=0.009) compared with warfarin only. The SSRI implicated in patients experienci addition of an SSRI was not associated with a change in warfarin dose or INR (p=0.48 and p=0.31 respe patient adherence, and exclusion of clopidogrel, dipyridamol, corticosteroids and anticoagulants other th

b) A population-based, case-controlled study of new coumarin users (acenocoumarol and phenprocoum increased risk of hospitalization due to nongastrointestinal bleeding. Using national pharmacy and hospit for abnormal bleeding and compared them with 5818 control subjects who were also taking a coumarin. on SSRIs showed greater risk for hospitalization for nongastrointestinal bleeding (adjusted odds ratio (O bleeding (adjusted OR 0.8, 95% CI, 0.4 to 1.5) was not significantly different (Schalekamp et al, 2008).

c) Sertraline 50 mg to 200 mg daily for 21 days produced an 8% increase in prothrombin time in subject given prior to sertraline; this compared with a 1% decrease with placebo. Normalization of the prothromb findings is unknown (Prod Info ZOLOFT(R) oral tablets, concentrate, 2008).

d) In a non-blinded, randomized, placebo-controlled trial involving 12 healthy volunteers, the effect of se study, all participants received warfarin 0.75 mg/kg. Beginning on day 11, each volunteer was randomize mg/day to 200 mg/day. Prothrombin time was measured prior to each dose of warfarin and periodically t enhanced by sertraline to a clinically significant degree, despite the fact that sertraline was given in a hig

3.5.1.AP Desvenlafaxine

1) Interaction Effect: increased risk of serotonin syndrome (hypertension, hyperthermia, myoclonus, mental s

2) Summary: Concurrent use of desvenlafaxine and a selective serotonin reuptake inhibitor (SSRI) may resu may include restlessness, hallucinations, loss of coordination, fast heart beat, rapid changes in blood pressur (Prod Info PRISTIQ(TM) oral extended-release tablets, 2008).

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Coadministration of desvenlafaxine and an SSRI may result in a life-threatening co serotonin syndrome with the patient and monitor closely for symptoms of serotonin syndrome (restlessness, l increases (Prod Info PRISTIQ(TM) oral extended-release tablets, 2008).

7) Probable Mechanism: additive serotonergic effect

3.5.1.AQ Dexfenfluramine

1) Interaction Effect: serotonin syndrome (hypertension, hyperthermia, myoclonus, mental status changes)

2) Summary: Dexfenfluramine is a nonspecific serotonin agonist that both enhances the release of serotonin selective serotonin reuptake inhibitor, such as sertraline, has the potential to cause serotonin syndrome (Sch by symptoms such as restlessness, myoclonus, changes in mental status, hyperreflexia, diaphoresis, shiverir Dexfenfluramine should not be used in combination with sertraline (Prod Info Redux(R), 1997).

3) Severity: major

4) Onset: rapid

5) Substantiation: theoretical

6) Clinical Management: Concurrent use of dexfenfluramine and sertraline may result in an additive increase (hypertension, hyperthermia, myoclonus, mental status changes). Dexfenfluramine should not be used in con

7) Probable Mechanism: additive serotonergic effects

3.5.1.AR Dexketoprofen

1) Interaction Effect: an increased risk of bleeding

2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control anc associated with an increased risk of bleeding. Bleeding events have included epistaxis, ecchymosis, hemator suspension, 2008) (Prod Info Lexapro(TM), 2003; Dalton et al, 2003a; Prod Info CELEXA (R) oral tablet, solu

3) Severity: moderate

4) Onset: unspecified

5) Substantiation: probable

6) Clinical Management: When an SSRI and an NSAID are given concurrently, monitor patient for signs of in

7) Probable Mechanism: unknown

8) Literature Reports

a) SSRIs increase the risk of upper gastrointestinal bleeding and this effect is potentiated by concurrent were searched among 26,005 users of antidepressant medications and compared with the number of ho amount of upper GI bleeding episodes was 3.6 times more than expected (95% confidence interval, 2.7 t 12.2 (95% confidence interval, 7.1 to 19.5) and 5.2 (95% confidence interval, 3.2 to 8), respectively. The SSRIs. Combined use of SSRIs and NSAIDs or low-dose aspirin increased the risk even further (Dalton

b) Coadministration of ketorolac with psychoactive drugs (such as fluoxetine) has been associated with

3.5.1.AS Diclofenac

1) Interaction Effect: an increased risk of bleeding

2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control anc associated with an increased risk of bleeding. Bleeding events have included epistaxis, ecchymosis, hemator

suspension, 2008) (Prod Info Lexapro(TM), 2003; Dalton et al, 2003a; Prod Info CELEXA (R) oral tablet, solu
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When an SSRI and an NSAID are given concurrently, monitor patient for signs of in
7) Probable Mechanism: unknown
8) Literature Reports
a) SSRIs increase the risk of upper gastrointestinal bleeding and this effect is potentiated by concurrent were searched among 26,005 users of antidepressant medications and compared with the number of ho amount of upper GI bleeding episodes was 3.6 times more than expected (95% confidence interval, 2.7 12.2 (95% confidence interval, 7.1 to 19.5) and 5.2 (95% confidence interval, 3.2 to 8), respectively. The SSRIs. Combined use of SSRIs and NSAIDs or low-dose aspirin increased the risk even further (Dalton
b) Coadministration of ketorolac with psychoactive drugs (such as fluoxetine) has been associated with

3.5.1.AT Dicumarol

1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and anticoagulants has been associated with an increased risk of bleeding (Wallerstedt et al, 2009; Schalekamp reported have included epistaxis, ecchymosis, hematoma, petechiae, and life-threatening hemorrhages. Alter coadministration of SSRIs with warfarin (Prod Info ZOLOFT(R) oral tablets, concentrate, 2008). Prothrombin 1997a).
3) Severity: major
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: When sertraline and an anticoagulant are given concurrently, monitor patient for sig closely for altered anticoagulant effects, including increased bleeding, when sertraline therapy is initiated or d
7) Probable Mechanism: unknown
8) Literature Reports
a) According to a retrospective cohort study (n=234), there was an increased risk of clinically relevant bl fibrillation during concomitant SSRI therapy or within 2 weeks following SSRI therapy termination. Patien with randomly selected patients who received warfarin only (n=117). SSRI included fluoxetine, citalopram bleeding episodes during 213.9 treatment years in the warfarin plus SSRI group, and 10 patients experie corresponding total incidences of bleedings were 51.4 and 23.9 per 1000 treatment years, respectively. (95% CI; 1.37 to 8.91, p=0.009) compared with warfarin only. The SSRI implicated in patients experienci addition of an SSRI was not associated with a change in warfarin dose or INR (p=0.48 and p=0.31 respe patient adherence, and exclusion of clopidogrel, dipyridamol, corticosteroids and anticoagulants other th
b) A population-based, case-controlled study of new coumarin users (acenocoumarol and phenprocoum increased risk of hospitalization due to nongastrointestinal bleeding. Using national pharmacy and hospit for abnormal bleeding and compared them with 5818 control subjects who were also taking a coumarin. on SSRIs showed greater risk for hospitalization for nongastrointestinal bleeding (adjusted odds ratio (O bleeding (adjusted OR 0.8, 95% CI, 0.4 to 1.5) was not significantly different (Schalekamp et al, 2008).
c) Sertraline 50 mg to 200 mg daily for 21 days produced an 8% increase in prothrombin time in subject given prior to sertraline; this compared with a 1% decrease with placebo. Normalization of the prothromb findings is unknown (Prod Info ZOLOFT(R) oral tablets, concentrate, 2008).
d) In a non-blinded, randomized, placebo-controlled trial involving 12 healthy volunteers, the effect of se study, all participants received warfarin 0.75 mg/kg. Beginning on day 11, each volunteer was randomize mg/day to 200 mg/day. Prothrombin time was measured prior to each dose of warfarin and periodically t enhanced by sertraline to a clinically significant degree, despite the fact that sertraline was given in a hig

3.5.1.AU Diflunisal

1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and associated with an increased risk of bleeding. Bleeding events have included epistaxis, ecchymosis, hemator suspension, 2008) (Prod Info Lexapro(TM), 2003; Dalton et al, 2003a; Prod Info CELEXA (R) oral tablet, solu
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When an SSRI and an NSAID are given concurrently, monitor patient for signs of in
7) Probable Mechanism: unknown
8) Literature Reports
a) SSRIs increase the risk of upper gastrointestinal bleeding and this effect is potentiated by concurrent were searched among 26,005 users of antidepressant medications and compared with the number of ho amount of upper GI bleeding episodes was 3.6 times more than expected (95% confidence interval, 2.7 12.2 (95% confidence interval, 7.1 to 19.5) and 5.2 (95% confidence interval, 3.2 to 8), respectively. The SSRIs. Combined use of SSRIs and NSAIDs or low-dose aspirin increased the risk even further (Dalton
b) Coadministration of ketorolac with psychoactive drugs (such as fluoxetine) has been associated with

3.5.1.AV Dipyridamole

1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and been associated with an increased risk of bleeding. Bleeding events reported have included epistaxis, ecchy tablets, suspension, 2008; Prod Info PROZAC(R) oral capsules, delayed-release capsules, solution, 2008).
3) Severity: major
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When an SSRI and an antiplatelet agent are given concurrently, monitor patient for PROZAC(R) oral capsules, delayed-release capsules, solution, 2008)
7) Probable Mechanism: unknown

3.5.1.AW Dipyrone

1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and associated with an increased risk of bleeding. Bleeding events have included epistaxis, ecchymosis, hemator suspension, 2008) (Prod Info Lexapro(TM), 2003; Dalton et al, 2003a; Prod Info CELEXA (R) oral tablet, solu
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When an SSRI and an NSAID are given concurrently, monitor patient for signs of in
7) Probable Mechanism: unknown
8) Literature Reports
a) SSRIs increase the risk of upper gastrointestinal bleeding and this effect is potentiated by concurrent were searched among 26,005 users of antidepressant medications and compared with the number of ho amount of upper GI bleeding episodes was 3.6 times more than expected (95% confidence interval, 2.7 12.2 (95% confidence interval, 7.1 to 19.5) and 5.2 (95% confidence interval, 3.2 to 8), respectively. The SSRIs. Combined use of SSRIs and NSAIDs or low-dose aspirin increased the risk even further (Dalton
b) Coadministration of ketorolac with psychoactive drugs (such as fluoxetine) has been associated with

3.5.1.AX Dothiepin

1) Interaction Effect: modest elevations in dothiepin serum levels or possible serotonin syndrome (hypertens
2) Summary: There is limited evidence suggesting that sertraline may inhibit tricyclic antidepressant (TCA) m P450 2D6 enzyme activity and may increase the plasma concentrations of coadministered drugs that are me 2002c; Preskorn et al, 1994a; Lydiard et al, 1993). Effects of the interaction may have little or no clinical impa were modest compared with those found when fluoxetine (another selective serotonin reuptake inhibitor) was sertraline therapy for TCA toxicity (dry mouth, urinary retention, CNS depression). Dothiepin doses may need
3) Severity: major
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: The combined use of tricyclic antidepressants (TCAs) and selective serotonin reupt serotonin syndrome have also been reported with concurrent TCA and SSRI therapy. Caution should be obs
7) Probable Mechanism: inhibition of dothiepin metabolism
8) Literature Reports
a) Desipramine pharmacokinetics were studied in 18 healthy male volunteers. Study subjects received daily) for 21 days. When sertraline was added to desipramine therapy, the mean maximum concentration increased by 26%. Trough concentrations of desipramine were close to baseline one week after sertralin interaction may not be clinically significant (Preskorn et al, 1994).

3.5.1.AY Doxepin

1) Interaction Effect: modest elevations in doxepin serum levels or possible serotonin syndrome (hypertensio
2) Summary: There is limited evidence suggesting that sertraline may inhibit tricyclic antidepressant (TCA) m P450 2D6 enzyme activity and may increase the plasma concentrations of coadministered drugs that are me 2002f; Preskorn et al, 1994e; Lydiard et al, 1993b). Effects of the interaction may have little or no clinical imp were modest compared with those found when fluoxetine (another selective serotonin reuptake inhibitor) was sertraline therapy for TCA toxicity (dry mouth, urinary retention, CNS depression). Doxepin doses may need
3) Severity: major
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: The combined use of tricyclic antidepressants (TCAs) and selective serotonin reupt serotonin syndrome have also been reported with concurrent TCA and SSRI therapy. Caution should be obs
7) Probable Mechanism: inhibition of doxepin metabolism
8) Literature Reports
a) Desipramine pharmacokinetics was studied in 18 healthy male volunteers. Study subjects received o daily) for 21 days. When sertraline was added to desipramine therapy, the mean maximum concentration increased by 26%. Trough concentrations of desipramine were close to baseline one week after sertralin interaction may not be clinically significant (Preskorn et al, 1994d).

3.5.1.AZ Droperidol

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Any drug known to have the potential to prolong the QT interval should not be used together w potentially arrhythmogenic agents such as antidepressants that prolong the QT interval (Prod Info Inapsine(R
3) Severity: major
4) Onset: rapid
5) Substantiation: theoretical
6) Clinical Management: Droperidol should be administered with extreme caution in the presence of risk fact
7) Probable Mechanism: additive cardiac effects

3.5.1.BA Droxicam

1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and associated with an increased risk of bleeding. Bleeding events have included epistaxis, ecchymosis, hemator suspension, 2008) (Prod Info Lexapro(TM), 2003; Dalton et al, 2003a; Prod Info CELEXA (R) oral tablet, solu
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When an SSRI and an NSAID are given concurrently, monitor patient for signs of in
7) Probable Mechanism: unknown
8) Literature Reports
a) SSRIs increase the risk of upper gastrointestinal bleeding and this effect is potentiated by concurrent were searched among 26,005 users of antidepressant medications and compared with the number of ho amount of upper GI bleeding episodes was 3.6 times more than expected (95% confidence interval, 2.7 12.2 (95% confidence interval, 7.1 to 19.5) and 5.2 (95% confidence interval, 3.2 to 8), respectively. The SSRIs. Combined use of SSRIs and NSAIDs or low-dose aspirin increased the risk even further (Dalton
b) Coadministration of ketorolac with psychoactive drugs (such as fluoxetine) has been associated with

3.5.1.BB Duloxetine

1) Interaction Effect: an increased risk of serotonin syndrome
2) Summary: Duloxetine is a selective serotonin and norepinephrine reuptake inhibitor. The concomitant use due to the potential for serotonin syndrome (Prod Info CYMBALTA(R) delayed-release oral capsules, 2008).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concomitant use of duloxetine and sertraline is not recommended due to the po oral capsules, 2008).
7) Probable Mechanism: additive serotonergic effects

3.5.1.BC Efavirenz

1) Interaction Effect: decreased sertraline plasma concentrations
2) Summary: Coadministration of efavirenz and sertraline resulted in significantly decreased concentrations sertraline doses based on clinical response (Prod Info SUSTIVA(R) oral capsules, tablets, 2008).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: established
6) Clinical Management: The concomitant use of efavirenz and sertraline resulted in significantly reduced ex sertraline are coadministered. Sertraline doses may need to be increased based on clinical response (Prod In
7) Probable Mechanism: induction of CYP3A4-mediated sertraline metabolism by efavirenz
8) Literature Reports
a) In a pharmacokinetics study, concurrent administration of efavirenz and sertraline significantly decrea sertraline 50 mg orally once daily concurrently with efavirenz 600 mg orally once daily for 14 days. Resul 40%), a 39% decrease in sertraline AUC (90% CI, 27% to 50%), and a 46% decrease in sertraline Cmin was a mean 11% (90% CI, 6% to 16%) increase in efavirenz Cmax (Prod Info SUSTIVA(R) oral capsules

3.5.1.BD Eletriptan

1) Interaction Effect: an increased risk of serotonin syndrome
2) Summary: There have been case reports of weakness, hyperreflexia, and incoordination following concon specific reuptake inhibitor (SSRI) (Prod Info Imitrex(R) Nasal Spray, 2003). Because eletriptan is a 5HT 1B/1 (R), 2003). Concurrent use of a triptan and an SSRI may result in serotonin syndrome which may be life-threa of coordination, fast heart beat, rapid changes in blood pressure, increased body temperature, overreactive r commonly used intermittently and that either the triptan or the SSRI may be prescribed by a different physicia combination and monitor them closely for symptoms of serotonin syndrome (US Food and Drug Administratio
3) Severity: major
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: Coadministration of a triptan, such as eletriptan, and an SSRI may result in a life-th used intermittently and that either the triptan or the SSRI may be prescribed by a different physician. If these monitor closely for symptoms of serotonin syndrome (restlessness, hyperthermia, hyperreflexia, incoordinatio

7) Probable Mechanism: additive pharmacologic effects resulting in excessive serotonergic stimulation

3.5.1.BE Enoxaparin

1) Interaction Effect: an increased risk of bleeding

2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and anticoagulants has been associated with an increased risk of bleeding (Wallerstedt et al, 2009; Schalekamp reported have included epistaxis, ecchymosis, hematoma, petechiae, and life-threatening hemorrhages. Alter coadministration of SSRIs with warfarin (Prod Info ZOLOFT(R) oral tablets, concentrate, 2008). Prothrombin 1997a).

3) Severity: major

4) Onset: delayed

5) Substantiation: probable

6) Clinical Management: When sertraline and an anticoagulant are given concurrently, monitor patient for sig closely for altered anticoagulant effects, including increased bleeding, when sertraline therapy is initiated or d

7) Probable Mechanism: unknown

8) Literature Reports

a) According to a retrospective cohort study (n=234), there was an increased risk of clinically relevant bl fibrillation during concomitant SSRI therapy or within 2 weeks following SSRI therapy termination. Patien with randomly selected patients who received warfarin only (n=117). SSRI included fluoxetine, citalopram bleeding episodes during 213.9 treatment years in the warfarin plus SSRI group, and 10 patients experie corresponding total incidences of bleedings were 51.4 and 23.9 per 1000 treatment years, respectively. (95% CI; 1.37 to 8.91, p=0.009) compared with warfarin only. The SSRI implicated in patients experienci addition of an SSRI was not associated with a change in warfarin dose or INR (p=0.48 and p=0.31 respe patient adherence, and exclusion of clopidogrel, dipyridamol, corticosteroids and anticoagulants other th

b) A population-based, case-controlled study of new coumarin users (acenocoumarol and phenprocoum increased risk of hospitalization due to nongastrointestinal bleeding. Using national pharmacy and hospit for abnormal bleeding and compared them with 5818 control subjects who were also taking a coumarin. on SSRIs showed greater risk for hospitalization for nongastrointestinal bleeding (adjusted odds ratio (O bleeding (adjusted OR 0.8, 95% CI, 0.4 to 1.5) was not significantly different (Schalekamp et al, 2008).

c) Sertraline 50 mg to 200 mg daily for 21 days produced an 8% increase in prothrombin time in subject given prior to sertraline; this compared with a 1% decrease with placebo. Normalization of the prothromb findings is unknown (Prod Info ZOLOFT(R) oral tablets, concentrate, 2008).

d) In a non-blinded, randomized, placebo-controlled trial involving 12 healthy volunteers, the effect of se study, all participants received warfarin 0.75 mg/kg. Beginning on day 11, each volunteer was randomize mg/day to 200 mg/day. Prothrombin time was measured prior to each dose of warfarin and periodically t enhanced by sertraline to a clinically significant degree, despite the fact that sertraline was given in a hig

3.5.1.BF Epoprostenol

1) Interaction Effect: an increased risk of bleeding

2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and been associated with an increased risk of bleeding. Bleeding events reported have included epistaxis, ecchy tablets, suspension, 2008; Prod Info PROZAC(R) oral capsules, delayed-release capsules, solution, 2008).

3) Severity: major

4) Onset: unspecified

5) Substantiation: probable

6) Clinical Management: When an SSRI and an antiplatelet agent are given concurrently, monitor patient for PROZAC(R) oral capsules, delayed-release capsules, solution, 2008)

7) Probable Mechanism: unknown

3.5.1.BG Eptifibatide

1) Interaction Effect: an increased risk of bleeding

2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and been associated with an increased risk of bleeding. Bleeding events reported have included epistaxis, ecchy tablets, suspension, 2008; Prod Info PROZAC(R) oral capsules, delayed-release capsules, solution, 2008).

3) Severity: major

4) Onset: unspecified

5) Substantiation: probable

6) Clinical Management: When an SSRI and an antiplatelet agent are given concurrently, monitor patient for PROZAC(R) oral capsules, delayed-release capsules, solution, 2008)

7) Probable Mechanism: unknown

3.5.1.BH Erythromycin

1) Interaction Effect: an increased risk of serotonin syndrome (hypertension, hyperthermia, myoclonus, ment

2) Summary: Serotonin syndrome was precipitated in a pediatric patient taking sertraline when erythromycin status had significantly improved. Erythromycin induces cytochrome P450 3A (CYP3A), becomes demethylat formation of this inactive complex is associated with decreased CYP3A activity both in the liver and the small route of metabolism may result in elevated sertraline levels (Lee & Lee, 1999a).

3) Severity: major

4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: All patients receiving a serotonergic medication should be monitored for signs and s
7) Probable Mechanism: inhibition by erythromycin of cytochrome P450 3A4-mediated sertraline metabolism
8) Literature Reports
a) Sertraline 37.5 mg daily was prescribed for a 12-year-old boy with severe obsessive-compulsive diso adverse effects before erythromycin 200 mg twice daily was initiated. Within four days of concurrent ther restlessness, paresthesias, tremulousness, and confusion. Erythromycin and sertraline were both discon

3.5.1.BI Etodolac

1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and associated with an increased risk of bleeding. Bleeding events have included epistaxis, ecchymosis, hematon suspension, 2008) (Prod Info Lexapro(TM), 2003; Dalton et al, 2003a; Prod Info CELEXA (R) oral tablet, solu
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When an SSRI and an NSAID are given concurrently, monitor patient for signs of in
7) Probable Mechanism: unknown
8) Literature Reports
a) SSRIs increase the risk of upper gastrointestinal bleeding and this effect is potentiated by concurrent were searched among 26,005 users of antidepressant medications and compared with the number of ho amount of upper GI bleeding episodes was 3.6 times more than expected (95% confidence interval, 2.7 t 12.2 (95% confidence interval, 7.1 to 19.5) and 5.2 (95% confidence interval, 3.2 to 8), respectively. The SSRIs. Combined use of SSRIs and NSAIDs or low-dose aspirin increased the risk even further (Dalton
b) Coadministration of ketorolac with psychoactive drugs (such as fluoxetine) has been associated with

3.5.1.BJ Etofenamate

1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and associated with an increased risk of bleeding. Bleeding events have included epistaxis, ecchymosis, hematon suspension, 2008) (Prod Info Lexapro(TM), 2003; Dalton et al, 2003a; Prod Info CELEXA (R) oral tablet, solu
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When an SSRI and an NSAID are given concurrently, monitor patient for signs of in
7) Probable Mechanism: unknown
8) Literature Reports
a) SSRIs increase the risk of upper gastrointestinal bleeding and this effect is potentiated by concurrent were searched among 26,005 users of antidepressant medications and compared with the number of ho amount of upper GI bleeding episodes was 3.6 times more than expected (95% confidence interval, 2.7 t 12.2 (95% confidence interval, 7.1 to 19.5) and 5.2 (95% confidence interval, 3.2 to 8), respectively. The SSRIs. Combined use of SSRIs and NSAIDs or low-dose aspirin increased the risk even further (Dalton
b) Coadministration of ketorolac with psychoactive drugs (such as fluoxetine) has been associated with

3.5.1.BK Etoricoxib

1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and associated with an increased risk of bleeding. Bleeding events have included epistaxis, ecchymosis, hematon suspension, 2008) (Prod Info Lexapro(TM), 2003; Dalton et al, 2003a; Prod Info CELEXA (R) oral tablet, solu
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When an SSRI and an NSAID are given concurrently, monitor patient for signs of in
7) Probable Mechanism: unknown
8) Literature Reports
a) SSRIs increase the risk of upper gastrointestinal bleeding and this effect is potentiated by concurrent were searched among 26,005 users of antidepressant medications and compared with the number of ho amount of upper GI bleeding episodes was 3.6 times more than expected (95% confidence interval, 2.7 t 12.2 (95% confidence interval, 7.1 to 19.5) and 5.2 (95% confidence interval, 3.2 to 8), respectively. The SSRIs. Combined use of SSRIs and NSAIDs or low-dose aspirin increased the risk even further (Dalton
b) Coadministration of ketorolac with psychoactive drugs (such as fluoxetine) has been associated with

3.5.1.BL Felbinac

1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and associated with an increased risk of bleeding. Bleeding events have included epistaxis, ecchymosis, hematon suspension, 2008) (Prod Info Lexapro(TM), 2003; Dalton et al, 2003a; Prod Info CELEXA (R) oral tablet, solu

3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When an SSRI and an NSAID are given concurrently, monitor patient for signs of in
7) Probable Mechanism: unknown
8) Literature Reports
a) SSRIs increase the risk of upper gastrointestinal bleeding and this effect is potentiated by concurrent were searched among 26,005 users of antidepressant medications and compared with the number of ho amount of upper GI bleeding episodes was 3.6 times more than expected (95% confidence interval, 2.7 t 12.2 (95% confidence interval, 7.1 to 19.5) and 5.2 (95% confidence interval, 3.2 to 8), respectively. The SSRIs. Combined use of SSRIs and NSAIDs or low-dose aspirin increased the risk even further (Dalton
b) Coadministration of ketorolac with psychoactive drugs (such as fluoxetine) has been associated with

3.5.1.BM Fenbufen
1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and associated with an increased risk of bleeding. Bleeding events have included epistaxis, ecchymosis, hemator suspension, 2008) (Prod Info Lexapro(TM), 2003; Dalton et al, 2003a; Prod Info CELEXA (R) oral tablet, solu
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When an SSRI and an NSAID are given concurrently, monitor patient for signs of in
7) Probable Mechanism: unknown
8) Literature Reports
a) SSRIs increase the risk of upper gastrointestinal bleeding and this effect is potentiated by concurrent were searched among 26,005 users of antidepressant medications and compared with the number of ho amount of upper GI bleeding episodes was 3.6 times more than expected (95% confidence interval, 2.7 t 12.2 (95% confidence interval, 7.1 to 19.5) and 5.2 (95% confidence interval, 3.2 to 8), respectively. The SSRIs. Combined use of SSRIs and NSAIDs or low-dose aspirin increased the risk even further (Dalton
b) Coadministration of ketorolac with psychoactive drugs (such as fluoxetine) has been associated with

3.5.1.BN Fenfluramine
1) Interaction Effect: serotonin syndrome (hypertension, hyperthermia, myoclonus, mental status changes)
2) Summary: Fenfluramine is a nonspecific serotonin agonist that both enhances the release of serotonin an serotonin reuptake inhibitor, such as sertraline, has the potential to cause serotonin syndrome (Schenck & M symptoms such as restlessness, myoclonus, changes in mental status, hyperreflexia, diaphoresis, shivering, more data are available, fenfluramine should not be used in combination with sertraline.
3) Severity: major
4) Onset: rapid
5) Substantiation: theoretical
6) Clinical Management: Concurrent use of fenfluramine and sertraline may result in an additive increase in s (hypertension, hyperthermia, myoclonus, mental status changes). Fenfluramine should not be used in combi
7) Probable Mechanism: additive serotonergic effects

3.5.1.BO Fenoprofen
1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and associated with an increased risk of bleeding. Bleeding events have included epistaxis, ecchymosis, hemator suspension, 2008) (Prod Info Lexapro(TM), 2003; Dalton et al, 2003a; Prod Info CELEXA (R) oral tablet, solu
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When an SSRI and an NSAID are given concurrently, monitor patient for signs of in
7) Probable Mechanism: unknown
8) Literature Reports
a) SSRIs increase the risk of upper gastrointestinal bleeding and this effect is potentiated by concurrent were searched among 26,005 users of antidepressant medications and compared with the number of ho amount of upper GI bleeding episodes was 3.6 times more than expected (95% confidence interval, 2.7 t 12.2 (95% confidence interval, 7.1 to 19.5) and 5.2 (95% confidence interval, 3.2 to 8), respectively. The SSRIs. Combined use of SSRIs and NSAIDs or low-dose aspirin increased the risk even further (Dalton
b) Coadministration of ketorolac with psychoactive drugs (such as fluoxetine) has been associated with

3.5.1.BP Fentiazac
1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and associated with an increased risk of bleeding. Bleeding events have included epistaxis, ecchymosis, hemator suspension, 2008) (Prod Info Lexapro(TM), 2003; Dalton et al, 2003a; Prod Info CELEXA (R) oral tablet, solu
3) Severity: moderate

4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When an SSRI and an NSAID are given concurrently, monitor patient for signs of in
7) Probable Mechanism: unknown
8) Literature Reports
a) SSRIs increase the risk of upper gastrointestinal bleeding and this effect is potentiated by concurrent were searched among 26,005 users of antidepressant medications and compared with the number of ho amount of upper GI bleeding episodes was 3.6 times more than expected (95% confidence interval, 2.7 t 12.2 (95% confidence interval, 7.1 to 19.5) and 5.2 (95% confidence interval, 3.2 to 8), respectively. The SSRIs. Combined use of SSRIs and NSAIDs or low-dose aspirin increased the risk even further (Dalton
b) Coadministration of ketorolac with psychoactive drugs (such as fluoxetine) has been associated with

3.5.1.BQ Flecainide
1) Interaction Effect: an increased risk of flecainide toxicity (cardiac arrhythmia)
2) Summary: No data are currently available related to concomitant flecainide - sertraline administration. Fle al, 1994). Sertraline inhibits the CYP2D6 isoenzyme (Prod Info Zoloft(R), 2002k; DeVane, 1994c). With flecai higher flecainide serum levels and possible flecainide toxicity. Controlled studies are needed to investigate th
3) Severity: major
4) Onset: rapid
5) Substantiation: probable
6) Clinical Management: Coadministration of these agents should be approached with caution. Monitor the E need to be reduced.
7) Probable Mechanism: inhibition of flecainide metabolism

3.5.1.BR Floctafenine
1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and associated with an increased risk of bleeding. Bleeding events have included epistaxis, ecchymosis, hemator suspension, 2008) (Prod Info Lexapro(TM), 2003; Dalton et al, 2003a; Prod Info CELEXA (R) oral tablet, solu
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When an SSRI and an NSAID are given concurrently, monitor patient for signs of in
7) Probable Mechanism: unknown
8) Literature Reports
a) SSRIs increase the risk of upper gastrointestinal bleeding and this effect is potentiated by concurrent were searched among 26,005 users of antidepressant medications and compared with the number of ho amount of upper GI bleeding episodes was 3.6 times more than expected (95% confidence interval, 2.7 t 12.2 (95% confidence interval, 7.1 to 19.5) and 5.2 (95% confidence interval, 3.2 to 8), respectively. The SSRIs. Combined use of SSRIs and NSAIDs or low-dose aspirin increased the risk even further (Dalton
b) Coadministration of ketorolac with psychoactive drugs (such as fluoxetine) has been associated with

3.5.1.BS Flufenamic Acid
1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and associated with an increased risk of bleeding. Bleeding events have included epistaxis, ecchymosis, hemator suspension, 2008) (Prod Info Lexapro(TM), 2003; Dalton et al, 2003a; Prod Info CELEXA (R) oral tablet, solu
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When an SSRI and an NSAID are given concurrently, monitor patient for signs of in
7) Probable Mechanism: unknown
8) Literature Reports
a) SSRIs increase the risk of upper gastrointestinal bleeding and this effect is potentiated by concurrent were searched among 26,005 users of antidepressant medications and compared with the number of ho amount of upper GI bleeding episodes was 3.6 times more than expected (95% confidence interval, 2.7 t 12.2 (95% confidence interval, 7.1 to 19.5) and 5.2 (95% confidence interval, 3.2 to 8), respectively. The SSRIs. Combined use of SSRIs and NSAIDs or low-dose aspirin increased the risk even further (Dalton
b) Coadministration of ketorolac with psychoactive drugs (such as fluoxetine) has been associated with

3.5.1.BT Fluphenazine
1) Interaction Effect: an increased risk of developing acute parkinsonism
2) Summary: The development of acute, severe parkinsonism has been observed in a patient receiving fluph sertraline, the parkinsonism resolved. A similar interaction has been observed when fluphenazine was given
3) Severity: moderate
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: Patients receiving concurrent therapy with fluphenazine and sertraline should be m

need to be discontinued.
7) Probable Mechanism: inhibition of cytochrome P450-mediated fluphenazine metabolism by sertraline
8) Literature Reports
a) A 45-year-old male with chronic, multiple motor and vocal tics since childhood was successfully contr
discontinued, and fluphenazine was instituted without an improvement in the patient's mood. Sertraline 1
parkinsonism after eight weeks. When fluphenazine was discontinued, the parkinsonism resolved, but th

3.5.1.BU Flurbiprofen
1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and
associated with an increased risk of bleeding. Bleeding events have included epistaxis, ecchymosis, hematon
suspension, 2008) (Prod Info Lexapro(TM), 2003; Dalton et al, 2003a; Prod Info CELEXA (R) oral tablet, solu
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When an SSRI and an NSAID are given concurrently, monitor patient for signs of in
7) Probable Mechanism: unknown
8) Literature Reports
a) SSRIs increase the risk of upper gastrointestinal bleeding and this effect is potentiated by concurrent
were searched among 26,005 users of antidepressant medications and compared with the number of ho
amount of upper GI bleeding episodes was 3.6 times more than expected (95% confidence interval, 2.7 t
12.2 (95% confidence interval, 7.1 to 19.5) and 5.2 (95% confidence interval, 3.2 to 8), respectively. The
SSRIs. Combined use of SSRIs and NSAIDs or low-dose aspirin increased the risk even further (Dalton
b) Coadministration of ketorolac with psychoactive drugs (such as fluoxetine) has been associated with

3.5.1.BV Fondaparinux
1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and
anticoagulants has been associated with an increased risk of bleeding (Wallerstedt et al, 2009; Schalekamp e
reported have included epistaxis, ecchymosis, hematoma, petechiae, and life-threatening hemorrhages. Alter
coadministration of SSRIs with warfarin (Prod Info ZOLOFT(R) oral tablets, concentrate, 2008). Prothrombin
1997a).
3) Severity: major
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: When sertraline and an anticoagulant are given concurrently, monitor patient for sig
closely for altered anticoagulant effects, including increased bleeding, when sertraline therapy is initiated or d
7) Probable Mechanism: unknown
8) Literature Reports
a) According to a retrospective cohort study (n=234), there was an increased risk of clinically relevant bl
fibrillation during concomitant SSRI therapy or within 2 weeks following SSRI therapy termination. Patien
with randomly selected patients who received warfarin only (n=117). SSRI included fluoxetine, citalopram
bleeding episodes during 213.9 treatment years in the warfarin plus SSRI group, and 10 patients experie
corresponding total incidences of bleedings were 51.4 and 23.9 per 1000 treatment years, respectively. T
(95% CI; 1.37 to 8.91, p=0.009) compared with warfarin only. The SSRI implicated in patients experienci
addition of an SSRI was not associated with a change in warfarin dose or INR (p=0.48 and p=0.31 respe
patient adherence, and exclusion of clopidogrel, dipyridamol, corticosteroids and anticoagulants other tha
b) A population-based, case-controlled study of new coumarin users (acenocoumarol and phenprocoum
increased risk of hospitalization due to nongastrointestinal bleeding. Using national pharmacy and hospit
for abnormal bleeding and compared them with 5818 control subjects who were also taking a coumarin.
on SSRIs showed greater risk for hospitalization for nongastrointestinal bleeding (adjusted odds ratio (OI
bleeding (adjusted OR 0.8, 95% CI, 0.4 to 1.5) was not significantly different (Schalekamp et al, 2008).
c) Sertraline 50 mg to 200 mg daily for 21 days produced an 8% increase in prothrombin time in subject
given prior to sertraline; this compared with a 1% decrease with placebo. Normalization of the prothromb
findings is unknown (Prod Info ZOLOFT(R) oral tablets, concentrate, 2008).
d) In a non-blinded, randomized, placebo-controlled trial involving 12 healthy volunteers, the effect of se
study, all participants received warfarin 0.75 mg/kg. Beginning on day 11, each volunteer was randomize
mg/day to 200 mg/day. Prothrombin time was measured prior to each dose of warfarin and periodically th
enhanced by sertraline to a clinically significant degree, despite the fact that sertraline was given in a hig

3.5.1.BW Fosphenytoin
1) Interaction Effect: an increased risk of phenytoin toxicity (ataxia, hyperreflexia, nystagmus, tremor)
2) Summary: Fosphenytoin is a prodrug of phenytoin and the same interactions that occur with phenytoin are
sertraline with phenytoin has been reported to result in elevated serum phenytoin levels in two elderly patient
verify the extent of this interaction.
3) Severity: moderate
4) Onset: delayed
5) Substantiation: probable

6) Clinical Management: Caution is warranted if fosphenytoin and sertraline are to be coadministered. Serun therapy or changing the sertraline dose. Monitor patients for signs and symptoms of phenytoin toxicity (ataxia downward.
7) Probable Mechanism: sertraline inhibition of phenytoin metabolism by cytochrome P450 isoenzymes
8) Literature Reports
a) Sertraline is known to be a moderate to weak inhibitor of the cytochrome P450IID6 isoenzyme (CYP2 metabolism of phenytoin may involve the cytochrome P450IID6 (Murray, 1992) and the CYP2C9 hepatic activity and pathways, it seems theoretically possible that concurrent sertraline may act to inhibit metabo
b) Two cases in which elderly patients developed elevated serum phenytoin concentrations during coad phenytoin 300 mg per day in addition to several other medications. After sertraline 25 mg every night for to 12.3 mcg/mL. After serial increases in the sertraline dose to 75 mg per day, the patient's serum pheny restarted at a dose of 200 mg per day. Sertraline 100 mg per day was also administered without further a levels (from 15.6 mcg/mL to 20 mcg/mL) after the addition of sertraline 25 mg every other day to phenyto within one week after starting sertraline therapy or initiating a change in sertraline dose (Haselberger et a

3.5.1.BX Frovatriptan
1) Interaction Effect: an increased risk of serotonin syndrome
2) Summary: There have been case reports of weakness, hyperreflexia, and incoordination following concon specific reuptake inhibitor (SSRI) (Prod Info Imitrex(R) Nasal Spray, 2003). Because frovatriptan is a 5HT 1B/ Frova(R), 2004). Concurrent use of frovatriptan and an SSRI may result in serotonin syndrome which may be hallucinations, loss of coordination, fast heart beat, rapid changes in blood pressure, increased body tempera that triptans may be commonly used intermittently and that either the triptan or the SSRI may be prescribed b prescribed this combination and monitor them closely for symptoms of serotonin syndrome (US Food and Dru
3) Severity: major
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: Coadministration of a triptan, such as frovatriptan, and an SSRI may result in a life- used intermittently and that either the triptan or the SSRI may be prescribed by a different physician. If these monitor closely for symptoms of serotonin syndrome (restlessness, hyperthermia, hyperreflexia, incoordinatio
7) Probable Mechanism: additive pharmacologic effects resulting in excessive serotonergic stimulation

3.5.1.BY Furazolidone
1) Interaction Effect: weakness, hyperreflexia, and incoordination
2) Summary: Although not its primary mechanism of action, furazolidone has monoamine oxidase inhibitor a receiving selective serotonin reuptake inhibitors (SSRI) in combination with monoamine oxidase inhibitors (M fluctuations of vital signs, and mental status changes that include extreme agitation progressing to delirium a SSRI, or within a minimum of 14 days of discontinuing therapy with a MAOI (Prod Info Furoxone(R), 1999).
3) Severity: contraindicated
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: If concurrent therapy with furazolidone and a selective serotonin reuptake inhibitor (excess (mental status changes, diaphoresis, fever, weakness, hyperreflexia, incoordination).
7) Probable Mechanism: additive pharmacologic effects resulting in excessive serotonergic stimulation

3.5.1.BZ Ginkgo
1) Interaction Effect: increased risk of serotonin syndrome (hypertension, hyperthermia, myoclonus, mental s
2) Summary: The addition of Ginkgo biloba and/or St. John's Wort to therapy with buspirone and fluoxetine r is unclear if Ginkgo or St. John's Wort, the combination of both, or other patient factors, contributed to the effe selective serotonin reuptake inhibitors (SSRIs). Caution is advised, especially when ginkgo is taken to counte (Sloley et al, 2000; White et al, 1996), and has demonstrated serotonergic activity in animals (Ramassamy et with SSRIs. The potential MAO inhibitory activity of ginkgo is questionable. A human study did not show MAO extract inhibited MAO-A/MAO-B in the rat brain in vitro (Sloley et al, 2000; White et al, 1996) and MAO-B in h following oral consumption (Porsolt et al, 2000).
3) Severity: moderate
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: Monitor patients closely for symptoms of serotonin syndrome if ginkgo is combined
7) Probable Mechanism: additive pharmacologic effects resulting in excessive serotonergic stimulation
8) Literature Reports
a) A 42-year-old female experienced symptoms consistent with a mixed hypomanic episode following co symptoms resolved following discontinuation of Ginkgo and St. John's Wort. The patient was being treate twice daily and buspirone 15 mg twice daily. Several weeks prior to presentation, buspirone was increase melatonin, and St. John's Wort in unspecified doses. Melatonin was considered unlikely to have contribu since they may potentiate antidepressants, and considering the temporal relationship between the use o symptoms. However, the brain injury was considered a possible contributor (Spinella & Eaton, 2002).

3.5.1.CA Heparin
1) Interaction Effect: an increased risk of bleeding

2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and
anticoagulants has been associated with an increased risk of bleeding (Wallerstedt et al, 2009; Schalekamp
reported have included epistaxis, ecchymosis, hematoma, petechiae, and life-threatening hemorrhages. Alter
coadministration of SSRIs with warfarin (Prod Info ZOLOFT(R) oral tablets, concentrate, 2008). Prothrombin
1997a).
3) Severity: major
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: When sertraline and an anticoagulant are given concurrently, monitor patient for sig
closely for altered anticoagulant effects, including increased bleeding, when sertraline therapy is initiated or d
7) Probable Mechanism: unknown
8) Literature Reports
a) According to a retrospective cohort study (n=234), there was an increased risk of clinically relevant bl
fibrillation during concomitant SSRI therapy or within 2 weeks following SSRI therapy termination. Patien
with randomly selected patients who received warfarin only (n=117). SSRI included fluoxetine, citalopram
bleeding episodes during 213.9 treatment years in the warfarin plus SSRI group, and 10 patients experie
corresponding total incidences of bleedings were 51.4 and 23.9 per 1000 treatment years, respectively.
(95% CI; 1.37 to 8.91, p=0.009) compared with warfarin only. The SSRI implicated in patients experienci
addition of an SSRI was not associated with a change in warfarin dose or INR (p=0.48 and p=0.31 respe
patient adherence, and exclusion of clopidogrel, dipyridamol, corticosteroids and anticoagulants other th
b) A population-based, case-controlled study of new coumarin users (acenocoumarol and phenprocoum
increased risk of hospitalization due to nongastrointestinal bleeding. Using national pharmacy and hospit
for abnormal bleeding and compared them with 5818 control subjects who were also taking a coumarin.
on SSRIs showed greater risk for hospitalization for nongastrointestinal bleeding (adjusted odds ratio (O
bleeding (adjusted OR 0.8, 95% CI, 0.4 to 1.5) was not significantly different (Schalekamp et al, 2008).
c) Sertraline 50 mg to 200 mg daily for 21 days produced an 8% increase in prothrombin time in subject
given prior to sertraline; this compared with a 1% decrease with placebo. Normalization of the prothromb
findings is unknown (Prod Info ZOLOFT(R) oral tablets, concentrate, 2008).
d) In a non-blinded, randomized, placebo-controlled trial involving 12 healthy volunteers, the effect of se
study, all participants received warfarin 0.75 mg/kg. Beginning on day 11, each volunteer was randomize
mg/day to 200 mg/day. Prothrombin time was measured prior to each dose of warfarin and periodically th
enhanced by sertraline to a clinically significant degree, despite the fact that sertraline was given in a hig

3.5.1.CB Hydroxytryptophan

1) Interaction Effect: an increased risk of serotonin syndrome (hypertension, hyperthermia, myoclonus, ment
2) Summary: Hydroxytryptophan (5-HTP) may potentiate the serotonergic effect of selective serotonin reupta
when combined with an SSRI, the serotonin level may be increased sufficiently to produce serotonin syndrom
3) Severity: moderate
4) Onset: rapid
5) Substantiation: theoretical
6) Clinical Management: No cases have been reported of serotonin syndrome resulting from this combinatio
inhibitor (SSRI) are used concomitantly. Monitor the patient for early signs of serotonin syndrome such as an
7) Probable Mechanism: additive serotonergic effect
8) Literature Reports
a) Hydroxytryptophan (5-HTP) (200 milligrams (mg) orally) as a single dose increased plasma cortisol a
obsessive compulsive disorder (OCD). These responses were greater if the patient was also taking fluox
mg/day,and for OCD patients it was 60 mg/day. Cortisol or prolactin (PRL) levels in patients taking 5-HT
significantly different from each other. A measurement of serotonergic effects of antidepressants can be
clinical manifestations of serotonin syndrome were reported in patients taking 5-HTP concomitantly with

3.5.1.CC Ibuprofen

1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and
associated with an increased risk of bleeding. Bleeding events have included epistaxis, ecchymosis, hematom
suspension, 2008) (Prod Info Lexapro(TM), 2003; Dalton et al, 2003a; Prod Info CELEXA (R) oral tablet, solu
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When an SSRI and an NSAID are given concurrently, monitor patient for signs of in
7) Probable Mechanism: unknown
8) Literature Reports
a) SSRIs increase the risk of upper gastrointestinal bleeding and this effect is potentiated by concurrent
were searched among 26,005 users of antidepressant medications and compared with the number of ho
amount of upper GI bleeding episodes was 3.6 times more than expected (95% confidence interval, 2.7
12.2 (95% confidence interval, 7.1 to 19.5) and 5.2 (95% confidence interval, 3.2 to 8), respectively. The
SSRIs. Combined use of SSRIs and NSAIDs or low-dose aspirin increased the risk even further (Dalton
b) Coadministration of ketorolac with psychoactive drugs (such as fluoxetine) has been associated with

3.5.1.CD Iloprost

1) Interaction Effect: an increased risk of bleeding

2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and
been associated with an increased risk of bleeding. Bleeding events reported have included epistaxis, ecchy
tablets, suspension, 2008; Prod Info PROZAC(R) oral capsules, delayed-release capsules, solution, 2008).

3) Severity: major

4) Onset: unspecified

5) Substantiation: probable

6) Clinical Management: When an SSRI and an antiplatelet agent are given concurrently, monitor patient for
PROZAC(R) oral capsules, delayed-release capsules, solution, 2008)

7) Probable Mechanism: unknown

3.5.1.CE Imipramine

1) Interaction Effect: modest elevations in imipramine serum levels or possible serotonin syndrome (hyperter

2) Summary: There is limited evidence suggesting that sertraline may inhibit tricyclic antidepressant (TCA) m
P450 2D6 enzyme activity and may increase the plasma concentrations of coadministered drugs that are me
Lydiard et al, 1993g; Prod Info Zoloft(R), 1999f). Effects of the interaction may have little or no clinical impact
modest compared with those found when fluoxetine (another selective serotonin reuptake inhibitor) was coml
therapy for TCA toxicity (dry mouth, urinary retention, CNS depression). Imipramine doses may need to be re

3) Severity: major

4) Onset: delayed

5) Substantiation: probable

6) Clinical Management: The combined use of tricyclic antidepressants (TCAs) and selective serotonin reupt
serotonin syndrome have also been reported with concurrent TCA and SSRI therapy. Caution should be obse

7) Probable Mechanism: inhibition of imipramine metabolism

8) Literature Reports

a) Desipramine pharmacokinetics was studied in 18 healthy male volunteers. Study subjects received o
daily) for 21 days. When sertraline was added to desipramine therapy, the mean maximum concentratio
increased by 26%. Trough concentrations of desipramine were close to baseline one week after sertralin
interaction may not be clinically significant (Preskorn et al, 1994n).

3.5.1.CF Indomethacin

1) Interaction Effect: an increased risk of bleeding

2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and
associated with an increased risk of bleeding. Bleeding events have included epistaxis, ecchymosis, hemator
suspension, 2008) (Prod Info Lexapro(TM), 2003; Dalton et al, 2003a; Prod Info CELEXA (R) oral tablet, solu

3) Severity: moderate

4) Onset: unspecified

5) Substantiation: probable

6) Clinical Management: When an SSRI and an NSAID are given concurrently, monitor patient for signs of in

7) Probable Mechanism: unknown

8) Literature Reports

a) SSRIs increase the risk of upper gastrointestinal bleeding and this effect is potentiated by concurrent
were searched among 26,005 users of antidepressant medications and compared with the number of ho
amount of upper GI bleeding episodes was 3.6 times more than expected (95% confidence interval, 2.7 t
12.2 (95% confidence interval, 7.1 to 19.5) and 5.2 (95% confidence interval, 3.2 to 8), respectively. The
SSRIs. Combined use of SSRIs and NSAIDs or low-dose aspirin increased the risk even further (Dalton

b) Coadministration of ketorolac with psychoactive drugs (such as fluoxetine) has been associated with

3.5.1.CG Indoprofen

1) Interaction Effect: an increased risk of bleeding

2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and
associated with an increased risk of bleeding. Bleeding events have included epistaxis, ecchymosis, hemator
suspension, 2008) (Prod Info Lexapro(TM), 2003; Dalton et al, 2003a; Prod Info CELEXA (R) oral tablet, solu

3) Severity: moderate

4) Onset: unspecified

5) Substantiation: probable

6) Clinical Management: When an SSRI and an NSAID are given concurrently, monitor patient for signs of in

7) Probable Mechanism: unknown

8) Literature Reports

a) SSRIs increase the risk of upper gastrointestinal bleeding and this effect is potentiated by concurrent
were searched among 26,005 users of antidepressant medications and compared with the number of ho
amount of upper GI bleeding episodes was 3.6 times more than expected (95% confidence interval, 2.7 t
12.2 (95% confidence interval, 7.1 to 19.5) and 5.2 (95% confidence interval, 3.2 to 8), respectively. The
SSRIs. Combined use of SSRIs and NSAIDs or low-dose aspirin increased the risk even further (Dalton

b) Coadministration of ketorolac with psychoactive drugs (such as fluoxetine) has been associated with

3.5.1.CH Iproniazid

1) Interaction Effect: CNS toxicity or serotonin syndrome (hypertension, hyperthermia, myoclonus, mental sta
2) Summary: Concurrent administration or overlapping therapy with sertraline and a monoamine oxidase (MA characterized by symptoms such as restlessness, myoclonus, changes in mental status, hyperreflexia, diaph concomitant use of serotonin specific reuptake inhibitors and MAO inhibitors (Prod Info Zoloft(R), 1999e; Lap & de Vries, 1990e). Concomitant use is contraindicated.
3) Severity: contraindicated
4) Onset: rapid
5) Substantiation: probable
6) Clinical Management: Concurrent use of sertraline and a MAO inhibitor is contraindicated. Wait at least 14 least 14 days after discontinuing sertraline before initiating therapy with a MAO inhibitor.
7) Probable Mechanism: inhibition of serotonin metabolism by monoamine oxidase
8) Literature Reports
a) Concomitant use of SSRIs and monoamine oxidase inhibitors can produce a toxic reaction known as hyperstimulation and manifests as restlessness, myoclonus, changes in mental status, hyperreflexia, dia fatality can result.
b) A 26-year old woman who had been taking isocarboxazid for eight weeks stopped taking the drug for the patient became restless and developed leg twitches. The patients was later admitted to the emergen disturbances. After treatment with diazepam and propranolol the patient did not improve. The patient was symptoms after the second dose (Lappin & Auchincloss, 1994f).
c) A drug interaction was reported in a 61-year old woman in which sertraline 100 mg twice daily was ad taking the first sertraline dose, the patient was found in a semicomatose state, with elevated body tempe Hg. After transportation to the hospital, the patient was misdiagnosed as having neuroleptic malignant sy sertraline and phenelzine. The authors suggest that monoamine oxidase inhibitor (MAOI) therapy should serotonin reuptake inhibitor (SSRI) and that before starting a MAOI, SSRI therapy should be discontinue 1994f).
d) Two cases reports suggested a possible interaction between fluoxetine and selegiline (Suchowersky approximately one month after adding selegiline to fluoxetine. The patient improved two months after bot involved diaphoresis, vasoconstriction, and cyanosis of the hands which occurred in close temporal relat quick resolution of symptoms. Rechallenge with fluoxetine alone occurred without incident.

3.5.1.CI Isocarboxazid

1) Interaction Effect: CNS toxicity or serotonin syndrome (hypertension, hyperthermia, myoclonus, mental sta
2) Summary: Concurrent administration or overlapping therapy with sertraline and a monoamine oxidase (MA characterized by symptoms such as restlessness, myoclonus, changes in mental status, hyperreflexia, diaph Zoloft(R), 2002l; Lappin & Auchincloss, 1994i; Graber et al, 1994i; Bhatara & Bandettini, 1993d; Suchowersky
3) Severity: contraindicated
4) Onset: rapid
5) Substantiation: probable
6) Clinical Management: Concurrent use of sertraline and a MAO inhibitor is contraindicated. Wait at least 14 least 14 days after discontinuing sertraline before initiating therapy with a MAO inhibitor.
7) Probable Mechanism: inhibition of serotonin metabolism by monoamine oxidase
8) Literature Reports
a) Concomitant use of serotonin specific reuptake inhibitors and monoamine oxidase inhibitors can prod syndrome is a condition of serotonergic hyperstimulation and manifests as restlessness, myoclonus, cha not recognized and correctly treated, death can result.
b) A 26-year old woman who had been taking isocarboxazid for eight weeks stopped taking the drug for the patient became restless and developed leg twitches. The patients was later admitted to the emergen disturbances. The patient did not improve after treatment with diazepam and propranolol. The patient wa in symptoms after the second dose (Lappin & Auchincloss, 1994h).
c) A drug interaction was reported in a 61-year old woman in which sertraline 100 mg twice daily was ad taking the first sertraline dose, the patient was found in a semicomatose state, with elevated body tempe mmHg. After transportation to the hospital, the patient was misdiagnosed as having neuroleptic malignar between sertraline and phenelzine. The authors suggest that MAO inhibitor therapy should be discontinu inhibitor (SSRI) and that before starting a MAOI, SSRI therapy should be discontinued for at least 5 half-
d) Two cases reports suggested a possible interaction between fluoxetine and selegiline (Suchowersky approximately 1 month after adding selegiline to fluoxetine therapy. The patient improved 2 months after involved diaphoresis, vasoconstriction, and cyanosis of the hands which occurred in close temporal relat quick resolution of symptoms. Rechallenge with fluoxetine alone occurred without incident.

3.5.1.CJ Isoxicam

1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and associated with an increased risk of bleeding. Bleeding events have included epistaxis, ecchymosis, hemator suspension, 2008) (Prod Info Lexapro(TM), 2003; Dalton et al, 2003a; Prod Info CELEXA (R) oral tablet, solu
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When an SSRI and an NSAID are given concurrently, monitor patient for signs of in

7) Probable Mechanism: unknown
8) Literature Reports
a) SSRIs increase the risk of upper gastrointestinal bleeding and this effect is potentiated by concurrent were searched among 26,005 users of antidepressant medications and compared with the number of ho amount of upper GI bleeding episodes was 3.6 times more than expected (95% confidence interval, 2.7 t 12.2 (95% confidence interval, 7.1 to 19.5) and 5.2 (95% confidence interval, 3.2 to 8), respectively. The SSRIs. Combined use of SSRIs and NSAIDs or low-dose aspirin increased the risk even further (Dalton
b) Coadministration of ketorolac with psychoactive drugs (such as fluoxetine) has been associated with

3.5.1.CK Ketoprofen
1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and associated with an increased risk of bleeding. Bleeding events have included epistaxis, ecchymosis, hemator suspension, 2008) (Prod Info Lexapro(TM), 2003; Dalton et al, 2003a; Prod Info CELEXA (R) oral tablet, solu
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When an SSRI and an NSAID are given concurrently, monitor patient for signs of in
7) Probable Mechanism: unknown
8) Literature Reports
a) SSRIs increase the risk of upper gastrointestinal bleeding and this effect is potentiated by concurrent were searched among 26,005 users of antidepressant medications and compared with the number of ho amount of upper GI bleeding episodes was 3.6 times more than expected (95% confidence interval, 2.7 t 12.2 (95% confidence interval, 7.1 to 19.5) and 5.2 (95% confidence interval, 3.2 to 8), respectively. The SSRIs. Combined use of SSRIs and NSAIDs or low-dose aspirin increased the risk even further (Dalton
b) Coadministration of ketorolac with psychoactive drugs (such as fluoxetine) has been associated with

3.5.1.CL Ketorolac
1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and associated with an increased risk of bleeding. Bleeding events have included epistaxis, ecchymosis, hemator suspension, 2008) (Prod Info Lexapro(TM), 2003; Dalton et al, 2003a; Prod Info CELEXA (R) oral tablet, solu
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When an SSRI and an NSAID are given concurrently, monitor patient for signs of in
7) Probable Mechanism: unknown
8) Literature Reports
a) SSRIs increase the risk of upper gastrointestinal bleeding and this effect is potentiated by concurrent were searched among 26,005 users of antidepressant medications and compared with the number of ho amount of upper GI bleeding episodes was 3.6 times more than expected (95% confidence interval, 2.7 t 12.2 (95% confidence interval, 7.1 to 19.5) and 5.2 (95% confidence interval, 3.2 to 8), respectively. The SSRIs. Combined use of SSRIs and NSAIDs or low-dose aspirin increased the risk even further (Dalton
b) Coadministration of ketorolac with psychoactive drugs (such as fluoxetine) has been associated with

3.5.1.CM Lamifiban
1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and been associated with an increased risk of bleeding. Bleeding events reported have included epistaxis, ecchyr tablets, suspension, 2008; Prod Info PROZAC(R) oral capsules, delayed-release capsules, solution, 2008).
3) Severity: major
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When an SSRI and an antiplatelet agent are given concurrently, monitor patient for PROZAC(R) oral capsules, delayed-release capsules, solution, 2008)
7) Probable Mechanism: unknown

3.5.1.CN Lamotrigine
1) Interaction Effect: an increased risk of lamotrigine toxicity (fatigue, sedation, confusion, decreased cognitic
2) Summary: Two case reports describe epileptic patients who experienced lamotrigine toxicity when sertrali sertraline relies on N-demethylation, hydroxylation, oxidative deamination, and glucuronidation. It is hypothes glucuronidation (Kaufman & Gerner, 1998a).
3) Severity: moderate
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: Caution should be exercised when combining sertraline and lamotrigine therapy. La
7) Probable Mechanism: inhibition of lamotrigine glucuronidation
8) Literature Reports

a) A 39-year-old female with epilepsy was maintained on lamotrigine 200 mg daily with a baseline lamot
25 mg daily was initiated. Six weeks later, the lamotrigine level was 5.1 mcg/mL and the patient complair
lamotrigine was decreased to 100 mg daily. This lower lamotrigine dose eliminated the patient's confusic
(Kaufman & Gerner, 1998).
b) Lamotrigine 450 mg daily was not controlling seizures in a 17-year-old female with mixed epileptic dis
any side effects. Lamotrigine was also increased to 600 mg daily, and six weeks later, the patient compla
mcg/mL at this time. The sertraline dose was decreased to 50 mg daily while the lamotrigine level was in
In this case report, the lamotrigine blood level decreased to approximately 50% with a 33% decrease in t
(Kaufman & Gerner, 1998).

3.5.1.CO Levomethadyl

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Any drug known to have the potential to prolong the QT interval should not be used with levom
potentially arrhythmogenic agents such as sertraline that prolong the QT interval (Prod Info Orlaam(R), 2001)
3) Severity: contraindicated
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: Levomethadyl is contraindicated in patients being treated with sertraline as it may p
7) Probable Mechanism: unknown

3.5.1.CP Lexipafant

1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and
been associated with an increased risk of bleeding. Bleeding events reported have included epistaxis, ecchyr
tablets, suspension, 2008; Prod Info PROZAC(R) oral capsules, delayed-release capsules, solution, 2008).
3) Severity: major
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When an SSRI and an antiplatelet agent are given concurrently, monitor patient for
PROZAC(R) oral capsules, delayed-release capsules, solution, 2008)
7) Probable Mechanism: unknown

3.5.1.CQ Linezolid

1) Interaction Effect: CNS toxicity or serotonin syndrome (hypertension, hyperthermia, myoclonus, mental sta
2) Summary: Linezolid is a reversible, nonselective inhibitor of monoamine oxidase. Concurrent administratio
result in CNS toxicity or serotonin syndrome, a hyperserotonergic state characterized by symptoms such as r
and tremor. Serious, even fatal, reactions have been reported. There have been spontaneous reports of sero
(Prod Info ZYVOX(R) IV injection, oral tablets, oral suspension, 2008; Prod Info Zoloft(R) sertraline HCl tablet
of serotonin syndrome. Serotonin syndrome can be life-threatening. If serotonin syndrome develops, disconti
(Boyer & Shannon, 2005).
3) Severity: contraindicated
4) Onset: rapid
5) Substantiation: probable
6) Clinical Management: Unless carefully monitored for serotonin syndrome, linezolid should not be administ
suspension, 2008). If linezolid and sertraline are used concomitantly, monitor closely for symptoms of serotor
muscle rigidity, clonus, peripheral hypertonicity, and shivering), autonomic hyperactivity (including tachycardi
and delirium). Serotonin syndrome can be life-threatening. If serotonin syndrome develops, discontinue the o
Shannon, 2005).
7) Probable Mechanism: inhibition of serotonin metabolism by monoamine oxidase
8) Literature Reports
a) A case of serotonin syndrome occurred in a patient who was prescribed linezolid and sertraline. A 45
service after an acute suicide attempt that resulted in a T6 level spinal cord injury and paraplegia. Pharm
after the patient was diagnosed with acute depression and psychosis. Bupropion 75 mg twice daily, trazo
patient underwent sacral flap closure with a bilateral gluteal myocutaneous flap and then developed a de
for several days. Culture of the ulcer revealed a vancomycin-resistant enterococcus fecalis. He was start
hours. Lithium was discontinued after the patients lithium carbonate level was found to be elevated at 1.
increasing tremor, nausea, vomiting, diarrhea, and dry mouth. Sertraline, bupropion and trazodone were
sodium, bisacodyl, megestrol, lansoprazole, and risperidone. The following day the patient became deliri
elevated to 100.1 degrees Fahrenheit, pulse 101, respirations 20/min, and blood pressure 100/71 mm Hg
minimally reactive. A diagnosis of serotonin syndrome was considered. Symptoms of serotonin syndrom
b) A retrospective chart review identified one highly probable case of serotonin syndrome in a patient wh
Charts of 72 inpatients who received linezolid and an SSRI or venlafaxine within 14 days of each other w
Hunter Serotonin Toxicity criteria. Of these patients, 52 (72%) were treated concomitantly with linezolid a
probability of SS. Of these, one case involved an 81-year-old woman who was diagnosed with a high pro
citalopram. Linezolid was given for a vancomycin-resistant Enterococcus urinary tract infection. When th
shouting. Although she appeared to have met 6 of the Sternbach criteria and 4 of the Hunter criteria for S
Hg with a heart rate of 120 beats/min, and a respiratory rate of 50 breaths/min. The following day, she ba
twitching and jerking, eyes rolled back in her head, and labored breathing. Linezolid was discontinued, a

after linezolid was stopped, she was extubated and had returned to baseline mental status with the abilit
c) In one case report, a 36-year-old male experience symptoms of serotonin syndrome after concomitar transplant after receiving high-doses of cyclophosphamide, total body irradiation, and antihymocyte globu versus-host disease, thrombotic thrombocytic purpura, renal failure, and multiple pulmonary infections. C medications consisted of tacrolimus, corticosteroids, thalidomide 100 mg daily, sertraline 50 mg daily, mo restlessness, delirium and agitation. He developed hypertension and a high fever (40 degrees Celsius). V all medications with neurological effects were discontinued, including sertraline, thalidomide, alprazolam, and morphine were reinstated with no reoccurrence of symptoms (Hachem et al, 2003).

3.5.1.CR Lithium

1) Interaction Effect: possible increased lithium concentrations and/or an increased risk of SSRI-related sero
2) Summary: Concomitant use of lithium and various SSRIs has been associated with enhanced side effects resulted in neurotoxicity and increased lithium levels in one case report (Salama & Shafey, 1989a). Signs and who demonstrated therapeutic serum lithium levels while on concurrent fluoxetine and lithium (Muly et al, 199 interaction between lithium and citalopram (Gram et al, 1993a; Baumann et al, 1996a). Combined administra significant effect on the pharmacokinetics of citalopram or lithium. However, plasma lithium levels should be m clinical practice. Lithium may enhance the serotonergic effects of citalopram, therefore caution should be exe Concurrent use of fluvoxamine and lithium has led to case reports of increased lithium levels and neurotoxicit Spigset, 1993a; Evans & Marwick, 1990; Burrai et al, 1991a). No pharmacokinetic interference was apparent (TM), 2003). If these two agents are to be given concomitantly, the manufacturer suggests that caution be us have been reported when lithium was coadministered with fluoxetine and fluvoxamine (both in the same phar Spigset, 1993a; Salama & Shafey, 1989a).
3) Severity: moderate
4) Onset: delayed
5) Substantiation: established
6) Clinical Management: Monitor patients on concurrent lithium and selective serotonin reuptake inhibitor the and symptoms associated with serotonin syndrome (hypertension, hyperthermia, myoclonus, mental status c
7) Probable Mechanism: unknown
8) Literature Reports

a) Concomitant administration of oral lithium carbonate and oral fluoxetine resulted in increased lithium s (Salama & Shafey, 1989). Fluoxetine 20 mg daily was added to a regimen of lithium 1200 mg daily follow morning awakening. Lithium serum levels increased to 1.7 mEq/L from a range of 0.75 to 1.15 mEq/L pri resulted in a decrease in the lithium serum level within 48 hours to 1.2 mEq/L. The neurologic symptoms contribution of fluoxetine to lithium toxicity in this patient was obscured by the fact that the lithium was re
b) A 53-year old woman who had been taking fluoxetine 20 mg daily and lorazepam 0.5 mg four times d order to augment her response to fluoxetine. Within 48 hours, the patient became confused, ataxic, and degrees F, and laboratory values were normal except for an elevated leukocyte count and slightly elevat resolved over the next four days. At no point did the lithium levels reach a toxic level, suggesting that the et al, 1989).
c) Serotonin syndrome was precipitated when lithium 300 mg twice daily was added to a three-month re measured at 0.65 mEq/L and the dose was increased to 300 mg three times daily. Two days after this do tremor, diarrhea, and incoordination. After discontinuation of lithium and initiation of cyproheptadine thera of fluoxetine 40 mg per day without further symptoms of serotonin syndrome (Muly et al, 1993).
d) Eight healthy male volunteers completed three phases of an interaction study to determine the effects sparteine, indicating normal cytochrome P450 2D6 enzyme activity. Although lithium is not influenced by subject received citalopram 40 mg alone as a single daily dose for 10 days, lithium 30 mmol (1980 mg) a two weeks separated each treatment phase. Results showed that the concurrent administration of citalop 1993).
e) Twenty-four patients experiencing depression (DSM III criteria) were randomized under double-blind daily) or placebo. All of the subjects had failed to respond to four weeks of citalopram monotherapy. Lithi between lithium and citalopram was noted, and cotherapy was well tolerated (Baumann et al, 1996).
f) Serotonin syndrome was described in a 53-year-old patient who was stabilized on lithium 1400 mg da period the fluvoxamine dose was increased to 200 mg daily; tremor and difficulty with fine hand moveme bilateral hyperreflexia of biceps and knee jerks, and clonus in both ankles were seen. After 12 weeks of daily replaced fluvoxamine, and the neuromuscular symptoms abated over a 2-week period. After four w
g) Three cases of mania were reported in patients who were treated with lithium and fluvoxamine. The r begun. Fluvoxamine was discontinued and, in two of the three patients, the mania resolved, and success depression reappeared within a month of fluvoxamine discontinuation (Burrai et al, 1991).
h) In an open-labeled, placebo-controlled study, lithium 600 mg was administered to 16 subjects orally t sertraline 100 mg or placebo was given twice, ten hours and two hours prior to lithium dosing on day nin renal clearance increased by 6.9% (0.11 L/hour) when sertraline was coadministered. Seven subjects ex subjects who ingested placebo and lithium experienced side effects (Wilner et al, 1991).

3.5.1.CS Lofepramine

1) Interaction Effect: modest elevations in lofepramine serum levels or possible serotonin syndrome (hyperte
2) Summary: There is limited evidence suggesting that sertraline may inhibit tricyclic antidepressant (TCA) m P450 2D6 enzyme activity and may increase the plasma concentrations of coadministered drugs that are me 2002i; Preskorn et al, 1994m; Lydiard et al, 1993f). Effects of the interaction may have little or no clinical impa

were modest compared with those found when fluoxetine (another selective serotonin reuptake inhibitor) was sertraline therapy for TCA toxicity (dry mouth, urinary retention, CNS depression). Lofepramine doses may ne

3) Severity: major
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: Concurrent use of lofepramine and sertraline may result in an additive increase in s (hypertension, hyperthermia, myoclonus, mental status changes). Lofepramine should not be used in combin
7) Probable Mechanism: inhibition of lofepramine metabolism
8) Literature Reports

a) Desipramine pharmacokinetics were studied in 18 healthy male volunteers. Study subjects received d daily) for 21 days. When sertraline was added to desipramine therapy, the mean maximum concentration increased by 26%. Trough concentrations of desipramine were close to baseline one week after sertralin interaction may not be clinically significant (Preskorn et al, 1994l).

3.5.1.CT Lornoxicam

1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and associated with an increased risk of bleeding. Bleeding events have included epistaxis, ecchymosis, hematom suspension, 2008) (Prod Info Lexapro(TM), 2003; Dalton et al, 2003a; Prod Info CELEXA (R) oral tablet, solu
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When an SSRI and an NSAID are given concurrently, monitor patient for signs of in
7) Probable Mechanism: unknown
8) Literature Reports

a) SSRIs increase the risk of upper gastrointestinal bleeding and this effect is potentiated by concurrent were searched among 26,005 users of antidepressant medications and compared with the number of ho amount of upper GI bleeding episodes was 3.6 times more than expected (95% confidence interval, 2.7 t 12.2 (95% confidence interval, 7.1 to 19.5) and 5.2 (95% confidence interval, 3.2 to 8), respectively. The SSRIs. Combined use of SSRIs and NSAIDs or low-dose aspirin increased the risk even further (Dalton
b) Coadministration of ketorolac with psychoactive drugs (such as fluoxetine) has been associated with

3.5.1.CU Meclofenamate

1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and associated with an increased risk of bleeding. Bleeding events have included epistaxis, ecchymosis, hematom suspension, 2008) (Prod Info Lexapro(TM), 2003; Dalton et al, 2003a; Prod Info CELEXA (R) oral tablet, solu
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When an SSRI and an NSAID are given concurrently, monitor patient for signs of in
7) Probable Mechanism: unknown
8) Literature Reports

a) SSRIs increase the risk of upper gastrointestinal bleeding and this effect is potentiated by concurrent were searched among 26,005 users of antidepressant medications and compared with the number of ho amount of upper GI bleeding episodes was 3.6 times more than expected (95% confidence interval, 2.7 t 12.2 (95% confidence interval, 7.1 to 19.5) and 5.2 (95% confidence interval, 3.2 to 8), respectively. The SSRIs. Combined use of SSRIs and NSAIDs or low-dose aspirin increased the risk even further (Dalton
b) Coadministration of ketorolac with psychoactive drugs (such as fluoxetine) has been associated with

3.5.1.CV Mefenamic Acid

1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and associated with an increased risk of bleeding. Bleeding events have included epistaxis, ecchymosis, hematom suspension, 2008) (Prod Info Lexapro(TM), 2003; Dalton et al, 2003a; Prod Info CELEXA (R) oral tablet, solu
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When an SSRI and an NSAID are given concurrently, monitor patient for signs of in
7) Probable Mechanism: unknown
8) Literature Reports

a) SSRIs increase the risk of upper gastrointestinal bleeding and this effect is potentiated by concurrent were searched among 26,005 users of antidepressant medications and compared with the number of ho amount of upper GI bleeding episodes was 3.6 times more than expected (95% confidence interval, 2.7 t 12.2 (95% confidence interval, 7.1 to 19.5) and 5.2 (95% confidence interval, 3.2 to 8), respectively. The SSRIs. Combined use of SSRIs and NSAIDs or low-dose aspirin increased the risk even further (Dalton
b) Coadministration of ketorolac with psychoactive drugs (such as fluoxetine) has been associated with

3.5.1.CW Meloxicam

1) Interaction Effect: an increased risk of bleeding

2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and associated with an increased risk of bleeding. Bleeding events have included epistaxis, ecchymosis, hemator suspension, 2008) (Prod Info Lexapro(TM), 2003; Dalton et al, 2003a; Prod Info CELEXA (R) oral tablet, solu

3) Severity: moderate

4) Onset: unspecified

5) Substantiation: probable

6) Clinical Management: When an SSRI and an NSAID are given concurrently, monitor patient for signs of in

7) Probable Mechanism: unknown

8) Literature Reports

a) SSRIs increase the risk of upper gastrointestinal bleeding and this effect is potentiated by concurrent were searched among 26,005 users of antidepressant medications and compared with the number of ho amount of upper GI bleeding episodes was 3.6 times more than expected (95% confidence interval, 2.7 12.2 (95% confidence interval, 7.1 to 19.5) and 5.2 (95% confidence interval, 3.2 to 8), respectively. The SSRIs. Combined use of SSRIs and NSAIDs or low-dose aspirin increased the risk even further (Dalton

b) Coadministration of ketorolac with psychoactive drugs (such as fluoxetine) has been associated with

3.5.1.CX Methadone

1) Interaction Effect: increased serum methadone levels

2) Summary: Coadministration of methadone and sertraline may result in increased or prolonged opioid effe these agents are coadministered, consider reducing the methadone dosage. Additionally, monitor patients fo METHADOSE(R) oral concentrate, sugar-free oral concentrate, 2005).

3) Severity: moderate

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Coadministration of methadone and sertraline may result in increased serum metha coadministered, consider reducing the methadone dosage. Also, monitor patients for increased methadone a concentrate, sugar-free oral concentrate, 2005).

7) Probable Mechanism: potential inhibition of CYP3A4-mediated methadone metabolism

3.5.1.CY Methylphenidate

1) Interaction Effect: increased selective serotonin reuptake inhibitor plasma concentrations

2) Summary: Human pharmacologic studies have demonstrated that methylphenidate may inhibit the metab the SSRI may be necessary when it is used concurrently with methylphenidate. Additionally, when initiating o Info METADATE CD(R) extended-release oral capsules, 2007).

3) Severity: moderate

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Use caution when prescribing methylphenidate to patients who take an selective se cause elevated SSRI plasma concentrations. Consider a decrease in the dose of SSRI when these agents ar initiating or discontinuing methylphenidate therapy (Prod Info METADATE CD(R) extended-release oral caps

7) Probable Mechanism: inhibition of selective serotonin reuptake inhibitor metabolism by methylphenidate

3.5.1.CZ Metoclopramide

1) Interaction Effect: an increased risk of developing extrapyramidal symptoms

2) Summary: In a case report, a 23-year old woman developed extrapyramidal symptoms after sertraline wa report describes a 14-year old female who experienced mandibular dystonia five days after starting metoclop controlled studies are necessary to confirm the clinical implications of this interaction.

3) Severity: moderate

4) Onset: delayed

5) Substantiation: probable

6) Clinical Management: Clinicians should be alerted to the possibility that patients may have an increased ri metoclopramide. Close patient monitoring is warranted.

7) Probable Mechanism: synergistic dopaminergic inhibition

8) Literature Reports

a) A 23-year-old woman developed mandibular dystonia after sertraline was added to a chronic regimen for six months when she was admitted to the hospital with depression. After two 50 mg doses of sertralin periauricular pain, jaw tightness, and the sensation of teeth clenching and grinding. After diphenhydrami recurrence of symptoms after her third dose of sertraline. After sertraline was discontinued the patient ex (Christensen & Byerly, 1996).

b) A 14-year-old patient stabilized on sertraline 100 mg for the previous two months presented to her ph times daily. Five days later, the patient was taken to the emergency room because of mandibular dyston

c) A risk of serotonin syndrome with serious extrapyramidal reactions may occur with the concomitant u 18 months for depression and agoraphobia. Other medications were celecoxib and hydrocortisone. After Metoclopramide was initiated on postoperative day 2 because of nausea. Two hours after the first metoc shoulders, twitching of the lips, stiffness of the tongue and jaw and difficulties in controlling tongue move Symptoms resolved in 4 hours after administration of diazepam. Upon reinstitution of metoclopramide, th

concentrations rose to 535 U/L, but CK MB fraction, troponin concentrations and ECG remained normal. normal the following day. Two days later a similar pattern of clinical features occurred 1.5 hours after she there was no recurrence of the previous symptoms. According to the Naranjo probability scale, the comb syndrome (Fisher & David, 2002).

3.5.1.DA Milnacipran

1) Interaction Effect: increased risk of serotonin syndrome (hypertension, hyperthermia, myoclonus, mental s
2) Summary: Concurrent use of milnacipran and an SSRI may result in hypertension, coronary artery vasocc syndrome may include restlessness, hallucinations, loss of coordination, fast heart beat, rapid changes in blo diarrhea (Prod Info SAVELLA(R) oral tablets, 2009).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Coadministration of milnacipran and an SSRI may result in hypertension and coron used together, discuss the risks of serotonin syndrome with the patient and monitor closely for symptoms of s during treatment initiation and dose increases (Prod Info SAVELLA(R) oral tablets, 2009).
7) Probable Mechanism: additive serotonergic effect

3.5.1.DB Moclobemide

1) Interaction Effect: CNS toxicity or serotonin syndrome (hypertension, hyperthermia, myoclonus, mental sta
2) Summary: Concurrent administration or overlapping therapy with sertraline and a monoamine oxidase (MA characterized by symptoms such as restlessness, myoclonus, changes in mental status, hyperreflexia, diaph Zoloft(R), 2002b; Lappin & Auchincloss, 1994c; Graber et al, 1994c; Neuvonen et al, 1993a; Bhatara & Band similar reaction may occur. Concomitant use is contraindicated.
3) Severity: contraindicated
4) Onset: rapid
5) Substantiation: probable
6) Clinical Management: Concurrent use of sertraline and a MAO inhibitor is contraindicated. Wait at least 14 least 14 days after discontinuing sertraline before initiating therapy with a MAO inhibitor.
7) Probable Mechanism: inhibition of serotonin metabolism by monoamine oxidase
8) Literature Reports
a) Concomitant use of selective serotonin reuptake inhibitors and monoamine oxidase inhibitors can pro syndrome is a condition of serotonergic hyperstimulation and manifests as restlessness, myoclonus, cha not recognized and correctly treated, death can result.
b) A 26-year old woman who had been taking isocarboxazid for 8 weeks stopped taking the drug for 11 patient became restless and developed leg twitches. The patients was later admitted to the emergency r disturbances. The patient did not improve after treatment with diazepam and propranolol. The patient wa in symptoms after the second dose (Lappin & Auchincloss, 1994b).
c) A drug interaction was reported in a 61-year old woman in which sertraline 100 mg twice daily was ac taking the first sertraline dose, the patient was found in a semicomatose state, with elevated body tempe mmHg. After transportation to the hospital, the patient was misdiagnosed as having neuroleptic malignar between sertraline and phenelzine. The authors suggest that MAO inhibitor therapy should be discontinu inhibitor (SSRI) and that before starting a MAOI, SSRI therapy should be discontinued for at least five ha
d) Five fatal cases of serotonin syndrome following overdoses have been reported. In three of the five c selective monoamine oxidase inhibitor, and citalopram. Of these three patients, moclobemide blood conc concentrations ranged from normal to five times the therapeutic level (Neuvonen et al, 1993).

3.5.1.DC Morniflumate

1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and associated with an increased risk of bleeding. Bleeding events have included epistaxis, ecchymosis, hemator suspension, 2008) (Prod Info Lexapro(TM), 2003; Dalton et al, 2003a; Prod Info CELEXA (R) oral tablet, solu
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When an SSRI and an NSAID are given concurrently, monitor patient for signs of in
7) Probable Mechanism: unknown
8) Literature Reports
a) SSRIs increase the risk of upper gastrointestinal bleeding and this effect is potentiated by concurrent were searched among 26,005 users of antidepressant medications and compared with the number of ho amount of upper GI bleeding episodes was 3.6 times more than expected (95% confidence interval, 2.7 t 12.2 (95% confidence interval, 7.1 to 19.5) and 5.2 (95% confidence interval, 3.2 to 8), respectively. The SSRIs. Combined use of SSRIs and NSAIDs or low-dose aspirin increased the risk even further (Dalton
b) Coadministration of ketorolac with psychoactive drugs (such as fluoxetine) has been associated with

3.5.1.DD Nabumetone

1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and

associated with an increased risk of bleeding. Bleeding events have included epistaxis, ecchymosis, hemator
suspension, 2008) (Prod Info Lexapro(TM), 2003; Dalton et al, 2003a; Prod Info CELEXA (R) oral tablet, solu
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When an SSRI and an NSAID are given concurrently, monitor patient for signs of in
7) Probable Mechanism: unknown
8) Literature Reports
a) SSRIs increase the risk of upper gastrointestinal bleeding and this effect is potentiated by concurrent
were searched among 26,005 users of antidepressant medications and compared with the number of ho
amount of upper GI bleeding episodes was 3.6 times more than expected (95% confidence interval, 2.7 t
12.2 (95% confidence interval, 7.1 to 19.5) and 5.2 (95% confidence interval, 3.2 to 8), respectively. The
SSRIs. Combined use of SSRIs and NSAIDs or low-dose aspirin increased the risk even further (Dalton
b) Coadministration of ketorolac with psychoactive drugs (such as fluoxetine) has been associated with

3.5.1.DE Nadroparin

1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and
anticoagulants has been associated with an increased risk of bleeding (Wallerstedt et al, 2009; Schalekamp e
reported have included epistaxis, ecchymosis, hematoma, petechiae, and life-threatening hemorrhages. Alter
coadministration of SSRIs with warfarin (Prod Info ZOLOFT(R) oral tablets, concentrate, 2008). Prothrombin
1997a).
3) Severity: major
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: When sertraline and an anticoagulant are given concurrently, monitor patient for sig
closely for altered anticoagulant effects, including increased bleeding, when sertraline therapy is initiated or d
7) Probable Mechanism: unknown
8) Literature Reports
a) According to a retrospective cohort study (n=234), there was an increased risk of clinically relevant bl
fibrillation during concomitant SSRI therapy or within 2 weeks following SSRI therapy termination. Patien
with randomly selected patients who received warfarin only (n=117). SSRI included fluoxetine, citalopram
bleeding episodes during 213.9 treatment years in the warfarin plus SSRI group, and 10 patients experie
corresponding total incidences of bleedings were 51.4 and 23.9 per 1000 treatment years, respectively. T
(95% CI; 1.37 to 8.91, p=0.009) compared with warfarin only. The SSRI implicated in patients experienci
addition of an SSRI was not associated with a change in warfarin dose or INR (p=0.48 and p=0.31 respe
patient adherence, and exclusion of clopidogrel, dipyridamol, corticosteroids and anticoagulants other th
b) A population-based, case-controlled study of new coumarin users (acenocoumarol and phenprocoum
increased risk of hospitalization due to nongastrointestinal bleeding. Using national pharmacy and hospit
for abnormal bleeding and compared them with 5818 control subjects who were also taking a coumarin.
on SSRIs showed greater risk for hospitalization for nongastrointestinal bleeding (adjusted odds ratio (O
bleeding (adjusted OR 0.8, 95% CI, 0.4 to 1.5) was not significantly different (Schalekamp et al, 2008).
c) Sertraline 50 mg to 200 mg daily for 21 days produced an 8% increase in prothrombin time in subject
given prior to sertraline; this compared with a 1% decrease with placebo. Normalization of the prothromb
findings is unknown (Prod Info ZOLOFT(R) oral tablets, concentrate, 2008).
d) In a non-blinded, randomized, placebo-controlled trial involving 12 healthy volunteers, the effect of se
study, all participants received warfarin 0.75 mg/kg. Beginning on day 11, each volunteer was randomize
mg/day to 200 mg/day. Prothrombin time was measured prior to each dose of warfarin and periodically th
enhanced by sertraline to a clinically significant degree, despite the fact that sertraline was given in a hig

3.5.1.DF Naproxen

1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and
associated with an increased risk of bleeding. Bleeding events have included epistaxis, ecchymosis, hemator
suspension, 2008) (Prod Info Lexapro(TM), 2003; Dalton et al, 2003a; Prod Info CELEXA (R) oral tablet, solu
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When an SSRI and an NSAID are given concurrently, monitor patient for signs of in
7) Probable Mechanism: unknown
8) Literature Reports
a) SSRIs increase the risk of upper gastrointestinal bleeding and this effect is potentiated by concurrent
were searched among 26,005 users of antidepressant medications and compared with the number of ho
amount of upper GI bleeding episodes was 3.6 times more than expected (95% confidence interval, 2.7 t
12.2 (95% confidence interval, 7.1 to 19.5) and 5.2 (95% confidence interval, 3.2 to 8), respectively. The
SSRIs. Combined use of SSRIs and NSAIDs or low-dose aspirin increased the risk even further (Dalton
b) Coadministration of ketorolac with psychoactive drugs (such as fluoxetine) has been associated with

3.5.1.DG Naratriptan

1) Interaction Effect: an increased risk of serotonin syndrome

2) Summary: Rare incidences of weakness, hyperreflexia, and incoordination have been reported with the co 1 (5HT-1) agonist (Prod Info Amerge(TM), 2002). Concurrent use of a triptan and an SSRI may result in sero include restlessness, hallucinations, loss of coordination, fast heart beat, rapid changes in blood pressure, in Clinicians should be aware that triptans may be commonly used intermittently and that either the triptan or th syndrome with patients who are prescribed this combination and monitor them closely for symptoms of seroto

3) Severity: major

4) Onset: delayed

5) Substantiation: probable

6) Clinical Management: Coadministration of a triptan, such as naratriptan, and an SSRI may result in a life-t used intermittently and that either the triptan or the SSRI may be prescribed by a different physician. If these monitor closely for symptoms of serotonin syndrome (restlessness, hyperthermia, hyperreflexia, incoordinatio

7) Probable Mechanism: additive pharmacologic effects resulting in excessive serotonergic stimulation

3.5.1.DH Nialamide

1) Interaction Effect: CNS toxicity or serotonin syndrome (hypertension, hyperthermia, myoclonus, mental st

2) Summary: Concurrent administration or overlapping therapy with sertraline and a monoamine oxidase (M characterized by symptoms such as restlessness, myoclonus, changes in mental status, hyperreflexia, diaph concomitant use of serotonin specific reuptake inhibitors and MAO inhibitors (Prod Info Zoloft(R), 1999h; Lap & de Vries, 1990i). Concomitant use is contraindicated.

3) Severity: contraindicated

4) Onset: rapid

5) Substantiation: probable

6) Clinical Management: Concurrent use of sertraline and a MAO inhibitor is contraindicated. Wait at least 1 least 14 days after discontinuing sertraline before initiating therapy with a MAO inhibitor.

7) Probable Mechanism: inhibition of serotonin metabolism by monoamine oxidase

8) Literature Reports

a) Concomitant use of SSRIs and monoamine oxidase inhibitors can produce a toxic reaction known as hyperstimulation and manifests as restlessness, myoclonus, changes in mental status, hyperreflexia, dia fatality can result.

b) A 26-year old woman who had been taking isocarboxazid for eight weeks stopped taking the drug for the patient became restless and developed leg twitches. The patients was later admitted to the emergen disturbances. After treatment with diazepam and propranolol the patient did not improve. The patient wa symptoms after the second dose (Lappin & Auchincloss, 1994j).

c) A drug interaction was reported in a 61-year old woman in which sertraline 100 mg twice daily was ac taking the first sertraline dose, the patient was found in a semicomatose state, with elevated body tempe Hg. After transportation to the hospital, the patient was misdiagnosed as having neuroleptic malignant sy sertraline and phenelzine. The authors suggest that monoamine oxidase inhibitor (MAOI) therapy should serotonin reuptake inhibitor (SSRI) and that before starting a MAOI, SSRI therapy should be discontinue 1994j).

d) Two cases reports suggested a possible interaction between fluoxetine and selegiline (Suchowersky approximately one month after adding selegiline to fluoxetine. The patient improved two months after bo involved diaphoresis, vasoconstriction, and cyanosis of the hands which occurred in close temporal relat quick resolution of symptoms. Rechallenge with fluoxetine alone occurred without incident.

3.5.1.DI Niflumic Acid

1) Interaction Effect: an increased risk of bleeding

2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control an associated with an increased risk of bleeding. Bleeding events have included epistaxis, ecchymosis, hemato suspension, 2008) (Prod Info Lexapro(TM), 2003; Dalton et al, 2003a; Prod Info CELEXA (R) oral tablet, solu

3) Severity: moderate

4) Onset: unspecified

5) Substantiation: probable

6) Clinical Management: When an SSRI and an NSAID are given concurrently, monitor patient for signs of in

7) Probable Mechanism: unknown

8) Literature Reports

a) SSRIs increase the risk of upper gastrointestinal bleeding and this effect is potentiated by concurrent were searched among 26,005 users of antidepressant medications and compared with the number of ho amount of upper GI bleeding episodes was 3.6 times more than expected (95% confidence interval, 2.7 12.2 (95% confidence interval, 7.1 to 19.5) and 5.2 (95% confidence interval, 3.2 to 8), respectively. The SSRIs. Combined use of SSRIs and NSAIDs or low-dose aspirin increased the risk even further (Dalton

b) Coadministration of ketorolac with psychoactive drugs (such as fluoxetine) has been associated with

3.5.1.DJ Nimesulide

1) Interaction Effect: an increased risk of bleeding

2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control an associated with an increased risk of bleeding. Bleeding events have included epistaxis, ecchymosis, hemato

suspension, 2008) (Prod Info Lexapro(TM), 2003; Dalton et al, 2003a; Prod Info CELEXA (R) oral tablet, solu
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When an SSRI and an NSAID are given concurrently, monitor patient for signs of in
7) Probable Mechanism: unknown
8) Literature Reports
a) SSRIs increase the risk of upper gastrointestinal bleeding and this effect is potentiated by concurrent were searched among 26,005 users of antidepressant medications and compared with the number of ho amount of upper GI bleeding episodes was 3.6 times more than expected (95% confidence interval, 2.7 12.2 (95% confidence interval, 7.1 to 19.5) and 5.2 (95% confidence interval, 3.2 to 8), respectively. The SSRIs. Combined use of SSRIs and NSAIDs or low-dose aspirin increased the risk even further (Dalton
b) Coadministration of ketorolac with psychoactive drugs (such as fluoxetine) has been associated with

3.5.1.DK Nortriptyline
1) Interaction Effect: elevated nortriptyline serum levels or possible serotonin syndrome (hypertension, hyper
2) Summary: There is limited evidence suggesting that sertraline may inhibit tricyclic antidepressant (TCA) m cytochrome P450 2D6 enzyme activity and may increase the plasma concentrations of coadministered drugs al, 1994q; Lydiard et al, 1993h). Effects of the interaction may have little or no clinical impact, however. Incre compared with those found when fluoxetine (another selective serotonin reuptake inhibitor) was combined wi therapy for TCA toxicity (dry mouth, urinary retention, CNS depression). Nortriptyline doses may need to be r
3) Severity: major
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: The combined use of tricyclic antidepressants (TCAs) and selective serotonin reupt serotonin syndrome have also been reported with concurrent TCA and SSRI therapy. Caution should be obs concentrations as the dose of TCA may need to be reduced.
7) Probable Mechanism: inhibition of nortriptyline metabolism
8) Literature Reports
a) Desipramine pharmacokinetics were studied in 18 healthy male volunteers. Study subjects received daily) for 21 days. When sertraline was added to desipramine therapy, the mean maximum concentratio increased by 26%. Trough concentrations of desipramine were close to baseline one week after sertralin interaction may not be clinically significant (Preskorn et al, 1994p).
b) Fourteen elderly depressed patients were retrospectively studied to determine the effect that sertralin and increased up to 150 mg daily. Overall, sertraline caused a median increase of only 2% in nortriptylin clinical implications. In patients taking sertraline in doses of 100 mg or 150 mg daily, the nortriptyline leve in the change of nortriptyline levels, careful monitoring of nortriptyline concentrations should be practiced

3.5.1.DL Oxaprozin
1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and associated with an increased risk of bleeding. Bleeding events have included epistaxis, ecchymosis, hemator suspension, 2008) (Prod Info Lexapro(TM), 2003; Dalton et al, 2003a; Prod Info CELEXA (R) oral tablet, solu
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When an SSRI and an NSAID are given concurrently, monitor patient for signs of in
7) Probable Mechanism: unknown
8) Literature Reports
a) SSRIs increase the risk of upper gastrointestinal bleeding and this effect is potentiated by concurrent were searched among 26,005 users of antidepressant medications and compared with the number of ho amount of upper GI bleeding episodes was 3.6 times more than expected (95% confidence interval, 2.7 12.2 (95% confidence interval, 7.1 to 19.5) and 5.2 (95% confidence interval, 3.2 to 8), respectively. The SSRIs. Combined use of SSRIs and NSAIDs or low-dose aspirin increased the risk even further (Dalton
b) Coadministration of ketorolac with psychoactive drugs (such as fluoxetine) has been associated with

3.5.1.DM Oxycodone
1) Interaction Effect: an increased risk of serotonin syndrome (tachycardia, hyperthermia, myoclonus, menta
2) Summary: Coadministration of oxycodone and sertraline has resulted in the development of symptoms su Caution is advised if oxycodone and sertraline are coadministered. Monitor patients for signs and symptoms
3) Severity: major
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: Concomitant administration of oxycodone and sertraline may increase the risk of de symptoms of serotonin syndrome (tachycardia, hyperthermia, myoclonus, mental status changes).
7) Probable Mechanism: additive pharmacologic effects resulting in excessive serotonergic stimulation
8) Literature Reports
a) Symptoms of serotonin syndrome developed in an 86-year-old woman following concurrent administr

resulted in a sacral fracture. Prior to hospitalization, medications included extended-release oxycodone 1
20 mg twice daily for pain control and following a brief hospital stay, she was transferred to a long-term c
increased muscle tone in lower extremities, truncal ataxia, and coarse tremors, with myoclonic jerks, in b
decreased which resolved the myoclonus, rigidity, and tremors within 2 days. It was postulated that the i
(Gnanadesigan et al, 2005).

b) A 34-year-old bone marrow transplant male patient experienced visual hallucinations and tremors foll
presentation, the patient had been discharged from the hospital, following extensive evaluation (includin
of sertraline 50 mg once daily, oxycodone 10 mg as needed (average daily dose 10 to 20 mg/day), and c
omeprazole, folinic acid, acyclovir, fluconazole, and trimethoprim/sulfamethoxazole. Within 48 hours afte
biopsy-site related pain and during this interval, he experienced severe tremors and visual hallucinations
year ago and his current cyclosporine level was 467 ng/mL, cyclosporine was believed to be the offendir
discontinued and hydromorphone (maximum 6 mg/day) was initiated for pain control. However, 72 hours
cyclosporine level had decreased to 128 ng/mL. It was postulated that increased oxycodone doses in co
Subsequently, sertraline was discontinued and oral cyproheptadine 8 mg was administered, which resol

3.5.1.DN Parecoxib

1) Interaction Effect: an increased risk of bleeding

2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control anc
associated with an increased risk of bleeding. Bleeding events have included epistaxis, ecchymosis, hemator
suspension, 2008) (Prod Info Lexapro(TM), 2003; Dalton et al, 2003a; Prod Info CELEXA (R) oral tablet, solu

3) Severity: moderate

4) Onset: unspecified

5) Substantiation: probable

6) Clinical Management: When an SSRI and an NSAID are given concurrently, monitor patient for signs of in

7) Probable Mechanism: unknown

8) Literature Reports

a) SSRIs increase the risk of upper gastrointestinal bleeding and this effect is potentiated by concurrent
were searched among 26,005 users of antidepressant medications and compared with the number of ho
amount of upper GI bleeding episodes was 3.6 times more than expected (95% confidence interval, 2.7 t
12.2 (95% confidence interval, 7.1 to 19.5) and 5.2 (95% confidence interval, 3.2 to 8), respectively. The
SSRIs. Combined use of SSRIs and NSAIDs or low-dose aspirin increased the risk even further (Dalton

b) Coadministration of ketorolac with psychoactive drugs (such as fluoxetine) has been associated with

3.5.1.DO Pargyline

1) Interaction Effect: CNS toxicity or serotonin syndrome (hypertension, hyperthermia, myoclonus, mental sta

2) Summary: Concurrent administration or overlapping therapy with sertraline and a monoamine oxidase (MA
characterized by symptoms such as restlessness, myoclonus, changes in mental status, hyperreflexia, diaph
concomitant use of serotonin specific reuptake inhibitors and MAO inhibitors (Prod Info Zoloft(R), 1999; Lapp
de Vries, 1990a). Concomitant use is contraindicated.

3) Severity: contraindicated

4) Onset: rapid

5) Substantiation: probable

6) Clinical Management: Concurrent use of sertraline and a MAO inhibitor is contraindicated. Wait at least 14
least 14 days after discontinuing sertraline before initiating therapy with a MAO inhibitor.

7) Probable Mechanism: inhibition of serotonin metabolism by monoamine oxidase

8) Literature Reports

a) Concomitant use of SSRIs and monoamine oxidase inhibitors can produce a toxic reaction known as
hyperstimulation and manifests as restlessness, myoclonus, changes in mental status, hyperreflexia, dia
fatality can result.

b) A 26-year old woman who had been taking isocarboxazid for eight weeks stopped taking the drug for
the patient became restless and developed leg twitches. The patients was later admitted to the emergen
disturbances. After treatment with diazepam and propranolol the patient did not improve. The patient wa
symptoms after the second dose (Lappin & Auchincloss, 1994).

c) A drug interaction was reported in a 61-year old woman in which sertraline 100 mg twice daily was ac
taking the first sertraline dose, the patient was found in a semicomatose state, with elevated body tempe
Hg. After transportation to the hospital, the patient was misdiagnosed as having neuroleptic malignant sy
sertraline and phenelzine. The authors suggest that monoamine oxidase inhibitor (MAOI) therapy should
serotonin reuptake inhibitor (SSRI) and that before starting a MAOI, SSRI therapy should be discontinue
1994).

d) Two cases reports suggested a possible interaction between fluoxetine and selegiline (Suchowersky
approximately one month after adding selegiline to fluoxetine. The patient improved two months after bot
involved diaphoresis, vasoconstriction, and cyanosis of the hands which occurred in close temporal relat
quick resolution of symptoms. Rechallenge with fluoxetine alone occurred without incident.

3.5.1.DP Parnaparin

1) Interaction Effect: an increased risk of bleeding

2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control anc
anticoagulants has been associated with an increased risk of bleeding (Wallerstedt et al, 2009; Schalekamp

reported have included epistaxis, ecchymosis, hematoma, petechiae, and life-threatening hemorrhages. Alter coadministration of SSRIs with warfarin (Prod Info ZOLOFT(R) oral tablets, concentrate, 2008). Prothrombin 1997a).

3) Severity: major

4) Onset: delayed

5) Substantiation: probable

6) Clinical Management: When sertraline and an anticoagulant are given concurrently, monitor patient for sig closely for altered anticoagulant effects, including increased bleeding, when sertraline therapy is initiated or d

7) Probable Mechanism: unknown

8) Literature Reports

a) According to a retrospective cohort study (n=234), there was an increased risk of clinically relevant bl fibrillation during concomitant SSRI therapy or within 2 weeks following SSRI therapy termination. Patien with randomly selected patients who received warfarin only (n=117). SSRI included fluoxetine, citalopram bleeding episodes during 213.9 treatment years in the warfarin plus SSRI group, and 10 patients experie corresponding total incidences of bleedings were 51.4 and 23.9 per 1000 treatment years, respectively. T (95% CI; 1.37 to 8.91, p=0.009) compared with warfarin only. The SSRI implicated in patients experienci addition of an SSRI was not associated with a change in warfarin dose or INR (p=0.48 and p=0.31 respe patient adherence, and exclusion of clopidogrel, dipyridamol, corticosteroids and anticoagulants other tha

b) A population-based, case-controlled study of new coumarin users (acenocoumarol and phenprocoum increased risk of hospitalization due to nongastrointestinal bleeding. Using national pharmacy and hospit for abnormal bleeding and compared them with 5818 control subjects who were also taking a coumarin. on SSRIs showed greater risk for hospitalization for nongastrointestinal bleeding (adjusted odds ratio (O bleeding (adjusted OR 0.8, 95% CI, 0.4 to 1.5) was not significantly different (Schalekamp et al, 2008).

c) Sertraline 50 mg to 200 mg daily for 21 days produced an 8% increase in prothrombin time in subject given prior to sertraline; this compared with a 1% decrease with placebo. Normalization of the prothromb findings is unknown (Prod Info ZOLOFT(R) oral tablets, concentrate, 2008).

d) In a non-blinded, randomized, placebo-controlled trial involving 12 healthy volunteers, the effect of se study, all participants received warfarin 0.75 mg/kg. Beginning on day 11, each volunteer was randomize mg/day to 200 mg/day. Prothrombin time was measured prior to each dose of warfarin and periodically th enhanced by sertraline to a clinically significant degree, despite the fact that sertraline was given in a hig

3.5.1.DQ Pentosan Polysulfate Sodium

1) Interaction Effect: an increased risk of bleeding

2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and anticoagulants has been associated with an increased risk of bleeding (Wallerstedt et al, 2009; Schalekamp reported have included epistaxis, ecchymosis, hematoma, petechiae, and life-threatening hemorrhages. Alter coadministration of SSRIs with warfarin (Prod Info ZOLOFT(R) oral tablets, concentrate, 2008). Prothrombin 1997a).

3) Severity: major

4) Onset: delayed

5) Substantiation: probable

6) Clinical Management: When sertraline and an anticoagulant are given concurrently, monitor patient for sig closely for altered anticoagulant effects, including increased bleeding, when sertraline therapy is initiated or d

7) Probable Mechanism: unknown

8) Literature Reports

a) According to a retrospective cohort study (n=234), there was an increased risk of clinically relevant bl fibrillation during concomitant SSRI therapy or within 2 weeks following SSRI therapy termination. Patien with randomly selected patients who received warfarin only (n=117). SSRI included fluoxetine, citalopram bleeding episodes during 213.9 treatment years in the warfarin plus SSRI group, and 10 patients experie corresponding total incidences of bleedings were 51.4 and 23.9 per 1000 treatment years, respectively. T (95% CI; 1.37 to 8.91, p=0.009) compared with warfarin only. The SSRI implicated in patients experienci addition of an SSRI was not associated with a change in warfarin dose or INR (p=0.48 and p=0.31 respe patient adherence, and exclusion of clopidogrel, dipyridamol, corticosteroids and anticoagulants other tha

b) A population-based, case-controlled study of new coumarin users (acenocoumarol and phenprocoum increased risk of hospitalization due to nongastrointestinal bleeding. Using national pharmacy and hospit for abnormal bleeding and compared them with 5818 control subjects who were also taking a coumarin. on SSRIs showed greater risk for hospitalization for nongastrointestinal bleeding (adjusted odds ratio (O bleeding (adjusted OR 0.8, 95% CI, 0.4 to 1.5) was not significantly different (Schalekamp et al, 2008).

c) Sertraline 50 mg to 200 mg daily for 21 days produced an 8% increase in prothrombin time in subject given prior to sertraline; this compared with a 1% decrease with placebo. Normalization of the prothromb findings is unknown (Prod Info ZOLOFT(R) oral tablets, concentrate, 2008).

d) In a non-blinded, randomized, placebo-controlled trial involving 12 healthy volunteers, the effect of se study, all participants received warfarin 0.75 mg/kg. Beginning on day 11, each volunteer was randomize mg/day to 200 mg/day. Prothrombin time was measured prior to each dose of warfarin and periodically th enhanced by sertraline to a clinically significant degree, despite the fact that sertraline was given in a hig

3.5.1.DR Phenelzine

1) Interaction Effect: CNS toxicity or serotonin syndrome (hypertension, hyperthermia, myoclonus, mental sta

2) Summary: Concurrent administration or overlapping therapy with sertraline and a monoamine oxidase (MA
characterized by symptoms such as restlessness, myoclonus, changes in mental status, hyperreflexia, diaph
Zoloft(R), 2002q; Lappin & Auchincloss, 1994q; Graber et al, 1994q; Bhatara & Bandettini, 1993h; Suchowers
3) Severity: contraindicated
4) Onset: rapid
5) Substantiation: probable
6) Clinical Management: Concurrent use of sertraline and a MAO inhibitor is contraindicated. Wait at least 14
least 14 days after discontinuing sertraline before initiating therapy with a MAO inhibitor.
7) Probable Mechanism: inhibition of serotonin metabolism by monoamine oxidase
8) Literature Reports
a) Concomitant use of serotonin specific reuptake inhibitors and monoamine oxidase inhibitors can prod
syndrome is a condition of serotonergic hyperstimulation and manifests as restlessness, myoclonus, cha
not recognized and correctly treated, death can result.
b) A 26-year old woman who had been taking isocarboxazid for eight weeks stopped taking the drug for
the patient became restless and developed leg twitches. The patients was later admitted to the emergen
disturbances. The patient did not improve after treatment with diazepam and propranolol. The patient wa
in symptoms after the second dose (Lappin & Auchincloss, 1994p).
c) A drug interaction was reported in a 61-year old woman in which sertraline 100 mg twice daily was ad
taking the first sertraline dose, the patient was found in a semicomatose state, with elevated body tempe
mmHg. After transportation to the hospital, the patient was misdiagnosed as having neuroleptic malignar
between sertraline and phenelzine. The authors suggest that MAO inhibitor therapy should be discontinu
inhibitor (SSRI) and that before starting a MAOI, SSRI therapy should be discontinued for at least 5 half-
d) Two cases reports suggested a possible interaction between fluoxetine and selegiline (Suchowersky
approximately 1 month after adding selegiline to fluoxetine therapy. The patient improved 2 months after
involved diaphoresis, vasoconstriction, and cyanosis of the hands which occurred in close temporal relat
quick resolution of symptoms. Rechallenge with fluoxetine alone occurred without incident.

3.5.1.DS Phenindione

1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and
anticoagulants has been associated with an increased risk of bleeding (Wallerstedt et al, 2009; Schalekamp e
reported have included epistaxis, ecchymosis, hematoma, petechiae, and life-threatening hemorrhages. Alter
coadministration of SSRIs with warfarin (Prod Info ZOLOFT(R) oral tablets, concentrate, 2008). Prothrombin
1997a).
3) Severity: major
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: When sertraline and an anticoagulant are given concurrently, monitor patient for sig
closely for altered anticoagulant effects, including increased bleeding, when sertraline therapy is initiated or d
7) Probable Mechanism: unknown
8) Literature Reports
a) According to a retrospective cohort study (n=234), there was an increased risk of clinically relevant bl
fibrillation during concomitant SSRI therapy or within 2 weeks following SSRI therapy termination. Patien
with randomly selected patients who received warfarin only (n=117). SSRI included fluoxetine, citalopram
bleeding episodes during 213.9 treatment years in the warfarin plus SSRI group, and 10 patients experie
corresponding total incidences of bleedings were 51.4 and 23.9 per 1000 treatment years, respectively. T
(95% CI; 1.37 to 8.91, p=0.009) compared with warfarin only. The SSRI implicated in patients experienci
addition of an SSRI was not associated with a change in warfarin dose or INR (p=0.48 and p=0.31 respe
patient adherence, and exclusion of clopidogrel, dipyridamol, corticosteroids and anticoagulants other tha
b) A population-based, case-controlled study of new coumarin users (acenocoumarol and phenprocoum
increased risk of hospitalization due to nongastrointestinal bleeding. Using national pharmacy and hospit
for abnormal bleeding and compared them with 5818 control subjects who were also taking a coumarin.
on SSRIs showed greater risk for hospitalization for nongastrointestinal bleeding (adjusted odds ratio (OR
bleeding (adjusted OR 0.8, 95% CI, 0.4 to 1.5) was not significantly different (Schalekamp et al, 2008).
c) Sertraline 50 mg to 200 mg daily for 21 days produced an 8% increase in prothrombin time in subject
given prior to sertraline; this compared with a 1% decrease with placebo. Normalization of the prothromb
findings is unknown (Prod Info ZOLOFT(R) oral tablets, concentrate, 2008).
d) In a non-blinded, randomized, placebo-controlled trial involving 12 healthy volunteers, the effect of se
study, all participants received warfarin 0.75 mg/kg. Beginning on day 11, each volunteer was randomize
mg/day to 200 mg/day. Prothrombin time was measured prior to each dose of warfarin and periodically th
enhanced by sertraline to a clinically significant degree, despite the fact that sertraline was given in a hig

3.5.1.DT Phenprocoumon

1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and
anticoagulants has been associated with an increased risk of bleeding (Wallerstedt et al, 2009; Schalekamp e
reported have included epistaxis, ecchymosis, hematoma, petechiae, and life-threatening hemorrhages. Alter
coadministration of SSRIs with warfarin (Prod Info ZOLOFT(R) oral tablets, concentrate, 2008). Prothrombin

1997a).
3) Severity: major
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: When sertraline and an anticoagulant are given concurrently, monitor patient for sig closely for altered anticoagulant effects, including increased bleeding, when sertraline therapy is initiated or d
7) Probable Mechanism: unknown
8) Literature Reports
a) According to a retrospective cohort study (n=234), there was an increased risk of clinically relevant bl fibrillation during concomitant SSRI therapy or within 2 weeks following SSRI therapy termination. Patien with randomly selected patients who received warfarin only (n=117). SSRI included fluoxetine, citalopram bleeding episodes during 213.9 treatment years in the warfarin plus SSRI group, and 10 patients experie corresponding total incidences of bleedings were 51.4 and 23.9 per 1000 treatment years, respectively. T (95% CI; 1.37 to 8.91, p=0.009) compared with warfarin only. The SSRI implicated in patients experienci addition of an SSRI was not associated with a change in warfarin dose or INR (p=0.48 and p=0.31 respe patient adherence, and exclusion of clopidogrel, dipyridamol, corticosteroids and anticoagulants other th
b) A population-based, case-controlled study of new coumarin users (acenocoumarol and phenprocoum increased risk of hospitalization due to nongastrointestinal bleeding. Using national pharmacy and hospit for abnormal bleeding and compared them with 5818 control subjects who were also taking a coumarin. on SSRIs showed greater risk for hospitalization for nongastrointestinal bleeding (adjusted odds ratio (O bleeding (adjusted OR 0.8, 95% CI, 0.4 to 1.5) was not significantly different (Schalekamp et al, 2008).
c) Sertraline 50 mg to 200 mg daily for 21 days produced an 8% increase in prothrombin time in subject given prior to sertraline; this compared with a 1% decrease with placebo. Normalization of the prothromb findings is unknown (Prod Info ZOLOFT(R) oral tablets, concentrate, 2008).
d) In a non-blinded, randomized, placebo-controlled trial involving 12 healthy volunteers, the effect of se study, all participants received warfarin 0.75 mg/kg. Beginning on day 11, each volunteer was randomize mg/day to 200 mg/day. Prothrombin time was measured prior to each dose of warfarin and periodically th enhanced by sertraline to a clinically significant degree, despite the fact that sertraline was given in a hig

3.5.1.DU Phenylbutazone
1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and associated with an increased risk of bleeding. Bleeding events have included epistaxis, ecchymosis, hematom suspension, 2008) (Prod Info Lexapro(TM), 2003; Dalton et al, 2003a; Prod Info CELEXA (R) oral tablet, solu
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When an SSRI and an NSAID are given concurrently, monitor patient for signs of in
7) Probable Mechanism: unknown
8) Literature Reports
a) SSRIs increase the risk of upper gastrointestinal bleeding and this effect is potentiated by concurrent were searched among 26,005 users of antidepressant medications and compared with the number of ho amount of upper GI bleeding episodes was 3.6 times more than expected (95% confidence interval, 2.7 t 12.2 (95% confidence interval, 7.1 to 19.5) and 5.2 (95% confidence interval, 3.2 to 8), respectively. The SSRIs. Combined use of SSRIs and NSAIDs or low-dose aspirin increased the risk even further (Dalton
b) Coadministration of ketorolac with psychoactive drugs (such as fluoxetine) has been associated with

3.5.1.DV Phenytoin
1) Interaction Effect: an increased risk of phenytoin toxicity (ataxia, hyperreflexia, nystagmus, tremor)
2) Summary: Coadministration of sertraline with phenytoin has been reported to result in elevated serum phe controlled studies are needed to verify the extent of this interaction.
3) Severity: moderate
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: Caution is warranted if phenytoin and sertraline are to be coadministered. Serum pl therapy or changing the sertraline dose. Monitor patients for signs and symptoms of phenytoin toxicity (ataxia downward.
7) Probable Mechanism: sertraline inhibition of phenytoin metabolism by cytochrome P450 isoenzymes
8) Literature Reports
a) Sertraline is known to be a moderate to weak inhibitor of the cytochrome P450IID6 isoenzyme (CYP2 metabolism of phenytoin may involve the cytochrome P450IID6 (Murray, 1992a) and the CYP2C9 hepati activity and pathways, it seems theoretically possible that concurrent sertraline may act to inhibit metabo
b) Two elderly patients developed elevated serum phenytoin concentrations during coadministration wit addition to several other medications. After sertraline 25 mg every night for depression was added to his increases in the sertraline dose to 75 mg per day, the patient's serum phenytoin level rose to 30.9 mcg/m per day. Sertraline 100 mg per day was also administered without further adverse effects. Patient 2, an 8 mcg/mL) after the addition of sertraline 25 mg every other day to phenytoin 260 mg per day. The authors sertraline therapy or initiating a change in sertraline dose (Haselberger et al, 1997b).

3.5.1.DW Pimozide

1) Interaction Effect: an increase in plasma pimozide levels
2) Summary: Due to the narrow therapeutic index of pimozide and due to the interaction noted at low dose o Info Zoloft(R), 2002s).
3) Severity: contraindicated
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: Concomitant use of sertraline in patients taking pimozide is contraindicated.
7) Probable Mechanism: unknown
8) Literature Reports
a) In a controlled trial of a single 2 mg dose of pimozide, sertraline 200 mg daily coadministration to stea time curve (AUC) and maximum plasma concentrations (Cmax) of about 40%, but was not associated w been evaluated in combination with sertraline, the effect on QT interval and pharmacokinetic parameters and observed interaction data with low doses, the combination should be avoided (Prod Info Zoloft(R), 2

3.5.1.DX Pirazolac

1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and associated with an increased risk of bleeding. Bleeding events have included epistaxis, ecchymosis, hemator suspension, 2008) (Prod Info Lexapro(TM), 2003; Dalton et al, 2003a; Prod Info CELEXA (R) oral tablet, solu
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When an SSRI and an NSAID are given concurrently, monitor patient for signs of in
7) Probable Mechanism: unknown
8) Literature Reports
a) SSRIs increase the risk of upper gastrointestinal bleeding and this effect is potentiated by concurrent were searched among 26,005 users of antidepressant medications and compared with the number of ho amount of upper GI bleeding episodes was 3.6 times more than expected (95% confidence interval, 2.7 12.2 (95% confidence interval, 7.1 to 19.5) and 5.2 (95% confidence interval, 3.2 to 8), respectively. The SSRIs. Combined use of SSRIs and NSAIDs or low-dose aspirin increased the risk even further (Dalton
b) Coadministration of ketorolac with psychoactive drugs (such as fluoxetine) has been associated with

3.5.1.DY Piroxicam

1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and associated with an increased risk of bleeding. Bleeding events have included epistaxis, ecchymosis, hemator suspension, 2008) (Prod Info Lexapro(TM), 2003; Dalton et al, 2003a; Prod Info CELEXA (R) oral tablet, solu
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When an SSRI and an NSAID are given concurrently, monitor patient for signs of in
7) Probable Mechanism: unknown
8) Literature Reports
a) SSRIs increase the risk of upper gastrointestinal bleeding and this effect is potentiated by concurrent were searched among 26,005 users of antidepressant medications and compared with the number of ho amount of upper GI bleeding episodes was 3.6 times more than expected (95% confidence interval, 2.7 12.2 (95% confidence interval, 7.1 to 19.5) and 5.2 (95% confidence interval, 3.2 to 8), respectively. The SSRIs. Combined use of SSRIs and NSAIDs or low-dose aspirin increased the risk even further (Dalton
b) Coadministration of ketorolac with psychoactive drugs (such as fluoxetine) has been associated with

3.5.1.DZ Pirprofen

1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and associated with an increased risk of bleeding. Bleeding events have included epistaxis, ecchymosis, hemator suspension, 2008) (Prod Info Lexapro(TM), 2003; Dalton et al, 2003a; Prod Info CELEXA (R) oral tablet, solu
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When an SSRI and an NSAID are given concurrently, monitor patient for signs of in
7) Probable Mechanism: unknown
8) Literature Reports
a) SSRIs increase the risk of upper gastrointestinal bleeding and this effect is potentiated by concurrent were searched among 26,005 users of antidepressant medications and compared with the number of ho amount of upper GI bleeding episodes was 3.6 times more than expected (95% confidence interval, 2.7 12.2 (95% confidence interval, 7.1 to 19.5) and 5.2 (95% confidence interval, 3.2 to 8), respectively. The SSRIs. Combined use of SSRIs and NSAIDs or low-dose aspirin increased the risk even further (Dalton

b) Coadministration of ketorolac with psychoactive drugs (such as fluoxetine) has been associated with

3.5.1.EA Procarbazine

1) Interaction Effect: CNS toxicity or serotonin syndrome (hypertension, hyperthermia, myoclonus, mental sta
2) Summary: Concurrent administration or overlapping therapy with sertraline and a monoamine oxidase (MA characterized by symptoms such as restlessness, myoclonus, changes in mental status, hyperreflexia, diaph concomitant use of serotonin specific reuptake inhibitors and MAO inhibitors (Prod Info Zoloft(R), 1999j; Lapp & de Vries, 1990q). Concomitant use is contraindicated.
3) Severity: contraindicated
4) Onset: rapid
5) Substantiation: probable
6) Clinical Management: Concurrent use of sertraline and a MAO inhibitor is contraindicated. Wait at least 14 least 14 days after discontinuing sertraline before initiating therapy with a MAO inhibitor.
7) Probable Mechanism: inhibition of serotonin metabolism by monoamine oxidase
8) Literature Reports

a) Concomitant use of SSRIs and monoamine oxidase inhibitors can produce a toxic reaction known as serotonergic hyperstimulation and manifests as restlessness, myoclonus, changes in mental status, hype correctly treated, fatality can result.

b) A 26-year old woman who had been taking isocarboxazid for eight weeks stopped taking the drug for the patient became restless and developed leg twitches. The patients was later admitted to the emergen disturbances. After treatment with diazepam and propranolol the patient did not improve. The patient was symptoms after the second dose (Lappin & Auchincloss, 1994r).

c) A drug interaction was reported in a 61-year old woman in which sertraline 100 mg twice daily was ac taking the first sertraline dose, the patient was found in a semicomatose state, with elevated body tempe Hg. After transportation to the hospital, the patient was misdiagnosed as having neuroleptic malignant sy sertraline and phenelzine. The authors suggest that monoamine oxidase inhibitor (MAOI) therapy should serotonin reuptake inhibitor (SSRI) and that before starting a MAOI, SSRI therapy should be discontinue 1994r).

d) Two cases reports suggested a possible interaction between fluoxetine and selegiline (Suchowersky approximately one month after adding selegiline to fluoxetine. The patient improved two months after bot involved diaphoresis, vasoconstriction, and cyanosis of the hands which occurred in close temporal relat quick resolution of symptoms. Rechallenge with fluoxetine alone occurred without incident.

3.5.1.EB Propafenone

1) Interaction Effect: an increased risk of propafenone toxicity (cardiac arrhythmias)
2) Summary: No data are currently available related to concomitant propafenone - sertraline administration. I 2000). Sertraline inhibits the CYP2D6 isoenzyme (Prod Info Zoloft(R), 1999d). With propafenone - sertraline propafenone serum levels and possible propafenone toxicity. Controlled studies are needed to investigate the
3) Severity: moderate
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: Coadministration of these agents should be approached with caution. Monitor the E may need to be reduced.
7) Probable Mechanism: inhibition of propafenone metabolism

3.5.1.EC Propranolol

1) Interaction Effect: an increased risk of chest pain
2) Summary: Sertraline is a moderate to weak inhibitor of the hepatic cytochrome P450IID6 isoenzyme (CYP report describes sudden chest pain when sertraline was added to existing propranolol therapy (Iruela, 1994a)
3) Severity: moderate
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: Monitor patients receiving propranolol and sertraline cotherapy for an increased inc coronary artery disease.
7) Probable Mechanism: endothelium vasoconstriction caused by serotonin
8) Literature Reports

a) A 53-year-old male physician was maintained on propranolol 160 mg daily and aspirin 200 mg daily fo depression, he experienced sudden precordial chest pain that was responsive to 2 mg of sublingual glyc occurred on the electrocardiogram. The next day, a similar reaction happened soon after the administrat nortriptyline 50 mg daily with no further episodes of chest pain. Possible mechanisms for this interaction artery disease (Iruela, 1994).

3.5.1.ED Propyphenazone

1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and associated with an increased risk of bleeding. Bleeding events have included epistaxis, ecchymosis, hemator suspension, 2008) (Prod Info Lexapro(TM), 2003; Dalton et al, 2003a; Prod Info CELEXA (R) oral tablet, solu
3) Severity: moderate

4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When an SSRI and an NSAID are given concurrently, monitor patient for signs of in
7) Probable Mechanism: unknown
8) Literature Reports
a) SSRIs increase the risk of upper gastrointestinal bleeding and this effect is potentiated by concurrent were searched among 26,005 users of antidepressant medications and compared with the number of ho amount of upper GI bleeding episodes was 3.6 times more than expected (95% confidence interval, 2.7 t 12.2 (95% confidence interval, 7.1 to 19.5) and 5.2 (95% confidence interval, 3.2 to 8), respectively. The SSRIs. Combined use of SSRIs and NSAIDs or low-dose aspirin increased the risk even further (Dalton
b) Coadministration of ketorolac with psychoactive drugs (such as fluoxetine) has been associated with

3.5.1.EE Proquazone

1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and associated with an increased risk of bleeding. Bleeding events have included epistaxis, ecchymosis, hemator suspension, 2008) (Prod Info Lexapro(TM), 2003; Dalton et al, 2003a; Prod Info CELEXA (R) oral tablet, solu
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When an SSRI and an NSAID are given concurrently, monitor patient for signs of in
7) Probable Mechanism: unknown
8) Literature Reports
a) SSRIs increase the risk of upper gastrointestinal bleeding and this effect is potentiated by concurrent were searched among 26,005 users of antidepressant medications and compared with the number of ho amount of upper GI bleeding episodes was 3.6 times more than expected (95% confidence interval, 2.7 t 12.2 (95% confidence interval, 7.1 to 19.5) and 5.2 (95% confidence interval, 3.2 to 8), respectively. The SSRIs. Combined use of SSRIs and NSAIDs or low-dose aspirin increased the risk even further (Dalton
b) Coadministration of ketorolac with psychoactive drugs (such as fluoxetine) has been associated with

3.5.1.EF Protriptyline

1) Interaction Effect: modest elevations in protriptyline serum levels or possible serotonin syndrome (hyperte
2) Summary: There is limited evidence suggesting that sertraline may inhibit tricyclic antidepressant (TCA) m P450 2D6 enzyme activity and may increase the plasma concentrations of coadministered drugs that are me Lydiard et al, 1993a; Prod Info Zoloft(R), 1999a). Effects of the interaction may have little or no clinical impac were modest compared with those found when fluoxetine (another selective serotonin reuptake inhibitor) was sertraline therapy for TCA toxicity (dry mouth, urinary retention, CNS depression). Protriptyline doses may ne
3) Severity: major
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: The combined use of tricyclic antidepressants (TCAs) and selective serotonin reupt serotonin syndrome have also been reported with concurrent TCA and SSRI therapy. Caution should be obse
7) Probable Mechanism: inhibition of protriptyline metabolism
8) Literature Reports
a) Desipramine pharmacokinetics were studied in 18 healthy male volunteers. Study subjects received c daily) for 21 days. When sertraline was added to desipramine therapy, the mean maximum concentration increased by 26%. Trough concentrations of desipramine were close to baseline one week after sertralin interaction may not be clinically significant (Preskorn et al, 1994b).

3.5.1.EG Rasagiline

1) Interaction Effect: CNS toxicity or serotonin syndrome (hypertension, hyperthermia, myoclonus, mental sta
2) Summary: Concurrent administration or overlapping therapy with selective serotonin reuptake inhibitors, in has been reported to cause serious, sometimes fatal reactions. Signs and symptoms included hyperthermia, status changes progressing to extreme agitation, delirium, and coma. Similar reactions have been reported w selegiline. Rasagiline clinical trials did allow concomitant use of sertraline in doses less than or equal to 100 m adequate to rule out the possibility of adverse events from the combination of rasagiline and sertraline, and s initiating therapy with sertraline (Prod Info AZILECT(R) oral tablets, 2006).
3) Severity: major
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: Concurrent use of sertraline and rasagiline Should be avoided. Wait at least 14 day
7) Probable Mechanism: inhibition of serotonin metabolism by monoamine oxidase
8) Literature Reports
a) Concomitant use of serotonin specific reuptake inhibitors and monoamine oxidase inhibitors can prod syndrome is a condition of serotonergic hyperstimulation and manifests as restlessness, myoclonus, cha not recognized and correctly treated, death can result.

3.5.1.EH Reviparin

1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and anticoagulants has been associated with an increased risk of bleeding (Wallerstedt et al, 2009; Schalekamp reported have included epistaxis, ecchymosis, hematoma, petechiae, and life-threatening hemorrhages. Alter coadministration of SSRIs with warfarin (Prod Info ZOLOFT(R) oral tablets, concentrate, 2008). Prothrombin 1997a).
3) Severity: major
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: When sertraline and an anticoagulant are given concurrently, monitor patient for sig closely for altered anticoagulant effects, including increased bleeding, when sertraline therapy is initiated or d
7) Probable Mechanism: unknown
8) Literature Reports
a) According to a retrospective cohort study (n=234), there was an increased risk of clinically relevant bl fibrillation during concomitant SSRI therapy or within 2 weeks following SSRI therapy termination. Patien with randomly selected patients who received warfarin only (n=117). SSRI included fluoxetine, citalopram bleeding episodes during 213.9 treatment years in the warfarin plus SSRI group, and 10 patients experie corresponding total incidences of bleedings were 51.4 and 23.9 per 1000 treatment years, respectively. (95% CI; 1.37 to 8.91, p=0.009) compared with warfarin only. The SSRI implicated in patients experienci addition of an SSRI was not associated with a change in warfarin dose or INR (p=0.48 and p=0.31 respe patient adherence, and exclusion of clopidogrel, dipyridamol, corticosteroids and anticoagulants other th
b) A population-based, case-controlled study of new coumarin users (acenocoumarol and phenprocoum increased risk of hospitalization due to nongastrointestinal bleeding. Using national pharmacy and hospit for abnormal bleeding and compared them with 5818 control subjects who were also taking a coumarin. on SSRIs showed greater risk for hospitalization for nongastrointestinal bleeding (adjusted odds ratio (O bleeding (adjusted OR 0.8, 95% CI, 0.4 to 1.5) was not significantly different (Schalekamp et al, 2008).
c) Sertraline 50 mg to 200 mg daily for 21 days produced an 8% increase in prothrombin time in subject given prior to sertraline; this compared with a 1% decrease with placebo. Normalization of the prothromb findings is unknown (Prod Info ZOLOFT(R) oral tablets, concentrate, 2008).
d) In a non-blinded, randomized, placebo-controlled trial involving 12 healthy volunteers, the effect of se study, all participants received warfarin 0.75 mg/kg. Beginning on day 11, each volunteer was randomize mg/day to 200 mg/day. Prothrombin time was measured prior to each dose of warfarin and periodically th enhanced by sertraline to a clinically significant degree, despite the fact that sertraline was given in a hig

3.5.1.EI Rifampin

1) Interaction Effect: loss of sertraline efficacy
2) Summary: Sertraline is metabolized by cytochrome P450 3A4 enzymes, which are induced by rifampin the of selective serotonin reuptake inhibitor (SSRI) withdrawal syndrome following seven days of concurrent rifam
3) Severity: moderate
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: Monitor patients for sertraline efficacy and signs of selective serotonin reuptake inh rifampin is given concomitantly.
7) Probable Mechanism: induction of cytochrome P450 3A4-mediated sertraline metabolism
8) Literature Reports
a) Rifampin administration was thought to precipitate selective serotonin reuptake inhibitor withdrawal sy concurrent therapy. The patient had been stabilized on sertraline 200 mg nightly for generalized anxiety mg was started for a methicillin-resistant Staphylococcus aureus skin infection. Seven days later, the pat a blood sample was drawn to determine the plasma sertraline concentration. Laboratory analysis reveale ng/mL. The patient finished the remainder of the 10-day course of rifampin. Seven days after rifampin wa an N-desmethylsertraline concentration of 136 ng/mL. Anxiety was still persistent in this patient, so sertra (Markowitz & DeVane, 2000).

3.5.1.EJ Rizatriptan

1) Interaction Effect: an increased risk of serotonin syndrome
2) Summary: There have been case reports of weakness, hyperreflexia, and incoordination following concon specific reuptake inhibitor (SSRI) (Prod Info Imitrex(R), 1998). Because rizatriptan is a 5HT 1B/1D receptor a 1998a). Concurrent use of a triptan and an SSRI may result in serotonin syndrome which may be life-threate coordination, fast heart beat, rapid changes in blood pressure, increased body temperature, overreactive refle commonly used intermittently and that either the triptan or the SSRI may be prescribed by a different physicia combination and monitor them closely for symptoms of serotonin syndrome (US Food and Drug Administratio
3) Severity: major
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: Coadministration of a triptan, such as rizatriptan, and an SSRI may result in a life-th used intermittently and that either the triptan or the SSRI may be prescribed by a different physician. If these monitor closely for symptoms of serotonin syndrome (restlessness, hyperthermia, hyperreflexia, incoordinatio
7) Probable Mechanism: additive pharmacologic effects resulting in excessive serotonergic stimulation

8) Literature Reports
a) Twelve healthy volunteers received paroxetine 20 mg daily for two weeks and a single dose of rizatrip paroxetine (Prod Info Maxalt(R), 1998).

3.5.1.EK Rofecoxib
1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and associated with an increased risk of bleeding. Bleeding events have included epistaxis, ecchymosis, hemator suspension, 2008) (Prod Info Lexapro(TM), 2003; Dalton et al, 2003a; Prod Info CELEXA (R) oral tablet, solu
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When an SSRI and an NSAID are given concurrently, monitor patient for signs of in
7) Probable Mechanism: unknown
8) Literature Reports
a) SSRIs increase the risk of upper gastrointestinal bleeding and this effect is potentiated by concurrent were searched among 26,005 users of antidepressant medications and compared with the number of ho amount of upper GI bleeding episodes was 3.6 times more than expected (95% confidence interval, 2.7 12.2 (95% confidence interval, 7.1 to 19.5) and 5.2 (95% confidence interval, 3.2 to 8), respectively. The SSRIs. Combined use of SSRIs and NSAIDs or low-dose aspirin increased the risk even further (Dalton
b) Coadministration of ketorolac with psychoactive drugs (such as fluoxetine) has been associated with

3.5.1.EL Selegiline
1) Interaction Effect: CNS toxicity or serotonin syndrome (hypertension, hyperthermia, myoclonus, mental sta
2) Summary: Concurrent administration or overlapping therapy with sertraline and a monoamine oxidase (MA characterized by symptoms such as restlessness, myoclonus, changes in mental status, hyperreflexia, diaph Zoloft(R), 2002u; Lappin & Auchincloss, 1994u; Graber et al, 1994u; Bhatara & Bandettini, 1993j; Suchowers contraindicated, and a minimum of 14 days should elapse after discontinuing selegiline before initiating thera before initiating therapy with selegiline (Prod Info EMSAM(R) transdermal patch, 2006).
3) Severity: contraindicated
4) Onset: rapid
5) Substantiation: probable
6) Clinical Management: Concurrent use of sertraline and selegiline is contraindicated. Wait at least 14 days after discontinuing sertraline before initiating therapy with selegiline.
7) Probable Mechanism: inhibition of serotonin metabolism by monoamine oxidase
8) Literature Reports
a) Concomitant use of serotonin specific reuptake inhibitors and monoamine oxidase inhibitors can prod syndrome is a condition of serotonergic hyperstimulation and manifests as restlessness, myoclonus, cha not recognized and correctly treated, death can result.
b) A 26-year old woman who had been taking isocarboxazid for eight weeks stopped taking the drug for the patient became restless and developed leg twitches. The patients was later admitted to the emergen disturbances. The patient did not improve after treatment with diazepam and propranolol. The patient wa in symptoms after the second dose (Lappin & Auchincloss, 1994t).
c) A drug interaction was reported in a 61-year old woman in which sertraline 100 mg twice daily was ad taking the first sertraline dose, the patient was found in a semicomatose state, with elevated body tempe mmHg. After transportation to the hospital, the patient was misdiagnosed as having neuroleptic malignar between sertraline and phenelzine. The authors suggest that MAO inhibitor therapy should be discontinu inhibitor (SSRI) and that before starting a MAOI, SSRI therapy should be discontinued for at least 5 half-
d) Two case reports suggested a possible interaction between fluoxetine and selegiline (Suchowersky *& approximately 1 month after adding selegiline to fluoxetine therapy. The patient improved 2 months after involved diaphoresis, vasoconstriction, and cyanosis of the hands which occurred in close temporal relat quick resolution of symptoms. Rechallenge with fluoxetine alone occurred without incident.

3.5.1.EM Sibrafiban
1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and been associated with an increased risk of bleeding. Bleeding events reported have included epistaxis, ecchyr tablets, suspension, 2008; Prod Info PROZAC(R) oral capsules, delayed-release capsules, solution, 2008).
3) Severity: major
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When an SSRI and an antiplatelet agent are given concurrently, monitor patient for PROZAC(R) oral capsules, delayed-release capsules, solution, 2008)
7) Probable Mechanism: unknown

3.5.1.EN Sibutramine
1) Interaction Effect: an increased risk of serotonin syndrome (hypertension, hyperthermia, myoclonus, ment
2) Summary: Sibutramine inhibits the reuptake of norepinephrine, dopamine, and serotonin. In addition, the t

neurotransmitters. A hyperserotonergic state, termed serotonin syndrome, may result if sibutramine is given c
and selective serotonin reuptake inhibitors is not recommended (Prod Info Meridia(R), 1997).
3) Severity: major
4) Onset: rapid
5) Substantiation: probable
6) Clinical Management: Sibutramine should not be administered with serotonergic agents, including selectiv
7) Probable Mechanism: additive pharmacologic effects resulting in excessive serotonergic stimulation
8) Literature Reports
a) Serotonin syndrome is a condition of serotonergic hyperstimulation and manifests as restlessness, m
the syndrome is not recognized and correctly treated, death can result (Sternbach, 1991b).

3.5.1.EO St John's Wort
1) Interaction Effect: an increased risk of serotonin syndrome (hypertension, hyperthermia, myoclonus, ment
2) Summary: Case reports describe the onset of serotonin syndrome-like symptoms, mania, and hypomania
(Spinella & Eaton, 2002c; Barbanel et al, 2000a; Waksman et al, 2000a; Lantz et al, 1999a). A patient exhibit
paroxetine therapy (Gordon, 1998a). St. John's Wort is thought to inhibit serotonin reuptake and may have m
which when added to selective serotonin reuptake inhibitors may result in serotonin syndrome.
3) Severity: major
4) Onset: rapid
5) Substantiation: probable
6) Clinical Management: Patients should be advised to wait two weeks after stopping St. John's Wort before
selective serotonin reuptake inhibitor (SSRI) therapy with St. John's Wort, the half-life of the specific SSRI sh
metabolized out of the body.
7) Probable Mechanism: additive serotonergic effect
8) Literature Reports
a) Five cases have been reported of serotonin syndrome in the elderly after combining prescription antic
headache 4 days after starting St. John's Wort 300 milligrams (mg) three times daily combined with sertr
2 developed nausea, epigastric pain and anxiety 3 days after starting St. John's Wort 300 mg twice daily
discontinuing both medications, and he resumed sertraline use without complications. The third case dev
mg twice daily combined with sertraline 50 mg daily. His symptoms improved in 4 to 5 days after stoppin
nausea, anxiety, restless, and irritability 2 days after starting St. John's Wort 300 mg three times daily co
seven days, and his symptoms improved in 1 week after stopping the medication. Cases 1 through 4 res
Case 5 developed nausea, vomiting and restlessness 3 days after starting St. John's Wort 300 mg three
John's Wort but discontinued the nefazodone and over 1 week her symptoms Improved. She refused to
moderate symptoms of depression and anxiety returned (Lantz et al, 1999).
b) A 50-year-old female taking St. John's Wort 600 mg daily experienced symptoms of sedative intoxica
slow-moving, and complained of nausea and weakness. Prior to starting St. John's Wort, she had been r
sleep, she returned to her baseline mental status (Gordon, 1998).
c) A 61-year-old female experienced restlessness and involuntary movements of her extremities after be
mg daily. The patient reported agitation and akathisia 8 hours after taking the first dose of paroxetine. Sh
hyperreflexia and rigidity. Blood pressure, heart rate, and temperature were normal. After admission, blo
minute. Creatine kinase increased from 212 units/liter (U/L) initially to 1024 U/L. The patient was manage
2000).
d) A 28-year-old male developed a manic syndrome following comedication with St. John's Wort and se
orchidectomy 2 years earlier, but testosterone levels were subtherapeutic. The patient was prescribed se
patient preference (dose not specified). Before sertraline was started, the patient was instructed to disco
improved mood so did not see his physician, believing that he did not need further treatment. Over 2 mo
afford, and was ultimately arrested for stealing fuel for the car. On arrest, he was referred to psychiatric s
distractible, have flight of ideas, and grandiose delusions, leading to a diagnosis of a manic episode. The
that St. John's Wort may have increased the risk as a result of monoamine oxidase inhibition. Since the
state was considered low. However, the patient had elevated gonadotropin levels (luteinizing hormone a
(Barbanel et al, 2000).
e) A 42-year-old female experienced symptoms consistent with a mixed hypomanic episode following co
symptoms resolved following discontinuation of Ginkgo and St. John's Wort. The patient was being treat
twice daily and buspirone 15 mg twice daily. Several weeks prior to presentation, buspirone was increas
melatonin, and St. John's Wort in unspecified doses. Melatonin was considered unlikely to have contribu
since they may potentiate antidepressants, and considering the temporal relationship between the use o
symptoms. However, the brain injury was considered a possible contributor (Spinella & Eaton, 2002b).

3.5.1.EP Sulfinpyrazone
1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and
been associated with an increased risk of bleeding. Bleeding events reported have included epistaxis, ecchy
tablets, suspension, 2008; Prod Info PROZAC(R) oral capsules, delayed-release capsules, solution, 2008).
3) Severity: major
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When an SSRI and an antiplatelet agent are given concurrently, monitor patient for

PROZAC(R) oral capsules, delayed-release capsules, solution, 2008)
7) Probable Mechanism: unknown

3.5.1.EQ Sulindac
1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and
associated with an increased risk of bleeding. Bleeding events have included epistaxis, ecchymosis, hematom
suspension, 2008) (Prod Info Lexapro(TM), 2003; Dalton et al, 2003a; Prod Info CELEXA (R) oral tablet, solu
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When an SSRI and an NSAID are given concurrently, monitor patient for signs of in
7) Probable Mechanism: unknown
8) Literature Reports
a) SSRIs increase the risk of upper gastrointestinal bleeding and this effect is potentiated by concurrent
were searched among 26,005 users of antidepressant medications and compared with the number of ho
amount of upper GI bleeding episodes was 3.6 times more than expected (95% confidence interval, 2.7 t
12.2 (95% confidence interval, 7.1 to 19.5) and 5.2 (95% confidence interval, 3.2 to 8), respectively. The
SSRIs. Combined use of SSRIs and NSAIDs or low-dose aspirin increased the risk even further (Dalton
b) Coadministration of ketorolac with psychoactive drugs (such as fluoxetine) has been associated with

3.5.1.ER Sulodexide
1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and
been associated with an increased risk of bleeding. Bleeding events reported have included epistaxis, ecchym
tablets, suspension, 2008; Prod Info PROZAC(R) oral capsules, delayed-release capsules, solution, 2008).
3) Severity: major
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When an SSRI and an antiplatelet agent are given concurrently, monitor patient for
PROZAC(R) oral capsules, delayed-release capsules, solution, 2008)
7) Probable Mechanism: unknown

3.5.1.ES Sumatriptan
1) Interaction Effect: an increased risk of serotonin syndrome
2) Summary: There have been case reports of weakness, hyperreflexia, and incoordination following concon
Zoloft(R), 2002t; Prod Info Imitrex(R), 2002). Concurrent use of a triptan and an SSRI may result in serotonin
restlessness, hallucinations, loss of coordination, fast heart beat, rapid changes in blood pressure, increased
should be aware that triptans may be commonly used intermittently and that either the triptan or the SSRI ma
patients who are prescribed this combination and monitor them closely for symptoms of serotonin syndrome (
3) Severity: major
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: Coadministration of a triptan, such as sumatriptan, and an SSRI, such as sertraline
triptans may be commonly used intermittently and that either the triptan or the SSRI may be prescribed by a c
syndrome with the patient and monitor closely for symptoms of serotonin syndrome (restlessness, hypertherr
7) Probable Mechanism: additive pharmacologic effects resulting in excessive serotonergic stimulation

3.5.1.ET Suprofen
1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and
associated with an increased risk of bleeding. Bleeding events have included epistaxis, ecchymosis, hematom
suspension, 2008) (Prod Info Lexapro(TM), 2003; Dalton et al, 2003a; Prod Info CELEXA (R) oral tablet, solu
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When an SSRI and an NSAID are given concurrently, monitor patient for signs of in
7) Probable Mechanism: unknown
8) Literature Reports
a) SSRIs increase the risk of upper gastrointestinal bleeding and this effect is potentiated by concurrent
were searched among 26,005 users of antidepressant medications and compared with the number of ho
amount of upper GI bleeding episodes was 3.6 times more than expected (95% confidence interval, 2.7 t
12.2 (95% confidence interval, 7.1 to 19.5) and 5.2 (95% confidence interval, 3.2 to 8), respectively. The
SSRIs. Combined use of SSRIs and NSAIDs or low-dose aspirin increased the risk even further (Dalton
b) Coadministration of ketorolac with psychoactive drugs (such as fluoxetine) has been associated with

3.5.1.EU Tapentadol
1) Interaction Effect: increased risk of serotonin syndrome (hypertension, hyperthermia, myoclonus, mental s

2) Summary: Concurrent use of tapentadol and a selective serotonin reuptake inhibitor (SSRI) may result in s include restlessness, hallucinations, loss of coordination, fast heart beat, rapid changes in blood pressure, inc Info tapentadol immediate release oral tablets, 2008).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Coadministration of tapentadol and an SSRI may result in a life-threatening conditio closely for symptoms of serotonin syndrome (restlessness, hyperthermia, hyperreflexia, incoordination), espe release oral tablets, 2008).
7) Probable Mechanism: additive serotonergic effect

3.5.1.EV Tenidap
1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and associated with an increased risk of bleeding. Bleeding events have included epistaxis, ecchymosis, hemator suspension, 2008) (Prod Info Lexapro(TM), 2003; Dalton et al, 2003a; Prod Info CELEXA (R) oral tablet, solu
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When an SSRI and an NSAID are given concurrently, monitor patient for signs of in
7) Probable Mechanism: unknown
8) Literature Reports
a) SSRIs increase the risk of upper gastrointestinal bleeding and this effect is potentiated by concurrent were searched among 26,005 users of antidepressant medications and compared with the number of ho amount of upper GI bleeding episodes was 3.6 times more than expected (95% confidence interval, 2.7 t 12.2 (95% confidence interval, 7.1 to 19.5) and 5.2 (95% confidence interval, 3.2 to 8), respectively. The SSRIs. Combined use of SSRIs and NSAIDs or low-dose aspirin increased the risk even further (Dalton
b) Coadministration of ketorolac with psychoactive drugs (such as fluoxetine) has been associated with

3.5.1.EW Tenoxicam
1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and associated with an increased risk of bleeding. Bleeding events have included epistaxis, ecchymosis, hemator suspension, 2008) (Prod Info Lexapro(TM), 2003; Dalton et al, 2003a; Prod Info CELEXA (R) oral tablet, solu
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When an SSRI and an NSAID are given concurrently, monitor patient for signs of in
7) Probable Mechanism: unknown
8) Literature Reports
a) SSRIs increase the risk of upper gastrointestinal bleeding and this effect is potentiated by concurrent were searched among 26,005 users of antidepressant medications and compared with the number of ho amount of upper GI bleeding episodes was 3.6 times more than expected (95% confidence interval, 2.7 t 12.2 (95% confidence interval, 7.1 to 19.5) and 5.2 (95% confidence interval, 3.2 to 8), respectively. The SSRIs. Combined use of SSRIs and NSAIDs or low-dose aspirin increased the risk even further (Dalton
b) Coadministration of ketorolac with psychoactive drugs (such as fluoxetine) has been associated with

3.5.1.EX Terfenadine
1) Interaction Effect: cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: In two in vivo studies, no pharmacokinetic interaction between terfenadine and sertraline was c likely to be of any clinical significance (Prod Info Zoloft(R), 2002a). However, the manufacturer of terfenadine Seldane(R), 1997).
3) Severity: major
4) Onset: rapid
5) Substantiation: probable
6) Clinical Management: Concomitant use of terfenadine and sertraline should be avoided.
7) Probable Mechanism: inhibition of cytochrome P450-mediated metabolism of terfenadine

3.5.1.EY Tiaprofenic Acid
1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and associated with an increased risk of bleeding. Bleeding events have included epistaxis, ecchymosis, hemator suspension, 2008) (Prod Info Lexapro(TM), 2003; Dalton et al, 2003a; Prod Info CELEXA (R) oral tablet, solu
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When an SSRI and an NSAID are given concurrently, monitor patient for signs of in
7) Probable Mechanism: unknown

8) Literature Reports
a) SSRIs increase the risk of upper gastrointestinal bleeding and this effect is potentiated by concurrent were searched among 26,005 users of antidepressant medications and compared with the number of ho amount of upper GI bleeding episodes was 3.6 times more than expected (95% confidence interval, 2.7 t 12.2 (95% confidence interval, 7.1 to 19.5) and 5.2 (95% confidence interval, 3.2 to 8), respectively. The SSRIs. Combined use of SSRIs and NSAIDs or low-dose aspirin increased the risk even further (Dalton
b) Coadministration of ketorolac with psychoactive drugs (such as fluoxetine) has been associated with

3.5.1.EZ Ticlopidine
1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and been associated with an increased risk of bleeding. Bleeding events reported have included epistaxis, ecchyr tablets, suspension, 2008; Prod Info PROZAC(R) oral capsules, delayed-release capsules, solution, 2008).
3) Severity: major
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When an SSRI and an antiplatelet agent are given concurrently, monitor patient for PROZAC(R) oral capsules, delayed-release capsules, solution, 2008)
7) Probable Mechanism: unknown

3.5.1.FA Tinzaparin
1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and anticoagulants has been associated with an increased risk of bleeding (Wallerstedt et al, 2009; Schalekamp e reported have included epistaxis, ecchymosis, hematoma, petechiae, and life-threatening hemorrhages. Alter coadministration of SSRIs with warfarin (Prod Info ZOLOFT(R) oral tablets, concentrate, 2008). Prothrombin 1997a).
3) Severity: major
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: When sertraline and an anticoagulant are given concurrently, monitor patient for sig closely for altered anticoagulant effects, including increased bleeding, when sertraline therapy is initiated or d
7) Probable Mechanism: unknown
8) Literature Reports
a) According to a retrospective cohort study (n=234), there was an increased risk of clinically relevant bl fibrillation during concomitant SSRI therapy or within 2 weeks following SSRI therapy termination. Patien with randomly selected patients who received warfarin only (n=117). SSRI included fluoxetine, citalopran bleeding episodes during 213.9 treatment years in the warfarin plus SSRI group, and 10 patients experie corresponding total incidences of bleedings were 51.4 and 23.9 per 1000 treatment years, respectively. T (95% CI; 1.37 to 8.91, p=0.009) compared with warfarin only. The SSRI implicated in patients experienci addition of an SSRI was not associated with a change in warfarin dose or INR (p=0.48 and p=0.31 respe patient adherence, and exclusion of clopidogrel, dipyridamol, corticosteroids and anticoagulants other th
b) A population-based, case-controlled study of new coumarin users (acenocoumarol and phenprocoum increased risk of hospitalization due to nongastrointestinal bleeding. Using national pharmacy and hospit for abnormal bleeding and compared them with 5818 control subjects who were also taking a coumarin. on SSRIs showed greater risk for hospitalization for nongastrointestinal bleeding (adjusted odds ratio (O bleeding (adjusted OR 0.8, 95% CI, 0.4 to 1.5) was not significantly different (Schalekamp et al, 2008).
c) Sertraline 50 mg to 200 mg daily for 21 days produced an 8% increase in prothrombin time in subject given prior to sertraline; this compared with a 1% decrease with placebo. Normalization of the prothromb findings is unknown (Prod Info ZOLOFT(R) oral tablets, concentrate, 2008).
d) In a non-blinded, randomized, placebo-controlled trial involving 12 healthy volunteers, the effect of se study, all participants received warfarin 0.75 mg/kg. Beginning on day 11, each volunteer was randomize mg/day to 200 mg/day. Prothrombin time was measured prior to each dose of warfarin and periodically th enhanced by sertraline to a clinically significant degree, despite the fact that sertraline was given in a hig

3.5.1.FB Tipranavir
1) Interaction Effect: increased sertraline plasma concentrations
2) Summary: Although the drug interaction between sertraline and tipranavir/ritonavir has not been studied, c plasma concentrations. Sertraline doses may need to be adjusted when tipranavir/ritonavir therapy is initiated
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Concurrent administration of sertraline and tipranavir/ritonavir may increase sertrali consider adjusting the sertraline dose as needed upon initiation of tipranavir/ritonavir (Prod Info APTIVUS(R)
7) Probable Mechanism: unknown

3.5.1.FC Tirofiban
1) Interaction Effect: an increased risk of bleeding

2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and
been associated with an increased risk of bleeding. Bleeding events reported have included epistaxis, ecchy
tablets, suspension, 2008; Prod Info PROZAC(R) oral capsules, delayed-release capsules, solution, 2008).
3) Severity: major
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When an SSRI and an antiplatelet agent are given concurrently, monitor patient for
PROZAC(R) oral capsules, delayed-release capsules, solution, 2008)
7) Probable Mechanism: unknown

3.5.1.FD Tolmetin

1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and
associated with an increased risk of bleeding. Bleeding events have included epistaxis, ecchymosis, hemator
suspension, 2008) (Prod Info Lexapro(TM), 2003; Dalton et al, 2003a; Prod Info CELEXA (R) oral tablet, solu
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When an SSRI and an NSAID are given concurrently, monitor patient for signs of in
7) Probable Mechanism: unknown
8) Literature Reports
a) SSRIs increase the risk of upper gastrointestinal bleeding and this effect is potentiated by concurrent
were searched among 26,005 users of antidepressant medications and compared with the number of ho
amount of upper GI bleeding episodes was 3.6 times more than expected (95% confidence interval, 2.7 t
12.2 (95% confidence interval, 7.1 to 19.5) and 5.2 (95% confidence interval, 3.2 to 8), respectively. The
SSRIs. Combined use of SSRIs and NSAIDs or low-dose aspirin increased the risk even further (Dalton
b) Coadministration of ketorolac with psychoactive drugs (such as fluoxetine) has been associated with

3.5.1.FE Toloxatone

1) Interaction Effect: CNS toxicity or serotonin syndrome (hypertension, hyperthermia, myoclonus, mental sta
2) Summary: Concurrent administration or overlapping therapy with sertraline and a monoamine oxidase (MA
characterized by symptoms such as restlessness, myoclonus, changes in mental status, hyperreflexia, diaph
concomitant use of serotonin specific reuptake inhibitors and MAO inhibitors (Prod Info Zoloft(R), 1999i; Lapp
& de Vries, 1990m). As a reversible and selective monoamine oxidase inhibitor, toloxatone may not potentiat
duration observed with other MAOIs. However, until further studies confirm the safety and efficacy of this con
3) Severity: contraindicated
4) Onset: rapid
5) Substantiation: probable
6) Clinical Management: Concurrent use of sertraline and a MAO inhibitor is contraindicated. Wait at least 14
least 14 days after discontinuing sertraline before initiating therapy with a MAO inhibitor.
7) Probable Mechanism: inhibition of serotonin metabolism by monoamine oxidase
8) Literature Reports
a) Concomitant use of SSRIs and monoamine oxidase inhibitors can produce a toxic reaction known as
hyperstimulation and manifests as restlessness, myoclonus, changes in mental status, hyperreflexia, dia
fatality can result.
b) A 26-year old woman who had been taking isocarboxazid for eight weeks stopped taking the drug for
the patient became restless and developed leg twitches. The patients was later admitted to the emergen
disturbances. After treatment with diazepam and propranolol the patient did not improve. The patient was
symptoms after the second dose (Lappin & Auchincloss, 1994n).
c) A drug interaction was reported in a 61-year old woman in which sertraline 100 mg twice daily was ad
taking the first sertraline dose, the patient was found in a semicomatose state, with elevated body tempe
Hg. After transportation to the hospital, the patient was misdiagnosed as having neuroleptic malignant sy
sertraline and phenelzine. The authors suggest that monoamine oxidase inhibitor (MAOI) therapy should
serotonin reuptake inhibitor (SSRI) and that before starting a MAOI, SSRI therapy should be discontinue
1994n).
d) Two cases reports suggested a possible interaction between fluoxetine and selegiline (Suchowersky
approximately one month after adding selegiline to fluoxetine. The patient improved two months after bot
involved diaphoresis, vasoconstriction, and cyanosis of the hands which occurred in close temporal relat
quick resolution of symptoms. Rechallenge with fluoxetine alone occurred without incident.

3.5.1.FF Tramadol

1) Interaction Effect: an increased risk of seizures and serotonin syndrome (hypertension, hyperthermia, myo
2) Summary: Seizures and serotonin syndrome have been reported in patients using tramadol. Some medica
and serotonin syndrome may be enhanced when sertraline and tramadol therapy are combined (Prod Info UL
3) Severity: major
4) Onset: rapid
5) Substantiation: theoretical
6) Clinical Management: Caution should be used if tramadol is to be administered to patients receiving conc

underlying conditions that might predispose to seizures. Observe the patient closely for signs and symptoms
7) Probable Mechanism: increased concentration of serotonin in the nervous system and periphery

3.5.1.FG Tranylcypromine
1) Interaction Effect: CNS toxicity or serotonin syndrome (hypertension, hyperthermia, myoclonus, mental sta
2) Summary: Concurrent administration or overlapping therapy with sertraline and a monoamine oxidase (MA
characterized by symptoms such as restlessness, myoclonus, changes in mental status, hyperreflexia, diaph
Zoloft(R), 2002n; Lappin & Auchincloss, 1994m; Graber et al, 1994m; Bhatara & Bandettini, 1993f; Suchowe
3) Severity: contraindicated
4) Onset: rapid
5) Substantiation: probable
6) Clinical Management: Concurrent use of sertraline and a MAO inhibitor is contraindicated. Wait at least 14
least 14 days after discontinuing sertraline before initiating therapy with a MAO inhibitor.
7) Probable Mechanism: inhibition of serotonin metabolism by monoamine oxidase
8) Literature Reports
a) Concomitant use of serotonin specific reuptake inhibitors and monoamine oxidase inhibitors can prod
syndrome is a condition of serotonergic hyperstimulation and manifests as restlessness, myoclonus, cha
not recognized and correctly treated, death can result.
b) A 26-year old woman who had been taking isocarboxazid for eight weeks stopped taking the drug for
the patient became restless and developed leg twitches. The patients was later admitted to the emergen
disturbances. The patient did not improve after treatment with diazepam and propranolol. The patient wa
in symptoms after the second dose (Lappin & Auchincloss, 1994l).
c) A drug interaction was reported in a 61-year old woman in which sertraline 100 mg twice daily was ac
taking the first sertraline dose, the patient was found in a semicomatose state, with elevated body tempe
mmHg. After transportation to the hospital, the patient was misdiagnosed as having neuroleptic malignar
between sertraline and phenelzine. The authors suggest that MAO inhibitor therapy should be discontinu
inhibitor (SSRI) and that before starting a MAOI, SSRI therapy should be discontinued for at least 5 half-
d) Two cases reports suggested a possible interaction between fluoxetine and selegiline (Suchowersky
approximately 1 month after adding selegiline to fluoxetine therapy. The patient improved 2 months after
involved diaphoresis, vasoconstriction, and cyanosis of the hands which occurred in close temporal relat
quick resolution of symptoms. Rechallenge with fluoxetine alone occurred without incident.

3.5.1.FH Triazolam
1) Interaction Effect: increased serum concentrations of triazolam and risk of adverse effects (excessive sed
2) Summary: To date, no information is available related to the effects of coadministered triazolam and sertra
sertraline was a moderate inhibitor in vitro of alprazolam metabolism (Von Moltke et al, 1994a). It is theoretica
cytochrome P450 system and sertraline is thought to inhibit one or more P450 isoenzymes (DeVane, 1994f).
family of isoenzymes and sertraline is suspected of inhibiting the CYP3A4 isozyme. Until further information i
3) Severity: minor
4) Onset: rapid
5) Substantiation: probable
6) Clinical Management: Caution is warranted if triazolam and sertraline are to be coadministered. Monitor p
Triazolam doses may need to be reduced.
7) Probable Mechanism: decreased triazolam metabolism

3.5.1.FI Trimipramine
1) Interaction Effect: modest elevations in trimipramine serum levels or possible serotonin syndrome (hyperte
2) Summary: There is limited evidence suggesting that sertraline may inhibit tricyclic antidepressant (TCA) m
P450 2D6 enzyme activity and may increase the plasma concentrations of coadministered drugs that are me
Lydiard et al, 1993c; Prod Info Zoloft(R), 1999b). Effects of the interaction may have little or no clinical impact
were modest compared with those found when fluoxetine (another selective serotonin reuptake inhibitor) was
sertraline therapy for TCA toxicity (dry mouth, urinary retention, CNS depression). Trimipramine doses may n
3) Severity: major
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: The combined use of tricyclic antidepressants (TCAs) and selective serotonin reupt
serotonin syndrome have also been reported with concurrent TCA and SSRI therapy. Caution should be obse
7) Probable Mechanism: inhibition of trimipramine metabolism
8) Literature Reports
a) Desipramine pharmacokinetics were studied in 18 healthy male volunteers. Study subjects received c
daily) for 21 days. When sertraline was added to desipramine therapy, the mean maximum concentration
increased by 26%. Trough concentrations of desipramine were close to baseline one week after sertralin
interaction may not be clinically significant (Preskorn et al, 1994f).

3.5.1.FJ Valdecoxib
1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and
associated with an increased risk of bleeding. Bleeding events have included epistaxis, ecchymosis, hemator

suspension, 2008) (Prod Info Lexapro(TM), 2003; Dalton et al, 2003a; Prod Info CELEXA (R) oral tablet, solu
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When an SSRI and an NSAID are given concurrently, monitor patient for signs of in
7) Probable Mechanism: unknown
8) Literature Reports
a) SSRIs increase the risk of upper gastrointestinal bleeding and this effect is potentiated by concurrent were searched among 26,005 users of antidepressant medications and compared with the number of ho amount of upper GI bleeding episodes was 3.6 times more than expected (95% confidence interval, 2.7 12.2 (95% confidence interval, 7.1 to 19.5) and 5.2 (95% confidence interval, 3.2 to 8), respectively. The SSRIs. Combined use of SSRIs and NSAIDs or low-dose aspirin increased the risk even further (Dalton
b) Coadministration of ketorolac with psychoactive drugs (such as fluoxetine) has been associated with

3.5.1.FK Warfarin

1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and anticoagulants has been associated with an increased risk of bleeding (Wallerstedt et al, 2009; Schalekamp reported have included epistaxis, ecchymosis, hematoma, petechiae, and life-threatening hemorrhages. Alter coadministration of SSRIs with warfarin (Prod Info ZOLOFT(R) oral tablets, concentrate, 2008). Prothrombin 1997a).
3) Severity: major
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: When sertraline and an anticoagulant are given concurrently, monitor patient for sig closely for altered anticoagulant effects, including increased bleeding, when sertraline therapy is initiated or d
7) Probable Mechanism: unknown
8) Literature Reports
a) According to a retrospective cohort study (n=234), there was an increased risk of clinically relevant bl fibrillation during concomitant SSRI therapy or within 2 weeks following SSRI therapy termination. Patien with randomly selected patients who received warfarin only (n=117). SSRI included fluoxetine, citalopram bleeding episodes during 213.9 treatment years in the warfarin plus SSRI group, and 10 patients experie corresponding total incidences of bleedings were 51.4 and 23.9 per 1000 treatment years, respectively. (95% CI; 1.37 to 8.91, p=0.009) compared with warfarin only. The SSRI implicated in patients experienci addition of an SSRI was not associated with a change in warfarin dose or INR (p=0.48 and p=0.31 respe patient adherence, and exclusion of clopidogrel, dipyridamol, corticosteroids and anticoagulants other th
b) A population-based, case-controlled study of new coumarin users (acenocoumarol and phenprocoum increased risk of hospitalization due to nongastrointestinal bleeding. Using national pharmacy and hospit for abnormal bleeding and compared them with 5818 control subjects who were also taking a coumarin. on SSRIs showed greater risk for hospitalization for nongastrointestinal bleeding (adjusted odds ratio (O bleeding (adjusted OR 0.8, 95% CI, 0.4 to 1.5) was not significantly different (Schalekamp et al, 2008).
c) Sertraline 50 mg to 200 mg daily for 21 days produced an 8% increase in prothrombin time in subject given prior to sertraline; this compared with a 1% decrease with placebo. Normalization of the prothromb findings is unknown (Prod Info ZOLOFT(R) oral tablets, concentrate, 2008).
d) In a non-blinded, randomized, placebo-controlled trial involving 12 healthy volunteers, the effect of se study, all participants received warfarin 0.75 mg/kg. Beginning on day 11, each volunteer was randomize mg/day to 200 mg/day. Prothrombin time was measured prior to each dose of warfarin and periodically t enhanced by sertraline to a clinically significant degree, despite the fact that sertraline was given in a hig

3.5.1.FL Xemilofiban

1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and been associated with an increased risk of bleeding. Bleeding events reported have included epistaxis, ecchy tablets, suspension, 2008; Prod Info PROZAC(R) oral capsules, delayed-release capsules, solution, 2008).
3) Severity: major
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When an SSRI and an antiplatelet agent are given concurrently, monitor patient for PROZAC(R) oral capsules, delayed-release capsules, solution, 2008)
7) Probable Mechanism: unknown

3.5.1.FM Zolmitriptan

1) Interaction Effect: an increased risk of serotonin syndrome
2) Summary: There have been case reports of weakness, hyperreflexia, and incoordination following concon specific reuptake inhibitor (SSRI) (Prod Info Imitrex(R), 1998a; Prod Info Zomig(TM), 1997). Because zolmitri occur (Prod Info Zomig(TM), 1997). Concurrent use of zolmitriptan and an SSRI may result in serotonin synd restlessness, hallucinations, loss of coordination, fast heart beat, rapid changes in blood pressure, increased should be aware that triptans may be commonly used intermittently and that either the triptan or the SSRI ma

patients who are prescribed this combination and monitor them closely for symptoms of serotonin syndrome
3) Severity: major
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: Coadministration of a triptan, such as zolmitriptan, and an SSRI may result in a life-
used intermittently and that either the triptan or the SSRI may be prescribed by a different physician. If these
monitor closely for symptoms of serotonin syndrome (restlessness, hyperthermia, hyperreflexia, incoordinatic
7) Probable Mechanism: additive pharmacologic effects resulting in excessive serotonergic stimulation
8) Literature Reports
a) The pharmacokinetics of a single 10 mg dose of zolmitriptan were not altered by four weeks of fluoxe
pressure were also not changed by fluoxetine therapy (Prod Info Zomig(R), 2002).

3.5.1.FN Zolpidem
1) Interaction Effect: an increased risk of hallucinations
2) Summary: The publication of five case reports from the Washington Poison Center elucidates potential int
reported hallucinations after concurrent use of zolpidem and antidepressant medication. The hallucination ep
1998a).
3) Severity: moderate
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: Observe patients for hallucinatory activity. Alternative anti-insomnia medication may
7) Probable Mechanism: unknown
8) Literature Reports
a) The Washington Poison Center reports that they received five different calls from patients experiencir
the five reports came from patients taking serotonin-reuptake inhibitors in addition to zolpidem. The antid
and bupropion. In each case, the hallucinatory activity lasted longer than one hour, but the patients' sym
which zolpidem might cause hallucinations has not been firmly established (Elko et al, 1998).

3.5.1.FO Zomepirac
1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and
associated with an increased risk of bleeding. Bleeding events have included epistaxis, ecchymosis, hemator
suspension, 2008) (Prod Info Lexapro(TM), 2003; Dalton et al, 2003a; Prod Info CELEXA (R) oral tablet, solu
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When an SSRI and an NSAID are given concurrently, monitor patient for signs of in
7) Probable Mechanism: unknown
8) Literature Reports
a) SSRIs increase the risk of upper gastrointestinal bleeding and this effect is potentiated by concurrent
were searched among 26,005 users of antidepressant medications and compared with the number of ho
amount of upper GI bleeding episodes was 3.6 times more than expected (95% confidence interval, 2.7 t
12.2 (95% confidence interval, 7.1 to 19.5) and 5.2 (95% confidence interval, 3.2 to 8), respectively. The
SSRIs. Combined use of SSRIs and NSAIDs or low-dose aspirin increased the risk even further (Dalton
b) Coadministration of ketorolac with psychoactive drugs (such as fluoxetine) has been associated with

3.5.2 Drug-Food Combinations

Ethanol

Grapefruit Juice

3.5.2.A Ethanol
1) Interaction Effect: an increased risk of impairment of mental and motor skills
2) Summary: In experiments with healthy subjects, sertraline did not potentiate cognitive or psychomotor effe
manufacturer of sertraline recommends that depressed patients be advised to avoid alcohol while using sertr
3) Severity: moderate
4) Onset: rapid
5) Substantiation: theoretical
6) Clinical Management: Patients receiving sertraline should be advised to avoid the use of alcohol.
7) Probable Mechanism: unknown

3.5.2.B Grapefruit Juice
1) Interaction Effect: elevated sertraline serum concentrations and an increased risk of adverse side effects
2) Summary: In a small study, grapefruit juice was shown to inhibit the metabolism of sertraline, resulting in i

cytochrome P450 3A4 (CYP3A4) enzymes, and sertraline relies on CYP3A4 for metabolism to its metabolite, this interaction (Lee et al, 1999a).
3) Severity: moderate
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: Counsel patients to avoid grapefruit juice while taking sertraline. Orange juice may metabolism.
7) Probable Mechanism: inhibition of cytochrome P450 3A4-mediated sertraline metabolism
8) Literature Reports
a) Five depressed patients stabilized on sertraline for more than six weeks participated in a prospective, pharmacokinetics of sertraline. During the first seven days of the study, each patient received their usual mL of grapefruit juice. The mean sertraline trough levels increased from 13.6 mcg/L to 20.2 mcg/L during effects reported between the two periods. Grapefruit juice had minimal effects on sertraline metabolism i activity. A larger study is needed to substantiate the clinical significance of the interaction between grape

4.0 Clinical Applications

Monitoring Parameters

Patient Instructions

Place In Therapy

Mechanism of Action / Pharmacology

Therapeutic Uses

Comparative Efficacy / Evaluation With Other Therapies

4.1 Monitoring Parameters

A) Sertraline Hydrochloride
1) Therapeutic
a) DEPRESSION
1) Improvement in target symptoms (depressed mood, suicidal thoughts or intent, change in appetite, la of excessive guilt/worthlessness, psychomotor retardation or agitation, difficulties in thinking/concentratic
2) Patients with thyroid disease who are also receiving treatment for depression should have thyroid fun and small increases in serum thyrotropin levels after starting treatment with sertraline and other antidepr
b) OBSESSIVE-COMPULSIVE DISORDER
1) Reduction or resolution of recurrent and persistent impulses, ideas or thoughts that are intrusive and
2) Reduction or resolution of repetitive and intentional behaviors performed in response to obsessive th
c) PANIC DISORDER
1) Reduction or resolution of signs/symptoms consistent with panic disorder (dyspnea, palpitations, trem experiencing an uncontrolled feeling).
2) Toxic
a) Physical Findings
1) Since EXTRAPYRAMIDAL REACTIONS including dystonic reactions, parkinsonian-like movement di weekly during the first 4 weeks of therapy is recommended (Gill et al, 1997).
2) Gastrointestinal adverse effects (nausea, vomiting) are common during initiation of therapy but usuall
3) Monitor patients receiving antidepressants for worsening of depression, suicidality, or unusual change decreases. Such monitoring should include at least weekly face-to-face contact with patients or their fam week for the next 4 weeks, then at 12 weeks, and then as clinically indicated beyond 12 weeks. Families observation) of patients and communication with the prescriber (Anon, 2004; Anon, 2004).
4) Patients who experience symptoms of anxiety, agitation, panic attacks, insomnia, irritability, hostility, depression or suicidality. If these symptoms are observed, therapy should be re-evaluated and it may be were not part of the patient's initial symptoms (Anon, 2004; Anon, 2004).

4.2 Patient Instructions

A) Sertraline (By mouth)
Sertraline

Treats depression, obsessive-compulsive disorder (OCD), posttraumatic stress disorder (PTSD), premenstrual dy is an antidepressant called a selective serotonin reuptake inhibitor (SSRI).

When This Medicine Should Not Be Used:

You should not use this medicine if you have had an allergic reaction to sertraline or if you are also using pimozid
such as Eldepryl®, Marplan®, Nardil®, or Parnate® within the past 14 days. Do not use the liquid form of sertralir

How to Use This Medicine:
Tablet, Liquid
Your doctor will tell you how much of this medicine to use and how often. Do not use more medicine or use it
Measure the oral liquid medicine with a marked measuring spoon, oral syringe, or medicine cup. The oral liqu
with 1/2 cup (4 ounces) of water, ginger ale, lemon-lime soda, lemonade, or orange juice. Do not mix this me
liquid until you are ready to take your dose. It is okay if the mixture looks hazy.
This medicine should come with a Medication Guide. Read and follow these instructions carefully. Ask your d
Guide if you do not have one. Your doctor might ask you to sign some forms to show that you understand this

If a Dose is Missed:
If you miss a dose or forget to use your medicine, use it as soon as you can. If it is almost time for your next d
medicine to make up for a missed dose.

How to Store and Dispose of This Medicine:
Store the medicine in a closed container at room temperature, away from heat, moisture, and direct light.
Ask your pharmacist, doctor, or health caregiver about the best way to dispose of any leftover medicine after
expiration date has passed.
Keep all medicine away from children and never share your medicine with anyone.

Drugs and Foods to Avoid:
Ask your doctor or pharmacist before using any other medicine, including over-the-counter medicines, vitamins, a
Make sure your doctor knows if you are also using cimetidine (Tagamet®), diazepam (Valium®), digitoxin, lin
sumatriptan (Imitrex®), tolbutamide, tramadol (Ultram®), tryptophan, or valproate (Depacon®). Tell your doct
depression such as amitriptyline, nortriptyline, Elavil®, Pamelor®, or Sinequan®. Your doctor will need to knc
Rythmol®, or Tambocor®.
Make sure your doctor knows if you are using a pain or arthritis medicine (sometimes called “NSAIDs”) such
Motrin®. Tell your doctor if you have used an MAO inhibitor such as Eldepryl®, Marplan®, Nardil®, or Parnat
Tell your doctor if you are using any medicines that make you sleepy. These include sleeping pills, cold and a
using this medicine.

Warnings While Using This Medicine:
Make sure your doctor knows if you are pregnant or breastfeeding, or if you have seizures, liver disease, blee
For some children, teenagers, and young adults, this medicine can increase thoughts of suicide. Tell your do
have thoughts about hurting yourselves. Report any unusual thoughts or behaviors that trouble you or your cl
you or your child have trouble sleeping, get upset easily, have a big increase in energy, or start to act reckles
nervous, angry, restless, violent, or scared. Let the doctor know if you, your child, or anyone in your family ha
This medicine may cause hyponatremia (low sodium in the blood). This is more common in elderly patients, t
decreased amounts of fluids in the body due to severe diarrhea or vomiting. Stop taking this medicine and ch
problems, confusion, weakness, or unsteadiness.
Tell your doctor if you are allergic to latex rubber. The oral liquid form of this medicine has a latex rubber drop
This medicine may make you dizzy or drowsy. Avoid driving, using machines, or doing anything else that cou
Do not stop using this medicine suddenly without asking your doctor. You may need to slowly decrease your
Your doctor will need to check your progress at regular visits while you are using this medicine. Be sure to ke

Possible Side Effects While Using This Medicine:
Call your doctor right away if you notice any of these side effects:
Allergic reaction: Itching or hives, swelling in your face or hands, swelling or tingling in your mouth or throat, d
Blistering, peeling, red skin rash.
Change in how much or how often you urinate.
Chest pain.
Fast or pounding heartbeat.
Headache, trouble concentrating, memory problems, weakness, or unsteadiness.
Muscle stiffness, twitching, shaking, or uncontrolled muscle movements.
Painful, prolonged erection of your penis, or trouble having sex.
Severe confusion, sweating, diarrhea, or fever.
Unusual bleeding or bruising.
Unusual thoughts, behavior, restlessness, nervousness, aggressive behavior, or anger.

If you notice these less serious side effects, talk with your doctor:
Decreased interest in sex.
Dizziness or drowsiness.
Dry mouth.
Loss of appetite.
Mild diarrhea, constipation, nausea, vomiting, or stomach pain.
Tiredness.

Trouble sleeping.
Weight loss.

If you notice other side effects that you think are caused by this medicine, tell your doctor.

4.3 Place In Therapy

A) SUMMARY

1) Sertraline has received approval by the United States Food and Drug Administration for treating depression, o numerous other psychiatric disorders.

B) DEPRESSION

1) All of the selective serotonin reuptake inhibitors (SSRIs) are effective for treating depression although selected NOT have any major therapeutic benefits over other SSRIs; however, it has less potential for drug interactions an an SSRI is dependent on clinical judgement and response of patients to previous therapy (Edwards & Anderson,

2) Preliminary data suggest that a trial of a second serotonin reuptake inhibitor (SSRI) is a viable clinical alternati (Joffe et al, 1996). In a retrospective review of 55 patients who had failed to respond to at least five weeks of thera dosages), 51% did respond to a trial of an alternative agent. The choice of the second agent was based on clinicia

4.4 Mechanism of Action / Pharmacology

A) MECHANISM OF ACTION

1) Sertraline is a potent and selective inhibitor of synaptosomal serotonin reuptake in the brain. It has a higher de including clomipramine, fluoxetine, fluvoxamine, and zimeldine (Heym & Koe, 1988a). It appears to have little effe

2) Like most other antidepressants (except fluoxetine), sertraline also causes an indirect down-regulation of posts therapeutic effect and for its delay in clinical efficacy (Doogan & Caillard, 1988; Heym & Koe, 1988a).

B) REVIEW ARTICLES

1) A comparison of selective serotonin reuptake inhibitors with a guide to selection is provided (Edwards & Ander

2) Two reviews provide a discussion of the efficacy of selective serotonin reuptake inhibitors and other antidepres

3) The efficacy of antidepressants in reducing panic attack frequency, symptoms of depression, social avoidance

4) A review article discusses the rational treatment of depression and each class of antidepressants (Cohen, 199

5) A review article describes the treatment of panic disorder, including the role of selective serotonin reuptake inh

6) Treatment of elderly patients with selective serotonin reuptake inhibitors is discussed with emphasis on improv

7) Pharmacological and therapeutic information about sertraline has been summarized (Peruche & Schulz, 1997

8) Drug-interactions of antidepressants are reviewed in German language (Zapotoczky & Simhandl, 1995).

4.5 Therapeutic Uses

4.5.A Sertraline Hydrochloride

Aggressive behavior

Alcoholism

Alzheimer's disease; Adjunct

Alzheimer's disease - Depression

Anorexia nervosa

Binging - Eating disorder

Cerebrovascular accident, Post - Depression; Prophylaxis

Cerebrovascular accident, Post - Mood swings

Clozapine adverse reaction - Obsessive-compulsive disorder

Complication of hemodialysis - Hypotensive episode

Depression - Myocardial infarction, Post

Drug-induced depressive state

Dysthymia

Flashbacks

Generalized anxiety disorder

Intermittent explosive disorder

Major depressive disorder

Myocardial infarction; Prophylaxis

Night eating syndrome

Non-cardiac chest pain

Obsessive-compulsive disorder

Panic disorder

Pathological laughing

Posttraumatic stress disorder

Premature ejaculation

Premenstrual dysphoric disorder

Respiratory obstruction

Schizophrenia

Severe major depression with psychotic features

Social phobia

4.5.A.1 Aggressive behavior

a) Overview

FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence is inconclusive
Recommendation: Adult, Class IIb
Strength of Evidence: Adult, Category C

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:

Sertraline has been effective in the treatment of severe aggressiveness and self-injurious behavior a
reports (Ranen et al, 1996; Hellings et al, 1996)

c) Adult:

1) Sertraline has been effective in the treatment of severe aggressiveness and self-injurious behavior as
reports (Ranen et al, 1996; Hellings et al, 1996). Because serotonergic mechanisms have been implicate
was attempted after multiple pharmacologic interventions had failed. Dosages in these cases ranged fro
mg to avoid akathisia or irritability. Marked improvement to complete cessation of aggressive behaviors
sertraline for this indication.

4.5.A.2 Alcoholism

a) Overview

FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence is inconclusive
Recommendation: Adult, Class IIb
Strength of Evidence: Adult, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:

Helpful in alcoholic patients without lifetime depression but not in alcoholic patients with lifetime dep

c) Adult:

1) Sertraline treatment was more effective than placebo in reducing alcohol intake of alcoholic subjects were currently experiencing or had previously experienced depression ("lifetime depression"). One hund (n=53) and those without (n=47) before being randomly assigned to receive sertraline 200 milligrams/da noted for frequency of drinking; however, the interaction between lifetime depression status and treatme never-depressed groups (p=0.33), whereas placebo was favored over sertraline in the lifetime-depressio never-depressed groups; there was no difference between treatments in the lifetime depression groups. adverse reactions (sexual disturbance, fatigue, and headache) were significantly more frequent in the se 2001).

4.5.A.3 Alzheimer's disease; Adjunct

a) Overview

FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence is inconclusive
Recommendation: Adult, Class III
Strength of Evidence: Adult, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:

May be effective as an adjunctive therapy in the treatment of behavioral and psychological symptom severe symptoms (Finkel et al, 2004)

c) Adult:

1) Sertraline therapy was not effective in the treatment of behavioral and psychological symptoms in the analysis of a subgroup of patients with moderate to severe symptoms. In a randomized, double-blind, pla received 8 weeks of open label treatment with donepezil (5 to 10 milligram (mg)/day) followed by 12 wee dose, 125.7 mg/day) or placebo (n=120). Primary endpoints included scores for the Neuropsychiatric Inv (CGI-S) scale. In the initial analyses, no significant improvements were found for any of the primary endp However, in a post hoc analyses of a subgroup of patients with moderate to severe behavioral and psych sertraline treatment was associated with a significant improvement on the mean NPI Behavioral and Psy significantly more patients in the donepezil-plus-sertraline group were rated as responders on the NPI Be placebo group (60% vs 33%, respectively; p=0.006). Sertraline was well tolerated with only diarrhea occu

4.5.A.4 Alzheimer's disease - Depression

a) Overview

FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence favors efficacy
Recommendation: Adult, Class IIa
Strength of Evidence: Adult, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:

Reduced depressive symptoms in patients with Alzheimer's disease in double-blind, placebo-control

c) Adult:

1) Sertraline therapy effectively reduced depressive symptoms in patients with Alzheimer's disease. In a disorder and probable Alzheimer's disease received sertraline (n=24; initial, 25 milligrams (mg)/day for 1 or placebo (n=20) for 12 weeks following a one-week placebo run-in phase. Response to treatment was Depression Rating Scale (HDRS). Significantly more sertraline-treated patients were full or partial respon Patients in the sertraline group also had significantly greater improvements on CSDD and HDRS scores Although not significant, sertraline-treated patients showed a stronger statistical trend toward stabilizatio Depression Rating Scale-ADL subscale, as compared with placebo. There was no difference between tr dizziness and gastrointestinal symptoms being the most frequently reported adverse events (Lyketsos et

2) Sertraline was more effective than placebo in reducing DSM-IV diagnosed major depressive disorder Alzheimer's disease and major depression were randomized to receive either sertraline (n=12) or placeb over 6 weeks to 150 mg/day or the maximum tolerated dose. Three of the 12 patients receiving sertraline response occurring by the third week of treatment. In the placebo group, there was one full responder an less than 0.05). Mean reductions in scores on the Cornell Scale for Depression were significantly greater placebo group reported nervous system side effects (tremor, restlessness) (Lyketsos et al, 2000).

4.5.A.5 Anorexia nervosa

a) Overview

FDA Approval: Adult, no; Pediatric, no
Efficacy: Pediatric, Evidence is inconclusive
Recommendation: Pediatric, Class III
Strength of Evidence: Pediatric, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:

Not better than non-drug treatment for anorexia nervosa (Santonastaso et al, 2001)

c) Pediatric:

1) Addition of sertraline to a multidisciplinary treatment of anorexia nervosa was not more effective than

DSM-IV criteria for restricting-type anorexia nervosa, were treated with open-label sertraline 50 milligram whose response had been unsatisfactory. Eleven other similar subjects were given no medication. All pa per week. At 14 weeks, 6 patients in each group (55%) still had a diagnosis of a full eating disorder. Bod months, rates of full remission were 54% in the sertraline group and 27% in the control group (not signifi headache, and insomnia. No subject interrupted treatment because of side effects (Santonastaso et al, 2

4.5.A.6 Binging - Eating disorder

a) Overview

FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence is inconclusive
Recommendation: Adult, Class IIb
Strength of Evidence: Adult, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:

A small double-blind study found sertraline to decrease the frequency of binges compared to placeb

c) Adult:

1) Sertraline reduced the frequency of binges, global clinical severity scores, and body mass index to a met DSM-IV criteria for binge eating disorder and had binge episodes at least 3 times weekly for 6 month placebo; doses were adjusted based on response up to 200 mg daily. Estimated mean weight loss was an underlying condition in most of the study patients. Of the 18 patients treated with sertraline, 11 had a disorder. In the 16 placebo-treated patients, 7 had a lifetime diagnosis and 3 had a current diagnosis of

4.5.A.7 Cerebrovascular accident, Post - Depression; Prophylaxis

a) Overview

FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence is inconclusive
Recommendation: Adult, Class IIb
Strength of Evidence: Adult, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:

Sertraline was more effective than placebo in the prevention of post-stroke depression (Rasmussen

c) Adult:

1) Sertraline treatment appeared to be more effective than placebo in the prevention of depression follo post-stroke patients received sertraline (n=70; initial, 50 milligrams (mg)/day for 2 weeks then titrated up months. The incidence rate of depression (assessed by the total score on the Hamilton Depression Scal placebo group (8.2% vs 22.8%, respectively). The depression occurrence rate as measured by scores o (11.5% vs 28%, respectively). Fewer sertraline-treated patients had Clinical Global Impression (CGI) sev given placebo (18% vs 29.8%, respectively; p=0.12). Sertraline was well tolerated and there were no sig

4.5.A.8 Cerebrovascular accident, Post - Mood swings

a) Overview

FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence is inconclusive
Recommendation: Adult, Class IIb
Strength of Evidence: Adult, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:

In a small study (n=28), sertraline reduced emotional lability after a stroke (Burns et al, 1999)

c) Adult:

1) More patients treated with sertraline than placebo experienced a reduction in emotional lability (Burns randomly assigned to receive placebo or sertraline 50 milligrams/day for 8 weeks. At 8 weeks, 93% of pa Clinician's Interview-based impression of change and the emotionalism/lability of mood questions (p=0.0 to placebo (p=0.041). Four patients did NOT complete the study; 2 patients receiving sertraline experien suggest that sertraline is useful for reducing emotional lability after stroke.

4.5.A.9 Clozapine adverse reaction - Obsessive-compulsive disorder

a) Overview

FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence is inconclusive
Recommendation: Adult, Class IIb
Strength of Evidence: Adult, Category C

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:

In a single case, sertraline effectively treated obsessive-compulsive behavior induced by clozapine(

c) Adult:

1) Addition of sertraline to clozapine reduced obsessive compulsive behavior without adversely affecting effectively reduced treatment-refractory psychosis, the patient developed obsessive compulsive behavio to risperidone and clomipramine which were ineffective so treatment with clozapine was reinstituted alon

plasma concentrations which were likely due to competitive inhibition of cytochrome P450 isoenzymes b
regimen, his psychotic and obsessive-compulsive symptoms were well controlled (Rahman et al, 1998).

4.5.A.10 Complication of hemodialysis - Hypotensive episode

a) Overview

FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence is inconclusive
Recommendation: Adult, Class III
Strength of Evidence: Adult, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:

Reduced the severity of hypotension during and after hemodialysis sessions (Yalcin et al, 2002)

c) Adult:

1) Sertraline treatment raised the systolic and diastolic nadirs during hemodialysis sessions and increas
hypotension. Of 12 patients selected for treatment, 3 were unable to tolerate sertraline at 100 milligrams
before sertraline treatment were compared to data from a 4-week sertraline period. The sertraline period
before data collection. Dry weights of the patients, ultrafiltration volumes, dialysate composition, dialysat
and diastolic blood pressure (DBP) were the same in the sertraline period as in the pre-sertraline period.
the pre-sertraline period to 87 in the sertraline period (p less than 0.05); the nadir of DSP rose from 51 to
than 0.005). Post-dialysis DPB did not change significantly (59 to 62). The need for therapeutic intervent
0.001) (Yalcin et al, 2002).

4.5.A.11 Depression - Myocardial infarction, Post

a) Overview

FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence favors efficacy
Recommendation: Adult, Class IIb
Strength of Evidence: Adult, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:

Sertraline relieved depression without causing adverse cardiac effects (Shapiro et al, 1999)
Heart rate variability recovery following acute MI was facilitated by sertraline (McFarlane et al, 2001)

c) Adult:

1) Sertraline improved depressive symptoms in patients with a recent myocardial infarction (MI). In this
milligrams daily beginning a mean of 30 days after the MI. At 16 weeks, 74% of patients had a positive re
Hamilton rating decreased from 19.7 to 7.8 (p less than 0.001). Fifteen (78.9%) of 19 patients who comp
completely resolved" by the Clinical Global Impression Scale. There were no significant changes in cardi
controlled study is underway to evaluate efficacy and safety of sertraline in this patient population (Shapi
2) Depressed, post-myocardial infarction (MI) patients treated with sertraline 50 milligrams (mg) daily ha
to a matched placebo group. Thirty-eight depressed patients were entered into a randomized, double-bli
sertraline) leaving 27 patients (16 males, average age 62 +/- 11 (SD) years) to complete the 22 week stu
and was composed of 11 age-matched, non-depressed, post MI patients (9 males). All three groups had
of mortality within the first year of an acute (MI), 2 weeks following the MI before sertraline or placebo wa
normal sinus-conducted N-N interbeat intervals, the average heart rate, and the standard deviation of all
sertraline group increased by 5% compared to a 28% increase in the reference group and a 9% decreas
depression (IDD) score for the sertraline group compared to the placebo group (p less than 0.05). The au
theoretically improve clinical outcomes (McFarlane et al, 2001).

4.5.A.12 Drug-induced depressive state

a) Overview

FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence is inconclusive
Recommendation: Adult, Class IIb
Strength of Evidence: Adult, Category C

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:

Relieved depression caused by interferon-alfa therapy in a small study (n=10) (Schramm et al, 2000

c) Adult:

1) Sertraline relieved symptoms of interferon-alfa (IA)-induced depression without the necessity of disco
who met the DSM-IV criteria for substance (interferon-alfa)-induced depressive disorder were treated wit
improvement in depressed mood and irritability, with 7 reporting complete resolution of symptoms. Mild a
8 weeks, 1 patient experienced erectile dysfunction, and his medication was changed to moclobemide (S

4.5.A.13 Dysthymia

a) Overview

FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence favors efficacy
Recommendation: Adult, Class IIb

Strength of Evidence: Adult, Category B
See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:
Sertraline was effective in the treating dysthymia, based upon improvement in psychiatric rating sco

c) Adult:
1) Sertraline was more effective than placebo in improving psychiatric rating scores in patients meeting concomitant diagnosis of major depressive disorder and who were not taking any other psychotropic dru mg or placebo daily. Dose adjustments up to 200 mg daily were allowed during the 12-week treatment p reductions in Structured Interview Guide for the Hamilton Depression Rating Scale-Seasonal Affective D Clinical Global Impressions-Severity of Illness scale (CGI-S), and Hospital Anxiety and Depression Scale achieving response, defined as reduction in SIGH-SAD or MADRS scores by 50%, or a CGI-Improveme and 60.1% based on the 3 respective scales), compared with response rates in the placebo group (33.8% significantly higher with sertraline (33.8%) than with placebo (21.6%). Quality of life rating scores also im

4.5.A.14 Flashbacks

a) Overview
FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence is inconclusive
Recommendation: Adult, Class IIb
Strength of Evidence: Adult, Category C
See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:
In a single patient, sertraline was effective for eliminating flashbacks associated with lysergic acid di

c) Adult:
1) Sertraline treatment, started at 25 milligrams (mg) daily and slowly titrated to a target dose of 100 mg and depressive symptoms in a single patient with an 8-month history of LSD intake and daily flashbacks days after each dose increase but then subsided. This patient had no history of seizures or migraines. H experience at a later time of the original effects of the hallucinogenic drug. The hallucinogen, LSD, is bel Sertraline decreased the typical physiologic responses to serotonergic agonists as well as attenuated the LSD which present as flashbacks (Young, 1997).

4.5.A.15 Generalized anxiety disorder

a) Overview
FDA Approval: Adult, no;
Efficacy: Adult, Evidence favors efficacy;
Recommendation: Adult, Class IIb;
Strength of Evidence: Adult, Category B; Pediatric, Category B
See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:
Sertraline-treated adults had significant decreases in the total Hamilton Rating Scale for Anxiety sco dose study of 326 adults with moderate to severe primary generalized anxiety disorder (Brawman-M Sertraline therapy in combination with cognitive behavioral therapy (CBT) was shown to be superior were both superior to placebo in a randomized, controlled trial among children and adolescents with Reduced psychic and somatic symptoms in children with generalized anxiety disorder (Rynn et al, 2

c) Adult:
1) Sertraline-treated adult outpatients had significant decreases in the total Hamilton Rating Scale for An double-blind, flexible-dose study of 326 evaluable adults with moderate to severe, primary generalized a GAD, had a total HAM-A symptom score of 20 or greater, a score of 2 or greater on item 1 of the HAM-A Scale score. There was no placebo run-in phase, but patients could not receive psychotropic drugs withi baseline. Patients were randomized to receive either placebo (n=162), or sertraline 25 milligrams/day (m and 7, up to a maximum of 200 mg/day. Decreases in dose were permitted at any time with only one sub was 149.1 mg +/- 59 mg. The mean age of patients was approximately 40 years, including 8.3% of patie measurement, the mean change in total HAM-A at 10 weeks compared with baseline was -12.71 +/- 7.1 between groups of -1.8 +/- 0.8 (95% CI, -3.4 to -0.2, p=0.032). There were significant improvements in to 6 and lasting through week 10. An analysis of the HAM-A somatic subscale in sertraline-treated patients subscale did demonstrate significant improvements (p=0.011). The response rate (at least 50% reductio (p=0.05). Significant adverse events (p less than 0.001) in the sertraline group (n=165) compared with pl libido 17.6% vs 2.4%. Diastolic blood pressure increases of 1.59 mmHg +/- 8.83 mmHg occurred in the s (p=0.0204) (Brawman-Mintzer et al, 2006).

d) Pediatric:
1) Sertraline therapy) was shown to be superior t both superior to placebo in a randomized, controlled trial among children and adolescents with childhood 10.7 years; 74.2% under the age of 13), with a primary diagnosis of social phobia, separation or generali receive sertraline plus CBT (n=140), sertraline alone (n=133), CBT alone (n=139) or placebo (n=76). Sul subjects receiving sertraline alone and placebo therapy were not aware which therapy they were receivi titrated on a fixed-flexible schedule beginning with 25 mg per day and adjusted upward in the absence o sessions which included anxiety-management skills and behavioral exposure to anxiety-provoking situati +/- 59.8 mg and the mean daily dose for sertraline-only patients was 146 +/- 60.8 mg. The primary outco

improvement on the Clinical Global Impression-Improvement scale (a scale of 1 to 7 with lower scores in
included all patients randomized. At week 12, a Clinical Global Impression-Improvement scale of 1 or 2 (
86.4) of patients receiving sertraline in combination with CBT, 54.9% (95% CI, 46.4 to 63.1) of patients re
23.7% (95% CI, 15.5 to 34.5) of patients receiving placebo therapy (all p less than 0.001 vs placebo). Pa
either sertraline alone (OR 3.4; 95% CI, 2 to 5.9; p less than 0.001) or CBT alone (OR 2.8; 95% CI, 1.6 t
patients receiving sertraline alone or CBT alone (p=0.41). In the number needed to treat (NNT) analysis,
event; treating 3 patients with sertraline alone or CBT alone prevented 1 additional event. The incidence
in the sertraline group compared to the placebo group. There were no suicide attempts (Walkup et al, 20
2) Sertraline was safe and efficacious in the treatment of generalized anxiety disorder in children and ac
DSM-IV diagnosis of generalized anxiety disorder were randomly assigned to receive sertraline or placel
first week and 50 mg/day thereafter. Significant treatment differences in favor of sertraline were evident f
Anxiety Rating Scale, as well as the psychic factor score, was significantly better in the sertraline group t
factor). Ten of 11 patients receiving sertraline were rated as improved, while only 1 of the placebo patien
marked improvement. There was no depression-by-treatment interaction effect, indicating that the obser
age effects on treatment were observed. Patients receiving sertraline reported less dizziness, nausea, ar
and restlessness occurred more frequently among those treated with sertraline than among those receiv

4.5.A.16 Intermittent explosive disorder

a) Overview

FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence is inconclusive
Recommendation: Adult, Class IIb
Strength of Evidence: Adult, Category C

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:

Three patients treated with sertraline noted a decrease in explosive behavior (Feder, 1999)

c) Adult:

1) Three patients (age range, 29 to 51 years old) who met DSM-IV diagnostic criteria for intermittent exp
sertraline. Two patients received sertraline 50 milligrams daily while the third required sertraline 100 milli
months to 2 years with continued treatment; family members and friends also observed the change. The
which is corrected with sertraline (Feder, 1999).

4.5.A.17 Major depressive disorder

FDA Labeled Indication

a) Overview

FDA Approval: Adult, yes; Pediatric, no
Efficacy: Adult, Effective; Pediatric, Evidence favors efficacy
Recommendation: Adult, Class I;
Strength of Evidence: Adult, Category B; Pediatric, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:

More effective than placebo in relieving acute depression
In comparison to placebo, reduced recurrence of chronic depression in 18-month study of responde
Sertraline has more favorable adverse effect profile than amitriptyline
Possibly efficacious in adolescents with major depression
Safe and effective in the treatment of moderate to severe depression in children and adolescents ag
Sertraline was safe and effective in reducing depressive symptoms in elderly patients
In elderly patients with depression, sertraline did not provide protection against relapse when given

c) Adult:

1) Treatment with sertraline effectively reduced depressive symptoms in patients with late-life depressio
(n=752), elderly patients (60 years and older) with major depressive disorder and with or without comorb
included in the comorbid illness group (n=442) had a vascular morbidity (ie, cardiovascular, cerebrovasc
endpoint, significantly greater score improvements for the Hamilton Depression scale (p=0.02), Clinical G
(p=0.001) were seen in sertraline-treated patients as compared with patients who received placebo. Sign
effective in the treatment of depression regardless of medical comorbidity. Sertraline was generally well t
2) Sertraline therapy following remission of depressive symptoms did not provide prophylaxis against re
major depressive disorder (mean age, 77.6 years of age) received open-label treatment with sertraline (r
achieving remission of depressive symptoms entered a randomized, double-blind, placebo- controlled, m
received sertraline (at their final therapeutic dose; range, 50 to 100 mg/day) or placebo. Increases in dos
in the prevention of recurrence of depression (Wilson et al, 2003).
3) Sertraline therapy was more effective than placebo in the treatment of symptoms associated with maj
controlled study, geriatric patients (mean age, 69.8 years; range, 59 to 97 years) with major depressive d
score of at least 18 received sertraline (n=371; initial, 50 milligrams (mg)/day for 4 weeks, then titrated to
period of 4 to 14 days. From baseline to endpoint, sertraline treatment produced significantly greater cha
p=0.01) and the Clinical Global Impressions (CGI) Severity score (-1 vs -0.8, respectively; p=0.009). Ser
endpoint as compared with placebo (2.7 vs 2.9, respectively; p=0.02). The CGI response rate (defined as
35% for those taking placebo (p=0.005). The HAM-D response rate (defined as at least a 50% reduction
placebo (35% vs 26%, respectively; p=0.007). Diarrhea, headache, somnolence, tremor, nausea, fatigue

(Schneider et al, 2003).

4) At the end of a 20-week continuation study, more patients receiving sertraline than placebo had a per sertraline-treated and 49% of placebo-treated patients withdrew or failed to complete the study. In this co with major depression. One hundred seven responders (66 sertraline; 41 placebo) from a 6-week acute p only responders had been entered into the continuation phase, a prospectively defined Clinical Global Im persistence of a treatment effect in this period (Olie, 1997).

5) After 6 weeks, sertraline produced significant improvement in depression compared to placebo at all compared to placebo in a double-blind, parallel study of 289 patients with depression.

6) In an 18-month continuation study of patients with chronic depression or dysthymic disorder with majo placebo. Following treatment for depression and a short continuation period, patients (n=161) who respo weeks; the maximum allowable dose was 200 milligrams (mg). The recurrence rate was 6% and 23% for recurrence of depressive symptoms compared to placebo. Of the 161 patients enrolled in the continuatio the patients treated with sertraline, the major reason for discontinuation was adverse effects, whereas in sertraline is useful for preventing recurrence or reemergence of depression in patients with chronic depre

d) Pediatric:

1) Sertraline therapy effectively treated depressive symptoms in children and adolescents with moderate placebo- controlled trials, pediatric patients (n=376; ages 6 to 17 years) with major depressive disorder c sertraline (50 to 200 milligrams (mg)/day; mean dose, 131 mg/day) or placebo for 10 weeks. Psychotrop allowed during the study. Response was defined as a 40% or greater reduction in the adjusted total scor Impression-Improvement (CGI-I) score of 2 or less ("very much" or "much" improved). From baseline to e significantly better for sertraline-treated patients as compared with placebo-treated patients (-22.84 vs -2 sertraline group as compared with placebo for both the CDRS-R (69% vs 59%, respectively; p=0.05) and with insomnia, diarrhea, anorexia, vomiting, agitation, purpura, and urinary incontinence being reported r ideation (3 patients) and aggressive reaction (1 patient) (Wagner et al, 2003).

2) In an uncontrolled, open-label study of adolescents (ages 12 to 18 years) with DSM-IV major depress depressive symptoms, although response patterns differed for MDD and DD. Patients (n=21) received se 200 mg/day. Response to treatment, as indicated by a 50% or greater improvement in the Hamilton-Dep was sustained to the end of the study (24 weeks). In the DD group (n=8), the HAM-D response rate was of a score of 2 or less on the Clinical Global Impression-Improvement Scale (CGI-I), the response rate re the end of the study. In the DD group, the CGI-I maximal response rate was 75% at week 6. That maxim were the most common adverse events, with of the DD group and 30% of the M of the MDD group. Two obese patients were withdrawn from the study for elevations in blood pressure a efficacious in the acute treatment of MDD and DD and in the continued treatment of MDD in adolescents

4.5.A.18 Myocardial infarction; Prophylaxis

a) Overview

FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence favors efficacy
Recommendation: Adult, Class III
Strength of Evidence: Adult, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:

Associated with decreases in platelet/endothelial activation in depressed, post-acute coronary syndr
May confer a protective effect against first myocardial infarction (Sauer et al, 2001)

c) Adult:

1) Sertraline therapy was associated with a decrease in platelet/endothelial activation in patients experie placebo-controlled sub-study of the Sertraline Antidepressant Heart Attack Randomized Trial (SADHART placebo for 24 weeks. The use of aspirin, anticoagulants, and ADP- receptor inhibitors was allowed throu platelet/endothelial activation as compared with placebo and may offer further advantage for this patient et al, 2003).

2) In a case-control study comprised of 653 cases of first myocardial infarction (MI) and 2990 control sul protective effect against first MI. The subjects in this study were smokers, between the ages of 30 to 65 y SSRIs investigated in this study were fluoxetine, fluvoxamine, paroxetine, and sertraline; doses taken by first MI compared to controls (after adjustment for potential confounders) was 0.35 (95% CI 0.18, 0.68; p inhibitory effect on serotonin-medicated platelet activation or amelioration of other factors associated with

4.5.A.19 Night eating syndrome

a) Overview

FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence favors efficacy
Recommendation: Adult, Class IIb
Strength of Evidence: Adult, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:

Treatment with sertraline reduced the symptoms of night eating syndrome compared to placebo in a (O'Reardon et al, 2006)

c) Adult:

1) In an 8-week, randomized, double-blind, placebo-controlled study (n=34), treatment with sertraline re

Patients meeting the standard criteria for night eating syndrome and with a body mass index of greater tl
depression, a lifetime diagnosis of bipolar disorder or any psychotic disorder, or who lacked awareness c
sertraline 50 milligrams (mg; n=17) or placebo (n=17) orally once daily for 8 weeks. Sertraline was adjus
conducted every other week. No other psychotropic medications were allowed during the study period. A
Inventory, and the Quality of Life Enjoyment and Satisfaction Questionnaire, and a physician administere
Hamilton Depression Rating scale. The primary outcome was the CGI-improvement scores, where patie
improved) were considered to have responded and remitted, respectively. An intent-to-treat analysis reve
achieved remission (p less than 0.001). Three of 17 patients (18%) in the placebo group responded (p le
In the sertraline group, the CGI severity scale decreased from 4.2 at baseline (moderate severity) to 2.2
decreased from 4.2 at baseline to 3.4 at week 8 (p=0.004). Among secondary endpoints, the night eating
the sertraline and placebo groups, respectively (p less than 0.0001). Although a significant correlation be
(r=0.68; p=0.01) indicated that early improvement with sertraline was predictive of ultimate response, 50
8. The number of nocturnal ingestions decreased from a baseline mean (+/- standard deviation) value of
to a decrease from the baseline mean of 6.4 +/- 4.9 per week to 5.5 +/- 4.9 per week at week 8 in the pla
placebo, improvements also occurred for patients treated with sertraline in the number of awakenings, ca
patients. Both groups had a modest level of depressive symptoms at baseline, and reductions in depress
symptom scores. Sertraline was well-tolerated, only mild side effects that included dry mouth, fatigue, dir

4.5.A.20 Non-cardiac chest pain

a) Overview

FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence is inconclusive
Recommendation: Adult, Class IIb
Strength of Evidence: Adult, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:

A small double-blind study found sertraline to significantly reduce noncardiac chest pain (Varia et al,

c) Adult:

1) Sertraline significantly reduced pain scores compared to placebo in patients with chest pain determin
30 patients were randomized to either sertraline 50 milligrams (mg) or placebo, with dose adjustments up
decreased significantly in the sertraline group compared with the placebo group. Sertraline's effect did no
were excluded and no effect was seen on the Beck Depression Inventory in these patients. Sertraline wa

4.5.A.21 Obsessive-compulsive disorder

FDA Labeled Indication

a) Overview

FDA Approval: Adult, yes; Pediatric, yes ((6 years or older))
Efficacy: Adult, Effective; Pediatric, Effective
Recommendation: Adult, Class I; Pediatric, Class I
Strength of Evidence: Adult, Category B; Pediatric, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:

Considered a first-line agent for treating obsessive-compulsive disorder (OCD)
Cognitive behavior therapy alone or in combination with sertraline was more effective in the treatme
placebo

c) Adult:

1) Effectiveness of sertraline for treatment of obsessive-compulsive disorder (OCD) was sustained with
Patients who had responded successfully to sertraline (final mean dose 189 milligrams/day) in a 52-weel
sertraline (n=109) or with placebo (n=114) for an additional 28 weeks. Study discontinuation due to relap
(9% vs 24%, p=0.006). Experiences of acute exacerbation (not resulting in study discontinuation) were a
groups in discontinuation due to adverse events. During the double-blind trial, patients in the sertraline g
decreases. During the entire 80 weeks of treatment, fewer than 20% of patients taking sertraline dropped
patients receiving placebo and 4.6% of those receiving sertraline dropped out because of adverse event
upper respiratory infection, headache, and malaise. The only notable difference in rates of adverse even
et al, 2002).

2) Sertraline was more effective than placebo for treatment of obsessive-compulsive disorder (OCD). In
were randomly assigned to receive placebo or sertraline 50 milligrams/day titrated to a maximum dose o
significantly more effective than placebo based on the Yale-Brown Obsessive Compulsive Scale (p less
less than 0.05), and the Clinical Global Impression Scale (p less than 0.01). Forty-one percent of sertrali
placebo-treated patients (p=0.01). Thirteen patients stopped treatment due to adverse effects primarily s
completed by 71% and 69% of patients treated with sertraline and placebo, respectively. Sertraline is an

3) Of the selective serotonin reuptake inhibitors (SSRIs) (ie, fluoxetine, sertraline, paroxetine, fluvoxamin
Limited clinical studies also suggest that the SSRIs are comparable to clomipramine; however, results of
& Bisserbe, 1997; Leonard, 1997). Selection of initial treatment is often based on the side effect profile o
(Leonard, 1997). Early studies used near maximal doses of an SSRI which resulted in a high incidence c
response in some patients and better tolerance in most (Leonard, 1997). While the optimal duration of tr
studies have shown relapse rates between 65% and 90% when pharmacologic treatment was stopped (I
doses of an SSRI and/or behavioral therapy are considered refractory to treatment. In about 20% of this

therapy with haloperidol or clonazepam may be beneficial (Rasmussen & Eisen, 1997).

4) Results of a study demonstrated significant improvement of obsessive compulsive disorder (OCD) on multicenter trial in 87 patients with OCD who did not meet criteria for depression, sertraline 200 milligram symptoms as measured by the Yale-Brown Obsessive-Compulsive Scale and the NIMH Scale. The Mau although there was a trend toward greater improvement in the sertraline-treated group; the physician-rat some improvement as compared with 26% of the placebo-treated group (Chouinard et al, 1990).

d) Pediatric:

1) Cognitive behavior therapy (CBT) either alone or in combination with sertraline was more effective in compared with sertraline monotherapy or placebo. In the randomized, controlled, multicenter Pediatric O age, 11.7 years) with a primary diagnosis of OCD and a Children's Young-Brown Obsessive-Compulsive over a 12-week period. Equal numbers of patients received either CBT alone, sertraline therapy alone, c titration schedule (25 to 200 milligrams/day over 6 weeks, after which no further dosage adjustments wer the 12-week study period. At 12 weeks, significantly greater reductions in CYBOCS scores were observe placebo (p less than 0.001). Monotherapy with sertraline or CBT was not significantly different when com scores as compared with placebo (p=0.007 and p=0.003, respectively). Significantly higher rates of clinic combination therapy (53.6%; 95% CI, 36% to 70%) as compared with sertraline (21.4%, 95% CI, 10% to differ from CBT alone (39.3%; 95% CI, 24% to 58%) (p=ns). As with reductions in CYBOCS scores, sert remission rates, however, CBT was superior to placebo (p=0.002) while sertraline was not (p=ns). Sertra attempt during the study. Common adverse effects included decreased appetite, diarrhea, enuresis, mot Team, 2004).

2) Sertraline was shown to be effective in a 12-week, multicenter, placebo-controlled, parallel group stud open extension study of 137 outpatients (ages 6 to 18) for the treatment of obsessive-compulsive disord score of 22 on the Children's Yale-Brown Obsessive-Compulsive Scale (CYBOCS). Children ages 6 to 1 to 17) were started on 50 mg/day. Doses were increased over the next four weeks to a maximum dose o sertraline group had a mean reduction of approximately 7 units on the CYBOCS total score which was si Response to treatment was not altered by either age or gender (Prod Info Zoloft(R), 2003a).

4.5.A.22 Panic disorder

FDA Labeled Indication

a) Overview

FDA Approval: Adult, yes; Pediatric, no
Efficacy: Adult, Effective
Recommendation: Adult, Class IIa
Strength of Evidence: Adult, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:

Sertraline has reduced the frequency of panic attacks in blinded studies (Pohl et al, 1998; Londborg

c) Adult:

1) Sertraline is an effective therapy for panic disorder. In a 10-week, double-blind, multicenter study, 166 titration to a maximum dose of 200 mg daily; at study endpoint, the mean sertraline dose was 126 mg/da number of panic attacks per week decreased by 77% and 51% in the sertraline and placebo groups, resp (62%) than placebo (46%) were free of panic attacks (p=0.04). Investigators also noted significant impro (severity and improvement: p less than 0.001). Adverse effects resulted in study discontinuation in 9% a effects had a mild-to-moderate severity rating (Pohl et al, 1998).

2) Sertraline was significantly more effective than placebo in the treatment of panic disorder. Patients we 200 mg daily (n=44), or placebo (n=44) for 12 weeks. The primary measure of efficacy was the number o the number of weekly panic attacks compared to a 39% reduction with placebo. There were no significar decreased the frequency of situational and unexpected panic attacks, anticipatory anxiety, and limited sy After 12 weeks, more patients were panic-free with sertraline than placebo, 57% and 41%, respectively. 200 mg group, and 31% of the placebo group discontinued the study. A significantly greater number of p placebo. Because efficacy was independent of plasma concentrations, 50 mg of sertraline daily is the re (Londborg et al, 1998).

4.5.A.23 Pathological laughing

a) Overview

FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence is inconclusive
Recommendation: Adult, Class IIb
Strength of Evidence: Adult, Category C

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:

Relieved pseudobulbar laughter in one patient (Okun et al, 2002)

c) Adult:

1) Sertraline resolved pseudobulbar laughter within 48 hours in a 46-year-old man who had suffered inju Parkinson's disease), the man underwent right gamma knife thalamotomy, targeting the ventral intermed numbness in his lip, which resolved, and numbness in his left hand, which persisted over the following ye symptoms of depression or elated mood. He was given sertraline 50 milligrams/day, which resolved the follow-up (Okun et al, 2002).

4.5.A.24 Posttraumatic stress disorder

FDA Labeled Indication

a) Overview

FDA Approval: Adult, yes; Pediatric, no
Efficacy: Adult, Effective
Recommendation: Adult, Class I
Strength of Evidence: Adult, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:

Effective for treating posttraumatic stress disorder (Rapaport et al, 2002)
Effectiveness maintained during extended treatment (Londborg et al, 2001)
Some nonresponders to acute treatment respond to longer treatment (Londborg et al, 2001)

c) Adult:

1) Quality of life (QOL) was significantly improved in patients with posttraumatic stress disorder (PSTD) In a manufacturer-funded study, 359 patients meeting DSM-III-R criteria for PTSD for at least 6 months v milligrams (mg) per day or placebo for 12 weeks. Completers of the acute phase (n=275), whether or not (n=234). Responders during the continuation phase (n=172) were eligible for a 28-week, randomized, do maintenance phase. In comparison to placebo treatment, acute sertraline treatment resulted in significan (Q-LES-Q) of patients without comorbid depression. Improvement in scores of those with comorbid depr measures of psychological functioning and well-being were significant (relative to placebo) for sertraline- occupational impairment scores were significantly better with sertraline than with placebo. During the cor the double-blind, maintenance phase, QOL and functioning scores deteriorated somewhat for both group

2) Effectiveness of sertraline for treating posttraumatic stress disorder (PTSD) was maintained in most p Furthermore, half of the nonresponders to acute treatment became responders during the 6 months of c the acute phase of 2 double-blind, placebo-controlled trials of sertraline for treatment of severe DSM-III-R during the acute phase. Blinding to acute-phase treatment was maintained throughout the open label stu (mg) daily for the first week. The dose was then increased to 50 mg/day, which was titrated on an individ sustained their initial response. Average scores on various investigator-completed and patient-completed patients who were nonresponders during the acute phase who became responders during the continuati response time was having a high baseline severity score (higher than 75) on the Clinician Administered I frequent moderate-to-severe treatment-related adverse events were headache, insomnia, dry mouth, an vital signs attributed to sertraline during the 24 weeks. Body weight increased by a mean of 0.8 kilogram

3) Sertraline was more effective than placebo in prevention of posttraumatic stress disorder (PTSD) rela for posttraumatic stress disorder (PTSD), were enrolled in this 28-week, double-blind, multicenter, placeb biweekly and were classified as relapsed if their Clinical Global Impression (CGI) improvement score inc increased by at least 30%, and there was significant worsening of the patient's clinical condition on two c relapse than the patients treated with sertraline (mean endpoint dose=137 milligrams). Forty percent of t 28-week trial (Davidson et al, 2001).

4) Sertraline was more effective than placebo for treating patients with chronic post-traumatic stress dis randomly assigned to sertraline 25 milligrams (mg)/day or placebo; after the first week, the sertraline dos patients who received treatment, 65 and 68 patients assigned to sertraline and placebo completed the tri follow-up. In patients completing the study, the mean daily dosage of sertraline was 151.3 mg. For 3 of th Clinical Global Impression-Severity scale (CGI-S), and the Clinical Global Impression-Improvement Scal 33 versus (vs) -23.2, p=0.02; CGI-S -1.2 vs -0.8, p=0.01; CGI-I 2.5 vs 3, p=0.01). In addition, a trend tow treated with sertraline versus placebo. About 70% of the reduction on the CAPS-2 and IES was achieved

4.5.A.25 Premature ejaculation

a) Overview

FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence is inconclusive
Recommendation: Adult, Class IIb
Strength of Evidence: Adult, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:

Sertraline effectively increased time to ejaculation during a randomized, placebo-controlled trial (n=3

c) Adult:

1) Thirty-seven men were successfully treated with sertraline 50 mg daily for premature ejaculation. Dur (n=19) for 4 weeks. Patients then underwent a 4-week washout period and entered phase 2 which consi open-label trial to evaluate the long-term effects of sertraline on premature ejaculation and the effects of significantly compared to those in the placebo group, from a mean of 0.3 minutes to 3.2 minutes (P less drug, efficacy was lost after 6 to 13 days. This suggests that long-term treatment with sertraline may be r

4.5.A.26 Premenstrual dysphoric disorder

FDA Labeled Indication

a) Overview

FDA Approval: Adult, yes; Pediatric, no
Efficacy: Adult, Effective

Recommendation: Adult, Class I
Strength of Evidence: Adult, Category B
See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:
Sertraline is effective for premenstrual dysphoric disorder (PMDD) (Prod Info Zoloft(R), 2002; Pearls
Administration during the luteal phase was as effective as continuous sertraline and more effective t
& Smoller, 1997)

c) Adult:
1) Women with PMDD demonstrated greater improvement in psychosocial function after treatment with
the psychosocial functioning results reported here. All women (n=243) completed the Daily Record of Se
form of the Quality of Life Enjoyment and Satisfaction Questionnaire (Q-LES-Q) before and after treatme
enrolled in this study showed impairment of psychosocial functioning during the luteal phase compared v
phase of 3 menstrual cycles versus placebo resulted in significant improvement on the SAS total score (
reduction of productivity, interference of hobbies and social activities, and interference with relationships
second menstrual cycle on (Pearlstein et al, 2000).
2) Sertraline produced greater improvement in symptoms associated with premenstrual dysphoric disor
50 mg or placebo daily during the first cycle; if needed, the sertraline dose was titrated to 100 mg in cycl
Severity of Problems (DRSP) showed a 32% versus 11% decrease in total scores (p less than 0.001) aft
beneficial effects of sertraline. This study also demonstrated significant improvement in productivity and
8% and 2% of patients treated with sertraline and placebo withdrew from treatment. Sertraline is an effec
3) Sertraline administered during the luteal phase was as effective as continuous sertraline and more ef
(Halbreich & Smoller, 1997). In this study, patients were initially treated with sertraline 100 milligrams (m
assigned to receive placebo or sertraline 100 mg daily for 2 weeks during the luteal phase; each treatme
Scale for Depression (HAM-D), Clinical Global Impressions scale (CGI), and Daily Rating Forms (DRF))

4.5.A.27 Respiratory obstruction

a) Overview
FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence is inconclusive
Recommendation: Adult, Class III
Strength of Evidence: Adult, Category C
See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:
Low doses of sertraline were effective in the treatment of patients with obstructive airway disease (n

c) Adult:
1) Sertraline 25 milligrams (mg) to 100 mg daily was effective in decreasing breathlessness and increas
Sertraline, however, had little effect on measures of forced expiratory volume at 1 second (FEV1). Only 3
experienced anxiety during attacks of dyspnea. Sertraline may decrease the anxiety associated with bre
patients did not have mood/anxiety disorders, sertraline may work on respiratory, rather than psychiatric
decreasing patient sensitivity to carbon dioxide concentrations. Further studies are needed to confirm the

4.5.A.28 Schizophrenia

a) Overview
FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Ineffective
Recommendation: Adult, Class III
Strength of Evidence: Adult, Category B
See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:
Sertraline had no effect on positive or negative symptoms of schizophrenia when added to an antips

c) Adult:
1) Addition of sertraline to haloperidol therapy had no effect on the positive or negative symptoms of sch
for an average of 10 years and required institutional care. Patients were randomly assigned to placebo o
differences between treatments on the Positive and Negative Syndrome Scale, the Clinical Global Impre
shown beneficial effects of adding a selective serotonin reuptake inhibitor to an anti-psychotic. In this stu
the study population, the short duration of treatment, and the fixed, low-dose of sertraline. Further studie

4.5.A.30 Social phobia

FDA Labeled Indication

a) Overview
FDA Approval: Adult, yes; Pediatric, no
Efficacy: Adult, Effective
Recommendation: Adult, Class I
Strength of Evidence: Adult, Category B
See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:
Effectively treated social phobia in short-term (12-20 weeks) and longer-term clinical trials (44 week
c) Adult:
1) Treatment with sertraline was more effective than placebo in reducing symptoms of severe generalize
controlled, flexible-dose study, patients (n=415) with a least a 2-year history of generalized social phobia
to 200 milligrams (mg) daily (mean dose, 158.8 mg/day) or placebo for 12 weeks. Response was define
Impressions-Improvement Scale (CGI-I). At endpoint, the CGI-I responder rate was significantly higher f
than 0.001). Additionally, the mean change in the LSAS score showed significantly greater reductions wi
and endpoint (p less than 0.001). The most commonly reported adverse events with sertraline treatment
mouth (14.4%), sweating (11.5%), and ejaculatory dysfunction (men, 14.3%) (Liebowitz et al, 2003).
2) Sertraline in doses of 50 to 200 milligrams per day was effective in the treatment of adult outpatients
also demonstrated a statistically significant lower relapse rate in a 24-week continuation study when com

4.6 Comparative Efficacy / Evaluation With Other Therapies

Amisulpride

Amitriptyline

Bupropion

Desipramine

Fluoxetine

Fluvoxamine

Imipramine

Mianserin

Mirtazapine

Nortriptyline

Paroxetine

Sildenafil

St John's Wort

Venlafaxine

4.6.A Amisulpride

Burning mouth syndrome

Dysthymia

4.6.A.1 Burning mouth syndrome

a) Amisulpride, sertraline, and paroxetine were all effective in reducing the symptoms of burning mouth synd
serotonin reuptake inhibitors (SSRIs). In a randomized, single-blind study, 76 patients with BMS and without
mg/day, or sertraline 50 mg/day for 8 weeks. Pain scores decreased significantly in all groups, as did depres
Anxiety), by week 8. The only difference among treatments was the shorter latency to response in the amisul
paroxetine and 6% with sertraline) (Maina et al, 2002a).

4.6.A.2 Dysthymia

a) Although amisulpride and sertraline were equally effective for treatment of dysthymia at 12 weeks of treat

amisulpride than with sertraline. In a 12-week, randomized, double-blind study, patients between the ages of depression, were given amisulpride (n=156) or sertraline (n=150), each drug at a starting dose of 50 milligran were eventually increased to 100 mg/day). The median time to onset of partial response (corresponding to a score) was significantly shorter with amisulpride: 11 days versus 15 days (p less than 0.0091). Percentages c sertraline (p less than 0.01). Patients reported perceiving improvement earlier with amisulpride: 8.4 days vs 1 HAMD score) also occurred earlier with amisulpride. By week 4, 63% of patients in the amisulpride group and corresponding values were 82% and 69% (p=0.009). By week 12, the percentage of responders did not differ percentage of patients reporting adverse events was about 45% for both groups but the adverse events were sertraline and endocrine adverse events with amisulpride (Amore & Jori, 2001).

4.6.B Amitriptyline

4.6.B.1 Depression

a) SUMMARY: Five clinical studies have reported similar efficacy between amitriptyline and sertraline in the Doogan & Caillard, 1988b; Reimherr et al, 1988a). Sertraline has had a higher incidence of gastrointestinal si with anticholinergic effects, sedation, dizziness, and hypotension (Cohen et al, 1990)(Reimherr et al, 1990).
b) In an 8-week, double-blind, parallel-group study (n=385), sertraline and amitriptyline were comparable for (Lydiard et al, 1997). Patients were randomly assigned to receive placebo, sertraline 50 milligrams (mg), or a in the protocol. Selected sections of Profile of Mood States (POMS) showed greater improvement in patients similar between treatments. Significantly more patients reported adverse effects (71.8%) and dropped out of adverse effects, blinding may have been inadequate in this study. Long-term studies are needed to compare
c) In an 8-week, double-blind placebo-controlled parallel study of 379 patients with major depression, sertral amitriptyline 50 to 150 mg/day. However, both drugs produced significant improvement over placebo. Patient Global Impressions (CGI) measurement (Doogan & Caillard, 1988b). Similar results were reported in 77 patie controlled trial, the investigators found that sertraline caused fewer adverse reactions than did amitriptyline.
d) However, in another study, patients receiving sertraline had a significantly higher incidence of gastrointest treated group. The amitriptyline-treated group had a high incidence of anticholinergic effects, sedation and di (mean dose 145 milligrams), amitriptyline (mean dose 104 milligrams), or placebo. As measured by both the groups showed significantly greater improvement than placebo (Reimherr et al, 1990).
e) In 241 elderly depressed patients, amitriptyline 50 to 150 milligrams daily or sertraline 50 to 200 milligrams effects varied greatly. A higher proportion of amitriptyline-treated patients (38%) withdrew from the study due compared with a 28% incidence of treatment-withdrawal with sertraline. Sertraline-treated patients had a high

4.6.C Bupropion

4.6.C.1 Depression

a) In a randomized, double-blind comparison trial between sustained- release bupropion (bupropion SR) and treated patients (Segraves et al, 2000). In the study, 248 patients diagnosed with moderate to severe major d dose of bupropion SR was 100 milligrams/day (mg/day). If indicated, the dose was increased to 200 mg/day was increased to 100 mg/day on day 8, 150 mg/day on day 15, and 200 mg/day on day 22, if clinically indicat dysfunction compared with bupropion SR (men: 63% and 15%, respectively, p less than 0.001; women: 41% disorder, sexual arousal disorder, orgasm dysfunction, decreased satisfaction with sexual functioning, and wo treated patients reported instances of premature ejaculation; however, this difference was not statistically sign determine the extent of influence of the natural course of depression. This data does suggest, however, that whom sexual dysfunction is of concern.
b) In an 8-week, double-blind trial, sertraline and bupropion produced similar antidepressant effects while bu received bupropion sustained release 150 to 400 milligrams (mg)/day (n=120), sertraline 50 to 200 mg/day (r were bupropion SR 293 mg/day and sertraline 121 mg/day. Both active treatment groups responded better th bupropion SR 66%, sertraline 68%, placebo 47%, p=0.002). At baseline, sexual desire disorder was reported patients. At the end of 8 weeks this problem decreased to only 19% of bupropion patients versus 31% receivi the disorder (not significant as compared to placebo). More sertraline patients also experienced orgasmic dys 0.001). Somnolence, insomnia, nausea, and diarrhea also occurred more often in the sertraline group than in
c) In a randomized, double-blind trial, bupropion sustained release (SR) and sertraline were similarly effectiv received either bupropion SR 100 to 300 milligrams (mg) daily in 2 doses (n=119) or sertraline 50 to 200 mg and sertraline 114 mg/day. Patients improved similarly on several scales including the Hamilton Rating Scale Scale for Severity of Illness and for Improvement. Nausea, diarrhea, somnolence and sweating were experie Orgasm delay and/or failure was also experienced more often in the sertraline group (p less than 0.001).

4.6.D Desipramine

Depression - Obsessive-compulsive disorder

Premenstrual dysphoric disorder

4.6.D.1 Depression - Obsessive-compulsive disorder

a) Sertraline was more effective than desipramine for reducing symptoms of major depressive disorder (MDD assigned to receive desipramine 50 milligrams (mg) per day or sertraline 50 mg per day for 12 weeks. The do desipramine was 300 mg/day. At study end-point, the mean dosage of sertraline and desipramine was 160.1 Rating Scale for Depression (HAM-D) and Yale-Brown Obsessive Compulsive Scale (Y-BOCS), sertraline wa treated with sertraline than desipramine had a 40% or greater reduction in the Y-BOCS (p=0.01); remission o patients in the sertraline than desipramine groups (p=0.04). Discontinuation due to adverse effects occurred i p=0.009). For patients with OCD and MDD, sertraline is an effective treatment (Hoehn-Saric et al, 2000).

4.6.D.2 Premenstrual dysphoric disorder

a) Sertraline more effectively reduced symptoms and improved functioning in women with premenstrual dysp al, 1999). After a 3-month screening period, patients (n=189) were randomly assigned to sertraline 50 milligra intervals to a maximum of 150 mg/day were allowed. Significantly more patients assigned to desipramine dis resulted in a significantly greater decrease from baseline to endpoint in the Premenstrual Daily Symptom Rep 17-item Hamilton Depression Rating Scale (p less than 0.001). Direct comparison of a sertraline and desipra

b) In an open-label trial of 32 women with a history of severe premenstrual symptoms, sertraline and desipra months treatment, 78% of sertraline-treated patients and 75% of desipramine-treated patients experienced at more sertraline-treated patients (68%) reported a 50% or more reduction in premenstrual symptoms than des the study, but this difference may not apply to long-term therapy. Long-term, placebo-controlled trials are nee syndrome.

4.6.E Fluoxetine

Depression

Obsessive-compulsive disorder

Weight gain

4.6.E.1 Depression

a) Paroxetine, fluoxetine, and sertraline were equally effective for the treatment of depression and for improv label trial (the ARTIST trial), depressed patients, whose symptoms warranted antidepressant treatment, acco (n=184) or sertraline (n=182). Starting doses were paroxetine 20 milligrams (mg), fluoxetine hydrochloride 20 response and could switch the treatment to one of the other study drugs. Final average doses were 23.5 mg substantial improvement in depressive symptoms and quality of life. Overall, the percentage of patients categ and 26% at 9 months. No significant differences were evident among the 3 groups. When data from subgroup assigned) were analyzed separately, still no differences among the drug treatments was evident. Patient satis to show improvement for all drug treatments. The drugs were associated with similar incidences of adverse e

b) An eight-week, double-blind, randomized study evaluated the efficacy and safety of fluoxetine vs sertralin with major depression entered into the study, but only 88 (48 sertraline and 40 fluoxetine) were evaluable. Th treatment groups showed a statistically significant improvement from baseline at one week, and this was mai between the two treatment groups on the primary efficacy variables measured by Hamilton Rating Scale for D Asberg Depression Rating Scale (MADRS), Leeds Sleep Score scale and Zung Anxiety Rating Scale. The in common were gastrointestinal (nausea and abdominal pain) and central nervous system (irritability, headach tolerated than fluoxetine overall; 9.6% of sertraline-treated patients discontinued treatment, compared with 19 population is warranted to definitively establish the comparative efficacy and safety of the two drugs (Aguagli

4.6.E.2 Obsessive-compulsive disorder

a) Both fluoxetine and sertraline were effective and well tolerated in the treatment of patients with obsessive- per day (mean 139.5 +/- 58.5 mg; N=76), or fluoxetine, 20 to 80 mg/day (mean 56.7 +/- 23.0 mg; N=72), in a matched patient populations. Safety and efficacy measures were taken at the end of study weeks 1, 2, 4, 6, 8 the study. Primary efficacy measures included the Yale-Brown Obsessive- Compulsive Scale (Y-BOCS), the the Clinical Global Impression Severity and Improvement scales (CGI-S and CGI-I). Secondary measures inc Anxiety Scale (CAS). By the end of the 24 week study, both medications were effective and there were no sig measures showed similar amounts of improvement. The time-course of improvement was also similar for bot measures (Y-BOCS change score and global severity of illness score) during some of the early assessments differences between the drug treatments during this time period. Adverse drug effects were described as mild sertraline or fluoxetine (Bergeron et al, 2002).

4.6.E.3 Weight gain

a) Weight gain is a common complaint during antidepressant therapy, and weight gain was significantly grea meeting DSM-IV criteria for major depressive disorder were randomized to double-blind treatment with sertra daily (n=96) for 4 weeks. Patients responding to this dose continued for an additional 6 weeks, and those not 60 mg fluoxetine, and 60 mg paroxetine, and then maintained at their optimal doses for 6 weeks. After this tre consecutive weeks) continued for 16 additional weeks. The number of responders participating in the 16 addi paroxetine. However, among these responders, the mean increase in weight in the paroxetine group (3.6%) v

with fluoxetine (-0.2%). A gain of 7% or greater in weight occurred in 25.5% of paroxetine patients, 4.2% of se
2000a).

4.6.F Fluvoxamine

4.6.F.1 Depression

a) In a small study (n=64), the incidence of recurrent depression was similar between patients treated prophy
received either sertraline 100 milligrams(mg)/day or fluvoxamine 200 mg/day for 2 years; increases in dose w
fluvoxamine-treated patients had a new episode of depression (p=0.88). Adverse effects were minor and tran
were effective for preventing recurrent depression episodes, but are limited by the absence of a placebo cont
b) The pharmacology, pharmacokinetics, adverse effects, drug interactions, efficacy, and dosage of fluvoxar
review (Grimsley & Jann, 1992b). All three agents have large volumes of distribution and are highly protein-b
lives (approximately 24 hours) and are metabolized to clinically-inactive compounds. These agents, therefore
commonly reported adverse effect for all three agents. Other reported adverse effects include sedation, head
be superior to placebo and equivalent to imipramine, clomipramine, desipramine, mianserin, and maprotiline
placebo in the treatment of obsessive-compulsive disorder (OCD). PRX has been found to be superior to pla
treatment of depression while SRT has been found to be superior to placebo and equivalent to amitriptyline.
depression. They may be especially useful in elderly patients, in those who cannot tolerate alternate treatmer

4.6.G Imipramine

Depression

Dysthymia

Mixed anxiety and depressive disorder

4.6.G.1 Depression

a) More than 50% of chronically depressed patients who were nonresponders to an antidepressant responde
randomized, 12-week, double-blind trial with either sertraline or imipramine for treatment of chronic depressio
double-blind treatment. Fifty-one patients were switched from imipramine to sertraline and 117 from sertraline
imipramine and 163 mg/day for sertraline. Ten percent of those switched to sertraline and 25% of those switc
intolerable adverse effects of imipramine. Those who switched to imipramine experienced significant reductio
switched to sertraline had significant decreases in 6 adverse effects and significant increases in one:

	SERTRALINE TO IMIPRAMINE	IMIPRAMINE TO SI
DECREASED INCIDENCE		
	Insomnia	Dry mout
	Diarrhea	Somnolen
	Abdominal Pain	Increased swe
		Constipati
		Dizzines
		Urinary comp
INCREASED INCIDENCE		
	Dry mouth	Insomnia
	Increased sweating	
	Constipation	
	Dizziness	

	Tremor
	Abnormal taste
	Increased appetite
	Urinary complaints

b) The intent-to-treat response rates were 60% for sertraline and 44% for imipramine (p=0.03). Among comp
averaging across the study weeks and adjusting for completion status, depression type, and baseline value, t
improvement over time did not differ for the 2 groups (Thase et al, 2002).
c) In a double-blind study of major depression with or without dysthymia, response to sertraline was highest
III-R criteria for chronic major depression (235 men and 400 women) were randomized to 12-week treatment
daily and titrated to a maximum of 300 mg for imipramine and 200 mg for sertraline. Although the overall resp
treatment interaction was observed. The highest response rates occurred in women taking sertraline and in n
imipramine (61/133; 46%); and more men responded to imipramine (43/69; 62%) than to sertraline (73/161; 4
women withdrew from the imipramine group than from the sertraline group; however, withdrawal rates by mer
between menopausal status and treatment. Withdrawal from treatment was highest in premenopausal womer
these gender differences is unknown, and may relate to interaction of female sex hormones and serotonin ac

4.6.G.2 Dysthymia

a) Sertraline and imipramine are equally effective for the treatment of dysthymia; however, sertraline is bette
in a group of 416 patients with early-onset primary dysthymia. Outcome was based on response based on cli
Rating Scale, Hopkins Symptom Checklist) and patient-rated version of the Inventory of Depressive Sympton
improved) demonstrated response rates of 59% for sertraline, 64% for imipramine, and 44% for placebo. The
159.7 milligrams for imipramine (Thase et al, 1996).
b) Of the 416 patients described in the study above by Thase et al, 355 had completed the Tridimensional P
temperament scores improved with improvement in dysthymia. At baseline, temperament in dysthymic patien
Personality Questionnaire than that reported for a community population. After 12 weeks of treatment, harm a
sertraline, imipramine, and placebo group. Scores decreased for those achieving remission and those who di
improvement in temperament was mainly related to disease improvement regardless of treatment. The result
measures, rather than the single measure used in this study, would be needed to determine treatment effects

4.6.G.3 Mixed anxiety and depressive disorder

a) Imipramine and sertraline were equally effective in the treatment of anxiety and depression in patients witl
double-blind study, patients with full Axis I panic disorder with concurrent major depressive disorder with a mi
Asberg Depression Rating Scale (MADRS) score of at least 20 received either sertraline (n=138; 50 to 100 m
144.2 mg/day) for 26 weeks. Sertraline was given at an initial dose of 25 mg/day for 1 week, then titrated to 5
The initial dose of imipramine was 25 mg/day, increased at weekly intervals to 50 mg, 100 mg, and 150 mg. I
outcome measures were weekly panic attack frequency and MADRS score. Sertraline and imipramine produ
(11.1 vs 11.2, respectively) total MADRS score and in the mean baseline (7.1 vs 7, respectively) to endpoint
patients reported significantly fewer adverse effects as compared with imipramine-treated patients (23% vs 4
p=0.04). Nausea and diarrhea was more frequently reported with sertraline treatment, while dizziness, dry mo
administration (Lepola et al, 2003).

4.6.H Mianserin

1) Adverse Effects
a) In a double-blind, placebo-controlled crossover study in elderly patients, sertraline doses of 100 to 200 mg
tests. The addition of alcohol did not affect these results. Conversely, mianserin doses of 10 to 30 mg daily pr
from the study (Hindmarch et al, 1990).

4.6.I Mirtazapine

4.6.I.1 Depression

a) The onset of response was faster with mirtazapine orally disintegrating tablets than with sertraline capsule
Rating Scale (HAM-D) scores were observed with both drugs by day 4, however, and dose titration schedules

4.6.J Nortriptyline

4.6.J.1 Depression

a) Sertraline and nortriptyline were equally effective in treating depression in elderly outpatients; however, se
In this double-blind study, 210 patients ages 60 years and older, and who met DSM III-R criteria for major dep
randomized to 12 weeks of sertraline or nortriptyline. Sertraline was given as 50 milligrams (mg) daily titrated
titrated weekly as needed to 100 mg daily. At 12 weeks, improvements in HAM-D scores were similar for the
72 (72.4%) sertraline-treated and in 43 of 70 (61.4%) nortriptyline-treated patients; this difference was not sig

those of patients younger than 70 years after treatment with nortriptyline, whereas sertraline decreased HAM
energy, and quality of life improved significantly with sertraline compared to scores with nortriptyline. (Bondar

4.6.K Paroxetine

Burning mouth syndrome

Depression

Weight gain

4.6.K.1 Burning mouth syndrome

a) Amisulpride, sertraline, and paroxetine were all effective in reducing the symptoms of burning mouth synd
serotonin reuptake inhibitors (SSRIs). In a randomized, single-blind study, 76 patients with BMS and without
mg/day, or sertraline 50 mg/day for 8 weeks. Pain scores decreased significantly in all groups, as did depress
Anxiety), by week 8. The only difference among treatments was the shorter latency to response in the amisul
paroxetine and 6% with sertraline) (Maina et al, 2002).

4.6.K.2 Depression

a) Paroxetine, fluoxetine, and sertraline were equally effective for the treatment of depression and for improv
label trial (the ARTIST trial), depressed patients, whose symptoms warranted antidepressant treatment, acco
(n=184) or sertraline (n=182). Starting doses were paroxetine 20 milligrams (mg), fluoxetine hydrochloride 20
response and could switch the treatment to one of the other study drugs. Final average doses were 23.5 mg
substantial improvement in depressive symptoms and quality of life. Overall, the percentage of patients categ
and 26% at 9 months. No significant differences were evident among the 3 groups. When data from subgroup
assigned) were analyzed separately, still no differences among the drug treatments was evident. Patient satis
to show improvement for all drug treatments. The drugs were associated with similar incidences of adverse e
b) Sertraline and paroxetine were equally effective in treating major depression, although side effects may b
criteria for major depression and having a score of at least 21 on the Montgomery-Asberg Depression Rating
randomized to receive 24 weeks of treatment with either sertraline 50 milligrams (mg) or paroxetine 20 mg. D
sertraline and 40 mg paroxetine. No significant differences were observed in the improvement of MADRS and
the 176 patients taking sertraline, 64% completed 24 weeks of treatment, and 65 % of 177 treated with parox
less than 7)was achieved in 80.2% of the sertraline and in 73.7% of the paroxetine-treated patients. Quality o
Comparable improvements also occurred for the 2 groups in measures of personality. Both treatments were
constipation, fatigue, decreased libido in women, and micturition problems significantly more common with pa
compared with sertraline (1.3 pound) (Aberg-Wistedt et al, 2000)

4.6.K.3 Weight gain

a) Weight gain is a common complaint during antidepressant therapy, and weight gain was significantly grea
meeting DSM-IV criteria for major depressive disorder were randomized to double-blind treatment with sertra
daily (n=96) for 4 weeks. Patients responding to this dose continued for an additional 6 weeks, and those not
60 mg fluoxetine, and 60 mg paroxetine, and then maintained at their optimal doses for 6 weeks. After this tre
consecutive weeks) continued for 16 additional weeks. The number of responders participating in the 16 addi
paroxetine. However, among these responders, the mean increase in weight in the paroxetine group (3.6%)
with fluoxetine (-0.2%). A gain of 7% or greater in weight occurred in 25.5% of paroxetine patients, 4.2% of s
al, 2000).

4.6.L Sildenafil

4.6.L.1 Premature ejaculation

a) According to a double-blind, randomized, cross-over study (n=31), as-needed SILDENAFIL was superior
SERTRALINE, and PAUSE-SQUEEZE technique. Clomipramine, paroxetine, and sertraline had generally sir
pause-squeeze, while efficacy and satisfaction were similar to pause-squeeze for clomipramine and sertraline
(min), 4 min, 3 min, 15 min, and 3 min from baseline 1 min for clomipramine, paroxetine, sertraline, sildenafil,
pause-squeeze with respect to IVELT (p=0.04) and sexual satisfaction (p=0.025). A significant positive correl
differences in adverse effects were found among the 4 drugs. Three patients dropped out due to side effects,
additional patients dropped out due to lack of efficacy related to clomipramine, paroxetine, sertraline, and/or
intercourse and not more than twice a week. Doses were clomipramine 25 milligrams (mg), paroxetine 20 mg

4.6.M St John's Wort

4.6.M.1 Depression

a) In a randomized, double-blind, 12-week study, there was no difference in improvement in depression scor
St. John's Wort (SJW). Eighty-seven subjects with major depression according to DSM-IV criteria and a score
to receive sertraline 50 to 100 milligrams (mg) per day (n=43) or SJW 900 to 1800 mg/day (n=44). The Hyper

patients in the sertraline group and 29 in the SJW group completed the study. In the intent-to-treat analysis, b
weeks . Scores on the self-rated Beck Depression Inventory (BDI) declined similarly for the 2 groups. Mean r
sertraline. Thereafter, differences between the groups were not statistically significant. One serious adverse r
required hospitalization. One-third of the subjects of each group dropped out before completion of the study,
efficacy; from the sertraline group, 7 withdrew because of side effects and 1 for lack of efficacy (van Gurp et a

4.6.N Venlafaxine

Bipolar disorder, depressed phase

Depression

Depression, Elderly

4.6.N.1 Bipolar disorder, depressed phase

a) There were no significant differences between bupropion, sertraline, and venlafaxine with regard to respo
switching into hypomania or mania was significantly higher with venlafaxine compared with bupropion and se
outpatients diagnosed with bipolar depression. All patients were receiving at least one mood stabilizer with in
bupropion 75 to 450 milligrams (mg)/day (n=51), sertraline 50 to 200 mg/day (n=58), or venlafaxine 37.5 to 3
Depression Symptomatology (IDS), the Young Mania Rating Scale (YMRS), and the Clinical Global Impressi
antidepressant response (defined as either a 50% or greater improvement in IDS score or a decrease of at le
IDS score less than 12 and/or a CGI-BP depression score of 1 at study endpoint), and antidepressant-relatec
score during any point of the trial or a CGI-BP manic severity score of 3 or more or a YMRS score above 13 a
were 49%, 53%, and 51%, respectively, while remission rates were 41%, 36%, and 34%, respectively. Differe
reported. Controlling for lithium use did not alter the results. Based on CGI-BP score, switching to mania or h
and sertraline (9%; p less than 0.01 overall). During post hoc analysis, it was demonstrated that the switch ef
venlafaxine and sertraline (p=0.01, adjusted for lithium) and bupropion (p less than 0.01, adjusted for lithium)
Based on YMRS score, switching occurred in 4%, 7%, and 15% of patients receiving bupropion, sertraline, a
(31%) and bupropion (14%) and sertraline (16%) treatment groups remained significant when the combinatio
for lithium; p=0.02 when controlled for lithium). Post hoc analysis results again showed that the difference wa
history of rapid cycling was also higher with venlafaxine (43%) compared to bupropion (14%) and sertraline (
for any reason were 31%, 41%, and 45% in the bupropion, sertraline and venlafaxine groups, respectively (P

4.6.N.2 Depression

a) An 8-week, randomized, double-blind, active-control study of outpatient adults with major depressive diso
not significantly different than that of venlafaxine XR (n=76). Patients were randomized to receive capsules c
to 3 capsules/day. Primary outcome measure was the change in Quality of Life Enjoyment and Satisfaction Q
endpoint (8-weeks). Secondary outcome measures were the changes from baseline to endpoint in the scores
Impressions - Severity of Illness scale (CGI-S), the Clinical Global Impressions - Improvement scale (CGI-I),
1 (very much improved) or 2 (much improved) on the CGI-I scale, or a reduction of HAM-D-17 score by at lea
less. There were no significant differences between study groups with any outcome measures, including rem
most common reported adverse effects during active treatment (10% or greater occurrence) were diarrhea, h
scores, response rates, and remission rates for the outcome measures (Shelton et al, 2006):

Endpoint Scores, Response Rates and Remiss	
Measure/Sample	Sertraline (n=82)
Q-LES-Q score, mean (SD)	0.69 (0.12)
HAM-D-17 score, mean (SD)	10.8 (6.4)
HAM-D-17 response rate, (N/N)	55%(45/82)
HAM-D-17 remission rate, (N/N)	38% (31/82)
CGI-S score, mean (SD)	2.6 (1.1)
CGI-I score, mean (SD)	2.3 (1.1)
HAM-A score, mean (SD)	9.1 (5.4)
CGI-I = Clinical Global Impressions-Improvement scale; CGI-S = Clinical Global Impressions-Severity of Rating Scale for Depression; Q-LES-Q = Quality of Life Enjoyment and Satisfaction Questionnaire; XR =	

b) In patients with major depressive disorder, almost twice as many experienced a remission with venlafaxin
depressive disorder randomly received venlafaxine 37.5 mg twice daily (n=75) or sertraline 50 mg daily (n=72
or the sertraline increased to 50 mg twice daily on day 15. After 8 weeks, patients in both groups showed sig
Montgomery- Asberg Depression Rating Scale (p less than 0.05). In the venlafaxine group 83% were respon
the venlafaxine group and in 45% of the sertraline group (p=0.008). The most common adverse events were
with sertraline (Mehtonen et al, 2000).

4.6.N.3 Depression, Elderly

a) Treatment with venlafaxine had a lower tolerability, but was equally effective to sertraline therapy in elderl
study, fifty-two elderly patients (mean age, 82.5 years) with depression received either sertraline (initial, 25 m
mg/day, titrated to 150 mg/day) for 10 weeks. No significant differences were found in Hamilton Rating Scale
groups. However, early termination and withdrawal rates due to serious adverse events were higher in venlaf
tract infection, cerebrovascular accident, hypertension, decreased renal function, rapid atrial fibrillation, anem
were observed in both treatment groups. From baseline to endpoint, heart rate increased in the venlafaxine g
bpm to 70.9 bpm, respectively). The authors suggest that the lowered tolerability of venlafaxine may be relate

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