DRUGDEX® Evaluations

PAROXETINE

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) Paroxetine Hydrochloride

1) Adult

a) Generalized anxiety disorder

1) 20 mg/day ORALLY in the morning

b) Major depressive disorder

1) 20 mg/day ORALLY in the morning; may increase dosage by 10 mg/day increments each week to a max dose of 50 mg/day

2) controlled release, 25 mg/day ORALLY in the morning; may increase dosage by 12.5 mg/day increments each week to a max dose of 62.5 mg/day

c) Obsessive-compulsive disorder

1) 20 mg/day ORALLY in the morning; may increase dosage by 10 mg/day increments each week to a max dose of 60 mg/day; usual effective dose is 40 mg/day

d) Panic disorder

1) 10 mg/day ORALLY in the morning; may increase dosage by 10 mg/day increments each week to a max dose of 60 mg/day; usual effective dose is 40 mg/day

2) controlled release, 12.5 mg/day ORALLY in the morning; may increase dosage by 12.5 mg/day increments each week to a max dose of 75 mg/day

e) Posttraumatic stress disorder

1) 20 mg/day ORALLY in the morning

f) Premenstrual dysphoric disorder

1) controlled release, 12.5 mg/day ORALLY in the morning; may increase to 25 mg/day at interval of at least one week; may be administered daily throughout the menstrual cycle or limited to daily administration during the luteal phase of the menstrual cycle

g) Social phobia

1) 20 mg/day ORALLY in the morning

2) Pediatric

a) Safety and effectiveness in pediatric patients have not been established

3) Contraindications

a) Paroxetine Hydrochloride

1) concomitant use of linezolid (Prod Info PAXIL CR(R) controlled-release oral tablets, 2009; Prod Info PAXIL(R) oral tablets, suspension, 2009)

2) concomitant use of monoamine oxidase inhibitors (MAOIs) (Prod Info PAXIL CR(R) controlled-release oral tablets, 2009; Prod Info PAXIL(R) oral tablets, suspension, 2009)

3) concomitant use of pimozide (Prod Info PAXIL CR(R) controlled-release oral tablets, 2009; Prod Info PAXIL (R) oral tablets, suspension, 2009)

4) concomitant use of thioridazine (Prod Info PAXIL CR(R) controlled-release oral tablets, 2009; Prod Info PAXIL(R) oral tablets, suspension, 2009)

5) hypersensitivity to paroxetine or any component of the product (Prod Info PAXIL CR(R) controlled-release oral tablets, 2009; Prod Info PAXIL(R) oral tablets, suspension, 2009)

4) Serious Adverse Effects

a) Paroxetine Hydrochloride

1) Acute hepatitis
2) Bleeding, Abnormal
3) Depression, exacerbation
4) Hypomania
5) Hyponatremia
6) Mania
7) Seizure
8) Serotonin syndrome
9) Suicidal thoughts
10) Suicide
11) Toxic epidermal necrolysis

5) Clinical Applications

a) Paroxetine Hydrochloride

1) FDA Approved Indications
- **a)** Generalized anxiety disorder
- **b)** Major depressive disorder
- **c)** Obsessive-compulsive disorder
- **d)** Panic disorder
- **e)** Posttraumatic stress disorder
- **f)** Premenstrual dysphoric disorder
- **g)** Social phobia

1.0 Dosing Information

Drug Properties

Adult Dosage

1.1 Drug Properties

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

B) Synonyms

Paroxetine
Paroxetine HCl
Paroxetine Hydrochloride
Paroxetine Mesylate

C) Physicochemical Properties

1) Molecular Weight

a) Paroxetine base: 329.37 (Fleeger, 1996); Paroxetine hydrochloride: 374.8 (Prod Info Paroxetine, 97) (Prod Info Paroxetine, 95)

2) Solubility

a) Systemic: 5.4 mg of paroxetine hydrochloride per mL water (Prod Info Paroxetine, 97).

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 Paroxetine Hydrochloride

1.3.1.A.1 Oral route

Generalized anxiety disorder

Major depressive disorder

Obsessive-compulsive disorder

Panic disorder

Posttraumatic stress disorder

Premenstrual dysphoric disorder

Social phobia

1.3.1.A.1.a Generalized anxiety disorder

1) The usual initial dosage is 20 milligrams (mg) daily. For generalized anxiety disorder, additional benefit has NOT been shown for doses above 20 mg daily; therefore, the recommended dosage is 20 mg daily. Paroxetine is usually taken in the morning and may be taken with or without food (Prod Info Paxil(R), 2002e).

1.3.1.A.1.b Major depressive disorder

1) The usual initial dosage is 20 milligrams (mg) daily. For patients who have an inadequate response, the dose may be increased in increments of 10 mg daily at intervals of 1 week or more. The maximum recommended dose is 50 mg daily. Paroxetine is usually taken in the morning and may be taken with or without food (Prod Info Paxil(R), 2002e; Gagiano et al, 1989a; Rickels et al, 1989a; Feighner & Boyer, 1989a; Byrne, 1989a; Oswald & Adam, 1986; Battegay et al, 1985b).
2) For the controlled-release tablet, the usual initial dosage is 25 milligrams (mg) daily. For patients who have an inadequate response, the dose may be increased in increments of 12.5 mg daily at intervals of 1 week or more. The maximum recommended dose is 62.5 mg daily. Paroxetine is usually taken in the morning and may be taken with or without food (Prod Info Paxil(R) CR(TM), 2002).
3) Allow a 14-day washout period when switching a patient from a monoamine oxidase inhibitor (MAOI) to paroxetine, or from paroxetine to a MAOI (Prod Info Paxil(R), 2002e); (Prod Info Paxil CR(TM),2002).

1.3.1.A.1.c Obsessive-compulsive disorder

1) The usual initial dosage is 20 milligrams (mg) daily; however, for this indication, the recommended dosage is 40 mg daily. The dose should be increased in increments of 10 mg daily at intervals of 1 week. The maximum recommended dose is 60 mg daily. Paroxetine is usually taken in the morning and may be taken with or without food (Prod Info Paxil(R), 2002e).
2) For maintenance therapy, the dose should be adjusted to the lowest effective dosage. Long-term treatment is usually necessary because OCD is a chronic condition (Prod Info Paxil(R), 2002e).

1.3.1.A.1.d Panic disorder

1) The usual initial dosage is 10 milligrams (mg) daily; however, for this indication, the recommended dosage is 40 mg daily. The dose should be increased in increments of 10 mg daily at intervals of 1 week. The maximum recommended dose is 60 mg daily. Paroxetine is usually taken in the morning and may be taken with or without food (Prod Info Paxil(R), 2002e).
2) For the controlled-release tablet, the usual initial dosage is 12.5 milligrams (mg) daily. For patients who have an inadequate response, the dose may be increased in increments of 12.5 mg daily at intervals of 1 week or more. The maximum recommended dose is 75 mg daily. Paroxetine is usually taken in the morning and may be taken with or without food (Prod Info Paxil CR(TM), 2002).
3) For maintenance therapy, the dose should be adjusted to the lowest effective dose. Long-term treatment is usually necessary because panic disorder is a chronic condition (Prod Info Paxil(R), 2002e); (Prod Info Paxil CR(TM), 2002).

1.3.1.A.1.e Posttraumatic stress disorder

1) The recommended dose is 20 milligrams per day (mg/day), in the morning, with or without food. There is insufficient evidence to suggest that a higher dose would provide increased benefit. Dosing adjustments, if desired, should be made in 10 mg increments (Prod Info Paxil(R), 2002e). Paroxetine in doses of 20 or 40 mg/day effectively treated all three components of posttraumatic stress disorder (reexperiencing, avoidance/numbing and hyperarousal) when compared to a matched placebo group (Marshall et, al, 2001).

1.3.1.A.1.f Premenstrual dysphoric disorder

1) Paroxetine controlled-release may be administered daily throughout the menstrual cycle or limited to daily administration during the luteal phase of the menstrual cycle. The usual initial dosage is 12.5 milligrams (mg) controlled- release as a single daily dose; the dose may be increased to 25 mg/day at intervals of at least 1 week. Doses of 12.5 mg/day and 25 mg/day have both been shown to be effective. Paroxetine controlled-release is usually taken in the morning and may be taken with or without food (Prod Info Paxil CR(TM), 2004b).
2) The effectiveness of paroxetine controlled-release for maintenance therapy beyond 3 menstrual cycles has not been evaluated; however, the continuation of treatment in a responding patient is reasonable due to the usual persistence of symptoms until menopause. Patients should be reassessed occasionally to determine the need for ongoing treatment (Prod Info Paxil CR (TM), 2003).

1.3.1.A.1.g Social phobia

1) The usual initial dosage is 20 milligrams (mg) daily. For social anxiety disorder, additional

benefit has NOT been shown for doses above 20 mg daily; therefore, the recommended dosage is 20 mg daily. Paroxetine is usually taken in the morning and may be taken with or without food (Prod Info Paxil(R), 2002e).

2) For the controlled-release tablet, the usual initial dosage is 12.5 milligrams (mg) daily; the dose may be increased in increments of 12.5 mg/day at intervals of 1 week or more. Doses of 12.5 mg/day to 37.5 mg/day have been shown to be effective. The maximum recommended dose is 37.5 mg daily. Paroxetine is usually taken in the morning and may be taken with or without food (Prod Info Paxil(R) CR(TM), 2002).

3) For maintenance therapy, the dose should be adjusted to the lowest effective dose and patients should be reassessed occasionally to determine the need for ongoing treatment. Long-term treatment is usually necessary because social anxiety disorder is a chronic condition (Prod Info Paxil CR (TM), 2003).

1.3.1.A.2 DRUG DISCONTINUATION

a) It is recommended that paroxetine dosage be reduced gradually when treatment is going to be discontinued. In some clinical trials paroxetine was decreased by 10 milligrams (mg) per day at weekly intervals. When a daily dose of 20 mg/day was reached, patients were continued on this dose for 1 week before treatment was stopped. If intolerable symptoms occur following a reduction in dose or upon discontinuation of treatment, then resuming the previously prescribed dose maybe be considered. Decreasing the dose at a more gradual rate is then recommended (Prod Info Paxil(R), 2002e); (Prod Info Paxil CR(TM), 2002).

1.3.1.A.3 MAXIMUM RECOMMENDED DOSAGE

a) The maximum recommended dosage is 60 milligrams daily (Prod Info Paxil(R), 2002e). For the controlled-release tablet, the maximum recommended dosage is 75 milligrams daily (Prod Info Paxil(R), 2002e); (Prod Info Paxil CR(TM), 2002).

1.3.2 Dosage in Renal Failure

A) Paroxetine Hydrochloride

1) The initial recommended dosage is 10 milligrams (mg) daily, and the maximum recommended dosage is 40 mg daily (Prod Info Paxil(R), 2002e). For paroxetine controlled release, the initial recommended dose is 12.5 mg daily with a maximum recommended dose of 50 mg daily; these dosing guidelines also apply to debilitated patients (Prod Info Paxil(R) CR(TM), 2002).

2) In a single-dose study involving subjects with varying degrees of renal impairment, maximum serum levels and area under the concentration-time curve (AUC) values of paroxetine tended to increase as renal function declined. The elimination half-life was prolonged significantly only in severe renal impairment (creatinine clearance less than 30 milliliters/minute) (Doyle et al, 1989a).

1.3.3 Dosage in Hepatic Insufficiency

A) Paroxetine Hydrochloride

1) The initial recommended dosage is 10 milligrams (mg) daily, and the maximum recommended dosage is 40 mg daily (Prod Info Paxil(R), 2002e). For paroxetine controlled release, the initial recommended dose is 12.5 mg daily with a maximum recommended dose of 50 mg daily; these dosing guidelines also apply to debilitated patients (Prod Info Paxil CR (TM), 2002).

2) Higher plasma levels and slower elimination of paroxetine were observed in patients with cirrhosis (Dalhoff et al, 1991a). This was observed in a 14-day multiple-dose study in 12 patients with alcoholic cirrhosis and 6 patients with no liver disease. The trough paroxetine concentration at steady state and AUC were significantly higher in patients with liver disease.

1.3.4 Dosage in Geriatric Patients

A) Paroxetine Hydrochloride

1) The initial recommended dosage is 10 milligrams (mg) daily, and the maximum recommended dosage is 40 mg daily for elderly or debilitated patients (Prod Info Paxil(R), 2002e). For paroxetine controlled release, the initial recommended dose is 12.5 mg daily with a maximum recommended dose of 50 mg daily; these dosing guidelines also apply to debilitated patients (Prod Info Paxil CR(TM), 2002).

2) Although considerable interindividual variation in paroxetine pharmacokinetics has been observed, higher plasma levels of paroxetine have been observed, as well as slowed elimination in the elderly, compared with younger subjects (Kaye et al, 1989d; Ghose, 1989a; Bayer et al, 1989a; Lundmark et al, 1989a). In 1 study of elderly depressed patients receiving paroxetine 20 milligrams daily, pharmacokinetic parameters observed were similar to those in younger subjects receiving 30 milligrams daily (Lundmark et al, 1989a).

3) It is recommended that paroxetine dosage be reduced gradually when treatment is going to be discontinued. In some clinical trials paroxetine was decreased by 10 milligrams (mg) per day at weekly intervals. When a daily dose of 20 mg/day was reached, patients were continued on this dose for 1 week before treatment was stopped. If intolerable symptoms occur following a reduction in dose or upon discontinuation of treatment, then resuming the previously prescribed dose maybe be considered. Decreasing the dose at a more gradual rate is then recommended (Prod Info Paxil(R), 2002e); (Prod Info Paxil CR(TM), 2002).

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 (Feighner & Boyer, 1989c; Rickels et al, 1989b).

b) Depression, controlled release and regular release: 1 to 4 weeks (Prod Info Paxil(R), 2002d); (Prod Info Paxil CR(TM), 2002).

2.2 Drug Concentration Levels

A) Time to Peak Concentration

1) Oral, regular release: 3 to 8 hours (Kaye et al, 1989c).

a) After oral administration of paroxetine 20 milligrams (mg), mean peak serum concentrations were 10.7 nanograms/milliliter (ng/mL) (range, 0.8 to 32.5 ng/mL). With oral doses of 30 mg and 40 mg, mean peak concentrations were 17.6 ng/mL and 26.6 ng/mL, respectively, each occurring in approximately 6 hours (Kaye et al, 1989c). After oral administration of 30 mg paroxetine tablets daily for 30 days, the mean peak steady state concentration was 61.7 ng/mL (Prod Info Paxil(R), 2002d).

b) Steady-state plasma concentrations have not correlated with clinical improvement in depressed patients (Tasker et al, 1989a).

2) Oral, controlled release: 6 to 10 hours (Prod Info Paxil CR(TM), 2002).

a) After oral administration of paroxetine CR 12.5 mg, 25 mg, 37.5 mg, and 50 mg, the Cmax was 2, 5.5, 9, and 12.5 ng/mL, respectively (Prod Info Paxil CR(TM), 2002).

B) Area Under the Curve

1) 121 TO 540 ng x hr/mL (controlled release) (Prod Info Paxil CR(TM), 2002).

2.3 ADME

Absorption

Distribution

Metabolism

Excretion

Elimination Half-life

2.3.1 Absorption

A) Bioavailability

1) Oral, regular release: well-absorbed (Kaye et al, 1989c).

B) Effects of Food

1) Minimal (Prod Info Paxil(R), 2002d); (Prod Info Paxil CR(TM), 2002).

a) When administered with food, the Cmax and AUC increased by 6% and 29%, respectively (Prod Info Paxil(R), 2002d).

2.3.2 Distribution

A) Distribution Sites

1) Protein Binding

a) 95% (Kaye et al, 1989c).

B) Distribution Kinetics

1) Volume of Distribution

a) 8.7 L/kg (Kaye et al, 1989c).

1) The Vd, 17.2 L/kg (range, 8 to 28 L/kg), was greater following an intravenous infusion of paroxetine 23 to 28 mg over 24 to 30 minutes versus a bolus dose (Kaye et al, 1989c).

2.3.3 Metabolism

A) Metabolism Sites and Kinetics

1) Liver, extensive (Kaye et al, 1989c).

a) The cytochrome P4502D6 enzymes responsible in part for metabolizing paroxetine are saturable, resulting in non-linear kinetics at increased doses (Prod Info Paxil(R), 2002d).

B) Metabolites

1) Conjugates of paroxetine, inactive (Prod Info Paxil(R), 2002d; Kaye et al, 1989c).

2.3.4 Excretion

A) Kidney

1) Renal Excretion (%)

a) 65% to 67% (Kaye et al, 1989c).

2) Less than 2% of an oral dose of paroxetine is excreted unchanged in urine. Approximately 65% of a dose appears in the urine as metabolites (conjugates and other unknown polar metabolites) (Kaye et al, 1989c).

B) Total Body Clearance

1) 0.5 to 1 L/kg (Kaye et al, 1989c).

C) Other

1) Feces 36% to 37% (Prod Info Paxil(R), 2002d; Kaye et al, 1989c).

a) Excreted as metabolites (36%) and as parent drug (less than 1%) (Prod Info Paxil(R), 2002d; Kaye et al, 1989c).

2.3.5 Elimination Half-life

A) Parent Compound

1) ELIMINATION HALF-LIFE

a) 15 to 22 hours (Prod Info Paxil(R), 2002d); (Prod Info Paxil CR(TM), 2002)(Kaye et al, 1989c).

1) Considerable intersubject variation is observed as demonstrated by the range of half-lives between 3.8 to 65 hours (Kaye et al, 1989c).

3.0 Cautions

Contraindications

Precautions

Adverse Reactions

Teratogenicity/Effects in Pregnancy/Breastfeeding

Drug Interactions

3.0.A Black Box WARNING

1) Paroxetine Hydrochloride

a) Oral (Tablet; Tablet, Extended Release; Suspension)

Suicidality and Antidepressant Drugs

Antidepressants increased the risk compared to placebo of suicidal thinking and behavior (suicidality) in children, adolescents, and young adults in short-term studies of major depressive disorder (MDD) and other psychiatric disorders. Anyone considering the use of paroxetine hydrochloride or any other antidepressant in a child, adolescent, or young adult must balance this risk with the clinical need. Short-term studies did not show an increase in the risk of suicidality with antidepressants compared to placebo in adults beyond age 24; there was a reduction in risk with antidepressants compared to placebo in adults aged 65 and older. Depression and certain other psychiatric disorders are themselves associated with increases in the risk of suicide. Patients of all ages who are started on antidepressant therapy should be monitored appropriately and observed closely for clinical worsening, suicidality, or unusual changes in behavior. Families and caregivers should be advised of the need for close observation and communication with the prescriber. Paroxetine hydrochloride is not approved for use in pediatric patients (Prod Info PAXIL(R) oral tablets, suspension, 2009; Prod Info PAXIL CR(R) controlled-release oral tablets, 2009).

3.1 Contraindications

A) Paroxetine Hydrochloride

1) concomitant use of linezolid (Prod Info PAXIL CR(R) controlled-release oral tablets, 2009; Prod Info PAXIL(R) oral tablets, suspension, 2009)

2) concomitant use of monoamine oxidase inhibitors (MAOIs) (Prod Info PAXIL CR(R) controlled-release oral tablets, 2009; Prod Info PAXIL(R) oral tablets, suspension, 2009)

3) concomitant use of pimozide (Prod Info PAXIL CR(R) controlled-release oral tablets, 2009; Prod Info PAXIL (R) oral tablets, suspension, 2009)

4) concomitant use of thioridazine (Prod Info PAXIL CR(R) controlled-release oral tablets, 2009; Prod Info PAXIL(R) oral tablets, suspension, 2009)

5) hypersensitivity to paroxetine or any component of the product (Prod Info PAXIL CR(R) controlled-release oral tablets, 2009; Prod Info PAXIL(R) oral tablets, suspension, 2009)

3.2 Precautions

A) Paroxetine Hydrochloride

1) suicidal ideation and behavior or worsening depression; increased risk, particularly in children, adolescents, and young adults with major depressive disorder during the first few months of therapy or following changes in dosage (Prod Info PAXIL CR(R) controlled-release oral tablets, 2009; Prod Info PAXIL(R) oral tablets, suspension, 2009)

2) abnormal bleeding has been reported, including life-threatening hemorrhages (Prod Info PAXIL CR(R) controlled-release oral tablets, 2009; Prod Info PAXIL(R) oral tablets, suspension, 2009)

3) abrupt withdrawal; serious discontinuation symptoms have been reported (Prod Info PAXIL CR(R) controlled-release oral tablets, 2009; Prod Info PAXIL(R) oral tablets, suspension, 2009)

4) bipolar disorder; increased risk of precipitation of a mixed/manic episode (Prod Info PAXIL CR(R) controlled-release oral tablets, 2009; Prod Info PAXIL(R) oral tablets, suspension, 2009)

5) concomitant alcohol use; should be avoided (Prod Info PAXIL CR(R) controlled-release oral tablets, 2009; Prod Info PAXIL(R) oral tablets, suspension, 2009)

6) concomitant use of NSAIDs, aspirin, warfarin, or other drugs that affect coagulation; monitoring recommended during paroxetine initiation and discontinuation (Prod Info PAXIL CR(R) controlled-release oral tablets, 2009; Prod Info PAXIL(R) oral tablets, suspension, 2009)

7) concomitant serotonergic drug use (serotonin precursors (tryptophan), SSRIs, serotonin-norepinephrine reuptake inhibitors); use is not recommended (Prod Info PAXIL CR(R) controlled-release oral tablets, 2009; Prod Info PAXIL(R) oral tablets, suspension, 2009)

8) glaucoma, narrow-angle; increased risk of mydriasis (Prod Info PAXIL CR(R) controlled-release oral tablets, 2009; Prod Info PAXIL(R) oral tablets, suspension, 2009)

9) hepatic impairment, severe; lower or less frequent dose may be required (Prod Info PAXIL CR(R) controlled-release oral tablets, 2009; Prod Info PAXIL(R) oral tablets, suspension, 2009)

10) mania, history; risk of activation of mania/hypomania (Prod Info PAXIL CR(R) controlled-release oral tablets, 2009; Prod Info PAXIL(R) oral tablets, suspension, 2009)

11) medical diseases or conditions that could affect metabolism or hemodynamic responses (Prod Info PAXIL CR(R) controlled-release oral tablets, 2009; Prod Info PAXIL(R) oral tablets, suspension, 2009)

12) renal impairment, severe; lower or less frequent dose may be required (Prod Info PAXIL CR(R) controlled-release oral tablets, 2009; Prod Info PAXIL(R) oral tablets, suspension, 2009)

13) seizures, history (Prod Info PAXIL(R) oral tablets, suspension, 2007; Prod Info PAXIL CR(R) controlled-release oral tablets, 2007)

14) serotonin syndrome has been reported, including cases that are life-threatening or that resemble neuroleptic malignant syndrome; monitoring recommended (Prod Info PAXIL CR(R) controlled-release oral tablets, 2009; Prod Info PAXIL(R) oral tablets, suspension, 2009)

15) use of MAOI (including linezolid) within 14 days of paroxetine discontinuation (Prod Info PAXIL CR(R) controlled-release oral tablets, 2009; Prod Info PAXIL(R) oral tablets, suspension, 2009)

16) use of paroxetine within 14 days of MAOI (including linezolid) discontinuation (Prod Info PAXIL CR(R) controlled-release oral tablets, 2009; Prod Info PAXIL(R) oral tablets, suspension, 2009)

17) volume-depleted, elderly, or concurrent diuretic therapy; hyponatremia, syndrome of inappropriate antidiuretic hormone secretion (SIADH) has occurred with paroxetine hydrochloride (Prod Info PAXIL CR(R) controlled-release oral tablets, 2009; Prod Info PAXIL(R) oral tablets, suspension, 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 Paroxetine Hydrochloride

Cardiac dysrhythmia

Cardiovascular finding

ECG: extrasystole

EKG finding

Hypotension

Transient ischemic attack

3.3.1.A.1 Cardiac dysrhythmia

a) Summary

1) The occurrence of VENTRICULAR FIBRILLATION, VENTRICULAR TACHYCARDIA, and TORSADE DE POINTES have been documented in paroxetine postmarketing reports (Prod Info Paxil(R), 2002e); (Prod Info Paxil CR(TM), 2002).

3.3.1.A.2 Cardiovascular finding

a) Summary

1) During clinical trials of paroxetine regular-release, PALPITATION (2% to 3%) and VASODILATION (3% to 4%) were the primary cardiovascular adverse effects (Prod Info Paxil(R), 2002e; Edwards et al, 1989b; Feighner & Boyer, 1989b; Rickels et al, 1989; Warrington et al, 1989b). In some studies, cardiovascular effects (increase in heart rate, decrease in left ventricular ejection time index) have been less with paroxetine compared to amitriptyline (Kuhs & Rudolf, 1989a; Warrington et al, 1989b). In other studies, the incidence of cardiovascular adverse effects was similar for both agents (Byrne, 1989b). TACHYCARDIA (1%) and vasodilation (2%; FLUSHING) were also observed in clinical trials of paroxetine controlled-release (Prod Info Paxil CR(TM), 2002).

2) In a large cohort study including 481,744 persons and 1487 cases of SUDDEN CARDIAC DEATH occurring in a community setting, the use of selective serotonin reuptake inhibitors was not associated with an increased risk of sudden cardiac death (rate ratio, 0.95; 95% CI, 0.42 to 2.15). In contrast, users of tricyclic antidepressants in doses of 100 mg or higher (amitriptyline or its equivalent) had a 41% increased rate of sudden cardiac death (rate ratio, 1.41; 95% CI, 1.02 to 1.95) (Ray et al, 2004).

b) Palpitation, vasodilation, hypotension, tachycardia, arrhythmias, transient ischemic attack, premature ventricular contractions (PVC's), and minor electrocardiogram changes have been reported with paroxetine therapy.

3.3.1.A.3 ECG: extrasystole

a) Summary

1) Multiple preventricular contractions (PVCs) without associated symptoms developed in one

patient taking therapeutic doses of paroxetine (Battegay et al, 1985a).

3.3.1.A.4 EKG finding

a) Summary

1) Paroxetine 30 milligrams daily produced no significant effect on the electrocardiogram (EKG) in a 4-week, placebo-controlled study involving 20 depressed patients. Paroxetine therapy produced no significant effect on heart rate, PR or QT(c) intervals, or T-wave height. A small increase in QRS width was observed at week 4 of therapy, although this was of no clinical relevance. Blood pressure was unchanged during the study. These data suggest the lack of significant cardiac effects induced by paroxetine (Edwards et al, 1989b).

b) LITERATURE REPORTS

1) In 1 study comparing the electrocardiogram (EKG) effects of amitriptyline and paroxetine, amitriptyline was associated with increases in heart rate, prolongation of the PR interval, and a reduction in T-wave amplitude, whereas paroxetine produced no significant EKG abnormalities (Warrington et al, 1989b).

3.3.1.A.5 Hypotension

a) Summary

1) An asymptomatic decrease in systolic blood pressure was noted in patients taking therapeutic doses of paroxetine after 4 weeks on therapy (Battegay et al, 1985a). Orthostatic dizziness was reported in 6 of 19 patients taking therapeutic doses (Laurson et al, 1985).

b) LITERATURE REPORTS

1) SYNCOPE associated with a sudden fall in blood pressure and pulse developed in a 71 year-old-woman taking therapeutic doses (Lundmark et al, 1989a).

3.3.1.A.6 Transient ischemic attack

a) Transient ischemic attack occurred in a 57-year-old male patient with a history of high cholesterol and intermittent atrial fibrillation following the initiation of paroxetine therapy for the treatment of chronic hip pain. The man presented with right side facial droop and slurred speech after taking four doses of 20-milligram paroxetine at a twice-daily dosing regimen. On the day of presentation and subsequent admission to the hospital, the patient described residual bilateral paresthesia and "burning" pain that spread from the top of his head downward to his groin. He had experienced "burning" chest pain, sweating, and lightheadedness two days prior to admission. Paroxetine was stopped upon admission; anticoagulation therapy (ie, heparin and oral warfarin) was initiated and the patient's symptoms resolved. Two days later paroxetine was restarted at a dose of 10 mg twice daily. After two doses of medication, the patient experienced two more episodes similar to the initial one. Paroxetine was again discontinued and symptoms resolved with no recurrence of episodes over a 4-month follow-up period (Manos & Wechsler, 2004).

3.3.2 Dermatologic Effects

3.3.2.A Paroxetine Hydrochloride

Diaphoresis

Eczema

Photosensitivity

Rash

Toxic epidermal necrolysis

Vasculitis of the skin

3.3.2.A.1 Diaphoresis

a) Summary

1) Sweating has been reported with paroxetine regular- and controlled-release use in clinical trials including patients treated for the following disorders: major depressive, obsessive-compulsive, panic, social anxiety, generalized anxiety, posttraumatic stress, and premenstrual dysphoric (Prod Info PAXIL(R) oral tablets, suspension, 2009; Prod Info PAXIL CR(R) controlled-release oral tablets, 2009). In some reports, diaphoresis has occurred less frequently with paroxetine than with amitriptyline (Battegay et al, 1985a; Bascara, 1989a).

b) Incidence: 5% to 14% (Prod Info PAXIL(R) oral tablets, suspension, 2009; Prod Info PAXIL CR(R)

controlled-release oral tablets, 2009; Claghorn et al, 1992a; Dunbar, 1989; Rickels et al, 1989; Miller et al, 1989)
c) In 6-week, placebo-controlled, clinical trials for major depressive disorder, sweating was reported in 11% of patients treated with regular-release paroxetine 20 to 50 mg/day (n=421) and 2% of patients treated with placebo (n=421) (Prod Info PAXIL(R) oral tablets, suspension, 2009).
d) In placebo-controlled, clinical trials, sweating was reported in a greater percentage of patients treated with regular-release paroxetine 10 to 60 mg/day compared with patients treated with placebo for panic disorder (14% vs 6%), for social anxiety disorder (9% vs 2%), for generalized anxiety disorder (6% vs 2%), and for posttraumatic stress disorder (5% vs 1%) (Prod Info PAXIL(R) oral tablets, suspension, 2009).
e) In phase 3 double-blind, controlled, outpatient studies, sweating was reported in a greater percentage of patients treated with controlled-release paroxetine compared with patients treated with placebo for major depressive disorder (MDD; 6% vs 2%), MDD in the elderly (10% vs less than 1%), panic disorder (7% vs 2%), social anxiety disorder (14% vs 3%), premenstrual dysphoric disorder (PMDD) with continuous dosing (7% vs 1%), and PMDD with fixed dosing (8.9% vs 0.9%) (Prod Info PAXIL CR(R) controlled-release oral tablets, 2009).
f) Diaphoresis has been a fairly common adverse effect during paroxetine therapy, occurring in up to 12% of patients treated (Claghorn et al, 1992a; Dunbar, 1989; Rickels et al, 1989; Miller et al, 1989). The incidence of diaphoresis has been less than that observed with amitriptyline in some reports (Battegay et al, 1985a; Bascara, 1989a).

3.3.2.A.2 Eczema
a) Incidence: 1% (Prod Info PAXIL CR(R) controlled-release oral tablets, 2009)
b) In a clinical trial of patients with social anxiety disorder, eczema was reported in 1% of patients treated with paclitaxel controlled-release (n=186) and 0% of patients treated with placebo (n=184) (Prod Info PAXIL CR(R) controlled-release oral tablets, 2009).

3.3.2.A.3 Photosensitivity
a) Incidence: 2% (Prod Info PAXIL CR(R) controlled-release oral tablets, 2009)
b) In a pool of 2 studies including patients with major depressive disorder, photosensitivity was reported in 2% of patients treated with paclitaxel controlled-release (n=212) and 0% of patients treated with placebo (n=211) (Prod Info PAXIL CR(R) controlled-release oral tablets, 2009).

3.3.2.A.4 Rash
a) Summary
1) Rash has been reported in clinical, placebo-controlled trials with regular- and controlled-release paroxetine (Prod Info PAXIL(R) oral tablets, suspension, 2009; Prod Info PAXIL(R) oral tablets, suspension, 2009). A case report also described rash and pruritus in a 47-year-old woman treated with paroxetine (Sannicandro et al, 2002).
b) Incidence: up to 3% (Prod Info PAXIL(R) oral tablets, suspension, 2009; Prod Info PAXIL CR(R) controlled-release oral tablets, 2009)
c) In 6-week, placebo-controlled, clinical trials for major depressive disorder, rash was reported in 2% of patients treated with regular-release paroxetine 20 to 50 mg/day (n=421) and 1% of patients treated with placebo (n=421) (Prod Info PAXIL(R) oral tablets, suspension, 2009).
d) In 12-week, placebo-controlled, clinical trials for obsessive compulsive disorder, rash was reported in 3% of patients treated with regular-release paroxetine 20 to 60 mg/day (n=542) and 2% of patients treated with placebo (n=265) (Prod Info PAXIL(R) oral tablets, suspension, 2009).
e) In phase 3 double-blind, controlled, outpatient studies for major depressive disorder, panic disorder, social anxiety disorder, and premenstrual dysphoric disorder (n=1627), rash was reported in greater than 1% of patients treated with multiple doses of controlled-release paroxetine (Prod Info PAXIL CR(R) controlled-release oral tablets, 2009).
f) Skin rashes and pruritus have each been reported in 2% of patients treated with paroxetine (Claghorn et al, 1992a; Dunbar, 1989).
g) A 47-year-old African American woman developed a morbilliform-type rash and pruritus 3 days after beginning treatment with paroxetine for depression. At admission to hospital, she was started on paroxetine 20 mg at bedtime for major depression and lorazepam for potential alcohol withdrawal symptoms and for anxiety. The rash that developed on day 3 was generalized to her trunk, extremities, and neck, with some facial involvement but no palm or sole involvement. Paroxetine was discontinued and she was given diphenhydramine 25 mg every 6 hours as needed plus topical hydrocortisone 1% for treatment of pruritus. Venlafaxine extended-release was administered for treatment of depression. The rash resolved 3 to 4 days after discontinuation of paroxetine. Hydrocortisone was discontinued on day 10 and she was discharged on day 15. The woman had previously experienced a similar rash when treated with fluoxetine (Sannicandro et al, 2002).

3.3.2.A.5 Toxic epidermal necrolysis
a) Toxic epidermal necrolysis has been reported during postmarketing use of paroxetine; causality and frequency cannot be established (Prod Info PAXIL CR(R) controlled-release oral tablets, 2009)
b) A case report described toxic epidermal necrolysis in a 71-year-old woman following treatment with

paroxetine. The patient, who had been treated for 3 years with diltiazem, trimetazidine, lysine acetylsalicylate, rosuvastatin, and topical latanoprost, was initiated on alprazolam and tianeptine due to a recent depressive disorder. Because the tianeptine was not adequately controlling her depression, the drug was switched to paroxetine 60 mg/day. Fourteen days after paroxetine was initiated, she presented with malaise and pruritic cutaneous rash on her arms. Topical corticosteroids, antiseptic chlorhexidine, oral fusidic acid and betamethasone plus dexchlorpheniramine were prescribed. Over the following days, she presented to the emergency room with lesions on her thighs, lower back, abdomen, and axillae which her doctor thought to be TEN. Bacteriological samples showed Klebsiella pneumoniae and Morganella morganii on in the axillae and skin biopsy was indicative of TEN. Subsequently, all medications were discontinued and the patient was prescribed paracetamol and nalbuphine for pain for 2 days. The following day, all medications were reinitiated with the exception of paroxetine. On day 11, the patient was discharged after a complete recovery with the exception of hyperpigmentation and no further lesions were reported (Tudela et al, 2009).

3.3.2.A.6 Vasculitis of the skin

a) A case report described multiple painful purple lesions of the extremities of fingers on both hands in a 20-year-old woman with obsessive-compulsive disorder and a history of migraines 15 weeks after beginning treatment with paroxetine. After 6 weeks of treatment and while on a stable dose of 20 mg/day, she developed insomnia, a worsening of migraine headaches, and a "shaking feeling all over." Her dose was reduced to 10 mg/day at 10 weeks. Paroxetine was discontinued when cutaneous vasculitis developed, and the lesions vanished within a week. Reintroduction of paroxetine resulted in reappearance of cutaneous vasculitis lesions within 2 days. Paroxetine was again discontinued, and lesions again disappeared within a week (Margolese et al, 2001).

3.3.3 Endocrine/Metabolic Effects

3.3.3.A Paroxetine Hydrochloride

Disorder of fluid AND/OR electrolyte

Endocrine finding

Galactorrhea

Hyponatremia

Metabolic finding

Pheochromocytoma

Porphyria

Syndrome of inappropriate antidiuretic hormone secretion

3.3.3.A.1 Disorder of fluid AND/OR electrolyte

a) Hyponatremia (occasionally severe) has occurred with paroxetine therapy.

3.3.3.A.2 Endocrine finding

a) Drug induced syndrome of inappropriate antidiuretic hormone, galactorrhea, syndrome of inappropriate secretion of antidiuretic hormone (SIADH) and pheochromocytoma have been reported with therapeutic paroxetine use.

3.3.3.A.3 Galactorrhea

a) Summary

1) From the manufacturer's premarketing database, 3 cases of galactorrhea were reported in 4126 paroxetine-treated patients over 4 years. After paroxetine was marketed in the United States (2/93), the manufacturer received 9 reports of galactorrhea or nonpuerperal lactation. Eleven additional cases have been reported to the manufacturer since paroxetine was introduced in Europe (Pers Comm, 1994).

b) LITERATURE REPORTS

1) Over a 10-year period, the Netherlands Pharmacovigilance Foundation received 38 reports of NON-PUERPERAL LACTATION related to medications of which 15 cases were attributed to antidepressants primarily the selective serotonin reuptake inhibitors (SSRIs). The odds ratio for the

risk of galactorrhea due to all antidepressants versus other medications was 8.3 (95% confidence interval (CI), 4.3 to 16.1). The odds ratio for SSRIs was 12.7 (95% CI, 6.4 to 25.4) versus 1.6 (95% CI, 0.2 to 11.6) for other antidepressants. Of the 15 reports, 5, 4, and 4 were related to fluvoxamine, fluoxetine, and paroxetine, respectively. Women developing galactorrhea were significantly younger (mean age, 33 years) than women without galactorrhea (mean age, 51 years). Galactorrhea developed from 2 weeks to 2 years after starting the SSRI. In all cases, galactorrhea resolved with continuation of the SSRI, a reduction in the dose, or discontinuation of the SSRI. Several patients were taking other medications, which have caused galactorrhea, concurrently with the SSRI but galactorrhea only developed after adding the SSRI. While this is not a serious adverse reaction, increased awareness may prevent unnecessary diagnostic procedures (Pers Comm, 1994).

2) The probable mechanism for selective serotonin reuptake inhibitor-induced galactorrhea is an increase in serum prolactin. This may result from direct stimulation of postsynaptic serotonin receptors in the hypothalamus or presynaptic serotonin receptor mediated inhibition of dopamine release (Bronzo & Stahl, 1993).

3.3.3.A.4 Hyponatremia

a) Summary

1) Hyponatremia has been reported in several patients taking therapeutic doses and has been severe in some cases (Odeh et al, 1999); (Goddard & Patton, 1992)(Chua & Vong, 1994; Chua & Vong, 1993). An unusually rapid onset of hyponatremia, following only 3 doses, was reported in an 82-year-old female (Paul & Sankaran, 1998).

2) Hyponatremia developed in 12% of elderly, depressed patients taking paroxetine for the treatment of a major depressive episode. In this 12-week, prospective study, 9 of 75 patients ages 63 to 90 years (mean age, 75.3 years) developed hyponatremia (sodium level less than 135 milliequivalents/liter (mEq/L)) within 1 to 14 days (mean, 9.3 days; median 9 days) of beginning paroxetine therapy at a mean dose of 12.5 milligrams. The authors identified lower body mass index and lower baseline plasma sodium level (138 mEq/L or less) as significant risk factors in the development of hyponatremia in elderly patients treated with paroxetine (Fabian et al, 2004).

b) Incidence: rare

3.3.3.A.5 Metabolic finding

a) Porphyria has occurred with paroxetine therapy.

3.3.3.A.6 Pheochromocytoma

a) Summary

1) After increasing paroxetine to 40 milligrams daily, a 55-year-old man had variable blood pressure readings between 240/130 millimeters of mercury (mmHg) and 80/40 mmHg; after performing appropriate tests, a pheochromocytoma was diagnosed. Pathologic examination after a left-sided adrenalectomy was also compatible with a pheochromocytoma. The only other medications taken by this man were atenolol and a benzodiazepine. Possible explanations for the rapid change in blood pressure include increased inhibition of noradrenalin reuptake after increasing the dose or slow metabolism by cytochrome P450 which resulted in increased noradrenalin levels. These factors combined with increased catecholamines from the pheochromocytoma may have produced the hemodynamic changes in this patient (Seelen et al, 1997).

3.3.3.A.7 Porphyria

a) Summary

1) The occurrence of porphyria has been documented in post marketing paroxetine reports (Prod Info Paxil(R), 2002e); (Prod Info Paxil CR(TM), 2002).

3.3.3.A.8 Syndrome of inappropriate antidiuretic hormone secretion

a) Summary

1) Paroxetine may occasionally induce a SYNDROME OF INAPPROPRIATE SECRETION OF ANTIDIURETIC HORMONE (SIADH) with resultant hyponatremia. Elderly patients may be more susceptible to SIADH. Cases following therapeutic paroxetine use have been reported (Monmany et al, 1999; Odeh et al, 1999; Paul & Sankaran, 1998; Van Campen & Voets, 1996). Of the 63 case reports of selective serotonin reuptake inhibitor (SSRI)-induced SIADH reported to the Food and Drug Administration, the majority occurred in patients over 70 years of age, patients taking diuretics, or patients who were dehydrated (Chua & Vong, 1993; Goddard & Paton, 1992). Based on published reports, the onset of the SIADH was between 3 days and 4 months after starting therapy. Symptoms included confusion, lethargy, dizziness, fatigue, anorexia, delirium, and abdominal pain.

b) LITERATURE REPORTS

1) Abnormal laboratory findings in case report review consisted of a decreased serum osmolality (median 251 milliosmole/liter (mOsm/L); range 214 to 272 mOsm/L), decreased serum sodium concentration (median 118 milliequivalents/liter (mEq/L); range 98 to 130 mEq/L), and urine

osmolality (median 392.5 mOsm/L; 229 to 613 mOsm/L). In all but 1 case report, the selective serotonin reuptake inhibitor (SSRI) was stopped, and fluid restriction was required before hyponatremia resolved; 1 patient was also treated with sodium chloride 3%. Patients in their fifties generally recovered in 2 to 4 days versus patients in their eighties who required up to 14 days for complete recovery. Of the 6 patients rechallenged with an SSRI, 3 developed a decrease in serum sodium consistent with SIADH, and 3 tolerated rechallenge without adverse events. In many case reports, inadequate reporting of symptoms, laboratory results, and exclusion of other causes were NOT included, making it difficult to attribute SIADH to the SSRI (Woo & Smythe, 1997).

2) Nine days after starting paroxetine 20 milligrams daily, a 72-year-old man was diagnosed with paroxetine-induced syndrome of inappropriate secretion of antidiuretic hormone (SIADH). He presented to the emergency department with disorientation, confusion, verbal incoherence, and a depressed level of consciousness. Laboratory studies revealed a plasma sodium concentration of 118 millimoles/liter (mmol/L), plasma osmolality of 262 millimoles/kilogram (mmol/kg) water, urinary sodium concentration of 53 mmol/L, and urine osmolality of 940 mmol/kg water. Other drugs and medical causes of SIADH were excluded. Paroxetine was stopped, and his level of consciousness and plasma sodium returned to normal (Monmany et al, 1999).

3) An 89-year-old woman developed the syndrome of inappropriate antidiuretic hormone (SIADH) possibly due to paroxetine 10 milligrams daily added the previous week. At hospital admission, she had abdominal distention and lethargy; abnormal laboratory values included a serum sodium of 116 millimoles/liter (mmol/L), serum osmolality 250 milliosmole/liter (mOsm/L), urinary sodium excretion 97 mmol/24 hours, and urine osmolality of 410 mOsm/L. Paroxetine was stopped, and the patient was treated with an intravenous saline infusion. Medical causes for SIADH were ruled out; thus, the authors attributed the SIADH to paroxetine. It is recommended that patients treated with a selective serotonin reuptake inhibitor who develop symptoms of weakness, lethargy, headache, anorexia, weight gain, confusion, or constipation have a serum sodium measured (Meynaar et al, 1997).

3.3.4 Gastrointestinal Effects

3.3.4.A Paroxetine Hydrochloride

Constipation

Diarrhea

Gastric hemorrhage

Gastrointestinal hemorrhage

Gastrointestinal tract finding

Grinding teeth

Loss of appetite

Nausea and vomiting

Xerostomia

3.3.4.A.1 Constipation

a) Summary

1) Constipation is a commonly reported side effect of paroxetine therapy (Dunbar et al, 1993a; Claghorn et al, 1992a; Rickels et al, 1989). Constipation (5% TO 16%) occurred with paroxetine at a higher incidence than placebo (Prod Info Paxil(R), 2002e). The incidence of constipation was less with paroxetine than amitriptyline in some studies (Kuhs & Rudolf, 1989a; Hassan et al, 1985b; Laursen et al, 1985b); however, other studies did NOT show a significant difference between the 2 drugs (Bascara, 1989a; Battegay et al, 1985a). Constipation (10%) also occurred at a higher incidence than placebo in clinical trials of Paxil CR(TM) (Prod Info Paxil CR(TM), 2002).

3.3.4.A.2 Diarrhea

a) Summary

1) Diarrhea is reported at therapeutic paroxetine doses (Claghorn et al, 1992a). Diarrhea (9% TO 12%) occurred at a higher incidence than placebo (Prod Info Paxil(R), 2002e). Diarrhea (18%) also

occurred at a higher incidence than placebo in clinical trials of Paxil CR(TM) (Prod Info Paxil CR (TM), 2002). Paroxetine increases GI motility and reduces orocecal transit time at therapeutic doses (Gorard et al, 1994).

3.3.4.A.3 Gastric hemorrhage

a) Summary

1) In a retrospective cohort study of 317,824 elderly patients, it was reported that high inhibition of serotonin reuptake increased the risk of upper GI bleeding. An overall risk of 7.3 per 1000 person years was reported. Elderly patients and those with previous GI bleeding were at increased risk (van Walraven et al, 2001).

3.3.4.A.4 Gastrointestinal hemorrhage

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

3.3.4.A.5 Gastrointestinal tract finding

a) Summary

1) Gastrointestinal adverse effects that occurred at a higher incidence than placebo included FLATULENCE (4%) and DYSPEPSIA (2% to 4%), (Prod Info Paxil(R), 2002e). Flatulence (6%) also occurred at a higher incidence than placebo in clinical trials of Paxil CR(TM) (Prod Info Paxil CR(TM), 2002).

b) Anorexia, constipation, dry mouth, diarrhea, flatulence, dyspepsia, gastric bleeding, nausea and vomiting have been reported with paroxetine therapy.

3.3.4.A.6 Grinding teeth

a) Possible paroxetine-induced bruxism (ie, grinding and clenching of the teeth, usually during sleep) followed treatment with paroxetine 10 milligrams (mg) daily in the morning for 5 days, increasing to 20 mg daily. Four months later, routine dental cleaning revealed damaged teeth consistent with bruxism. Tooth damage or temporomandibular joint dysfunction were not observed at previous dental visits. The 20-year-old woman's only other medication was tetracycline 250 mg twice daily for acne. On the fourth day after addition of oral buspirone 5 mg at bedtime the patient reported a significant reduction of gritting, tooth pain, and jaw tenderness (Romanelli et al, 1996). A 67-year-old woman was given oral paroxetine 20 mg each morning. Eleven months later she reported diurnal bruxism and jaw clenching and her jaws and gums ached. Oral buspirone (dosage not noted) did not have any beneficial effects (Fitzgerald & Healy, 1995).

3.3.4.A.7 Loss of appetite

a) Summary

1) Anorexia and WEIGHT LOSS have been reported with therapeutic paroxetine doses (Feighner et al, 1993; Ohrberg et al, 1992) DECREASED APPETITE (4% TO 6%) occurred with paroxetine at a higher incidence than placebo (Prod Info Paxil(R), 2002e); (Prod Info Paxil CR(TM), 2002).

3.3.4.A.8 Nausea and vomiting

a) Summary

1) Gastrointestinal adverse effects that occurred at a higher incidence than placebo included nausea (23% to 26%) and vomiting (2%) (Prod Info Paxil(R), 2002e); (Prod Info Paxil CR(TM), 2002). In the majority of patients, nausea gradually decreases or resolves over approximately 3 weeks. However, in others, reduction of the dose or discontinuation of the drug is required. The proposed mechanism for SSRI- induced nausea and vomiting is increased serotonin levels within the chemoreceptor trigger zone and area postrema in the brainstem, the primary areas within the brain associated with nausea and vomiting (McManis & Talley, 1997).

b) LITERATURE REPORTS

1) The selective serotonin reuptake inhibitors (SSRIs) produce nausea and vomiting in 20% to 25% and 2% to 3% of patients, respectively. In the majority of patients, nausea gradually decreases or resolves over approximately 3 weeks. However, in others, reduction of the dose or discontinuation of the drug is required. For this group, ondansetron or cisapride administered for a few weeks may facilitate continued treatment with the SSRI. Limited data suggest that ondansetron is more effective than cisapride; however, it is also more expensive. Use of cisapride with careful monitoring for arrhythmias may be more cost effective, and open therapy to a broader group of patients (McManis & Talley, 1997).

3.3.4.A.9 Xerostomia

a) Summary

1) Dry mouth occurs with therapeutic paroxetine doses (Miller et al, 1989; Battegay et al, 1985a). Dry mouth (9% TO 18%) occurred with paroxetine at a higher incidence than placebo (Prod Info Paxil(R), 2002e); (Prod Info Paxil CR(TM), 2002). The incidence of dry mouth was less with paroxetine than amitriptyline in some studies (Kuhs & Rudolf, 1989a; Hassan et al, 1985b; Laursen et al, 1985b); however, other studies did NOT show a significant difference between the 2 drugs

(Bascara, 1989a; Battegay et al, 1985a).

3.3.5 Hematologic Effects

3.3.5.A Paroxetine Hydrochloride

Ecchymosis

Hematology finding

3.3.5.A.1 Ecchymosis

a) Summary

1) Spontaneous ecchymosis has been reported in two patients taking therapeutic paroxetine doses (Ottervanger et al, 1994). Routine coagulation studies were normal in these patients, but in one patient there was no spontaneous platelet aggregation. Spontaneous ecchymoses due to therapeutic paroxetine doses occurred in a 47-year-old patient. Discontinuation of paroxetine resulted in resolution of ecchymoses (Cooper et al, 1998).

3.3.5.A.2 Hematology finding

a) Summary

1) The incidence of hemostatic disturbances is rare (0.1%) with paroxetine therapy. Common adverse effects include; APLASTIC ANEMIA, AGRANULOCYTOSIS, bone marrow aplasia, BRUISING, EOSINOPHILIA, EPISTAXIS, HEMOLYTIC ANEMIA, LEUKOCYTOSIS, LEUKOPENIA, PANCYTOPENIA, PROLONGED BLEEDING TIME, and RECTAL BLEEDING. Many cases have occurred in patients taking doses at the higher end of the dose range and are mild (Berk & Jacobson, 1998). Vitamin C 500 milligrams (mg) daily stopped bleeding and bruising associated with paroxetine and fluvoxamine therapy (Teilens, 1997).

b) Aplastic anemia, agranulocytosis, bone marrow aplasia, eosinophilia, epistaxis, hemolytic anemia, leukocytosis, leukopenia, pancytopenia, prolonged bleeding time, ecchymoses and rectal bleeding have occurred with paroxetine therapy.

c) LITERATURE REPORTS

1) INCIDENCE - Rare (incidence less than 0.1%).

a) The majority cases have been reported in patients taking fluoxetine but case reports are also available for paroxetine, sertraline, and fluvoxamine (Berk & Jacobson, 1998).

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

3) ASSOCIATED SYMPTOMS - Symptoms include: aplastic anemia, agranulocytosis, bone marrow aplasia, bruising, ecchymoses, eosinophilia, epistaxis, hemolytic anemia, leukocytosis, leukopenia, pancytopenia, prolonged bleeding time, rectal bleeding.

a) ONSET/DURATION

1) EARLIEST ONSET - 2 weeks (Tielens, 1997).

b) CLINICAL MANAGEMENT

1) PHARMACOLOGIC: For minor bleeding diatheses (ie, bruising), treatment is usually unnecessary because it usually resolves with continued treatment. However, if bleeding is clinically significant, occurs with other underlying medical illnesses, or fails to improve with time, the drug should be discontinued (Berk & Jacobson, 1998). Vitamin C 500 milligrams/day effectively reduced bleeding and bruising in 1 woman (Tielens, 1997).

c) PREDISPOSING RISK FACTORS

1) DOSE-RELATED ? YES. Many cases have occurred in patients taking doses at the higher end of the dose range (Berk & Jacobson, 1998).

2) DISEASE STATES: More common in patients with underlying diseases; 1 case occurred in a patient with HIV (Berk & Jacobson, 1998).

d) PROBABLE MECHANISM

1) Pharmacologic (extension of the expected effects of the drug). Selective serotonin reuptake inhibitors reduce uptake of serotonin by platelets; therefore, reduction in granular storage of serotonin is observed. Serotonin-mediated platelet aggregation may be decreased (Berk & Jacobson, 1998).

e) DOCUMENTATION QUALITY

1) Fair

f) CASE REPORTS

1) Vitamin C 500 milligrams (mg) daily stopped bleeding and bruising associated with paroxetine and fluvoxamine therapy (Teilens, 1997). A 33-year-old woman began taking paroxetine 40 mg daily for panic attacks and noted spontaneous bruising on her arms and legs and excessive menstrual BLEEDING within 2 weeks. No gynecologic or hematologic abnormalities were identified. Vitamin C added to paroxetine therapy stopped bleeding in

3 weeks; discontinuation of vitamin C resulted in recurrent bleeding. Her medication was switched to fluvoxamine which also caused bleeding that resolved with vitamin C (Tielens, 1997).

3.3.6 Hepatic Effects

3.3.6.A Paroxetine Hydrochloride

Acute hepatitis

Hepatitis

Hepatotoxicity

Liver finding

3.3.6.A.1 Acute hepatitis

a) Incidence: rare

b) An 84-year-old woman developed clinical symptoms of acute hepatitis after the first dose of paroxetine 10 mg/day prescribed for chronic mild depression. Symptoms of mental confusion, hyporexia, nausea and vomiting began after the first dose of paroxetine which was 3 days prior to hospitalization. The patient's medical history included chronic mild depression, chronic atrial fibrillation, arterial hypertension, brain atherosclerosis (two previous episodes of transitory ischemic attacks), and medications included verapamil 80 mg/day, tilopidine 500 mg/day, spironolactone 25 mg/day, and nimodipine 60 mg/day. Results from a clinical evaluation from 1 week prior to hospitalization, reported normal physical examination and normal serum levels of common biochemical markers, and serum transaminase levels (eg, AST (13 international units/L), ALT (17 international units/L), alkaline phosphatase (180 international units/L) and total bilirubin (1.03 mg/dL)). Upon hospitalization, the laboratory analysis revealed abnormal serum transaminase levels, including AST (186 international units/L), ALT (245 international units/L), mild hyperbilirubinemia (1.5 mg/dL), mild renal failure, and increased WBC levels without eosinophilia. The paroxetine was discontinued immediately. The next day, the laboratory analysis revealed a marked increase in serum transaminase levels (eg, AST (2208 international units/L), ALT (2110 international units/L)), normal alkaline phosphatase (277 international units/L), hyperbilirubinemia (2.5 mg/dL), hematochemical signs of liver failure and the patient developed clinical signs of hepatic encephalopathy stage I (bilateral asterixis, confusion and lethargy). An ultrasound study showed normal finding of the liver, spleen, pancrease and kidneys. The serum markers of viral, autoimmune and metabolic liver disease were negative. The patient was treated with parenteral administration of branched chain amino acids and lactulose given by retention enema. Within three days after hospitalization, the patient's clinical condition and mental status improved, and serum transaminase and ammonia levels were decreased. After 15 days, all liver-related laboratory values normalized and the patient was discharged in good clinical condition. The Naranjo probability scale suggests that paroxetine was the probable cause of the acute hepatitis (total score of 7) (Pompili et al, 2008).

3.3.6.A.2 Hepatitis

a) Summary

1) CASE REPORT - Chronic active hepatitis attributed to paroxetine was reported in a 54-year-old woman with depression. About 10 months after starting paroxetine 20 milligrams daily, the aspartate transaminase was elevated at 256 international units/liter (IU/L); 6 months later, it was 299 IU/L with an elevated alkaline phosphatase. Liver ultrasonography and serological tests for hepatitis were normal; however, a liver biopsy showed chronic active hepatitis with eosinophilic infiltration suggesting a drug reaction. Paroxetine was stopped, and laboratory tests returned to normal within 13 weeks (Benbow & Gill, 1997).

3.3.6.A.3 Hepatotoxicity

a) Summary

1) Rare cases of severe hepatotoxicity with jaundice associated with paroxetine therapy have been reported. Hepatotoxicity has been of the hepatocellular type or hepatocellular and cholestatic mixed type. Liver damage is generally reversible on discontinuation of the drug. Liver damage is most likely idiosyncratic (Odeh et al, 2001).

2) Although no causal relationship to paroxetine was established, deaths with liver necrosis and cases of severe hepatic dysfunction with gross elevations of transaminase levels were reported in non-US postmarketing reports (Prod Info Paxil(R), 2001). Isolated reports of elevations in liver enzymes (transaminases) have been observed during paroxetine therapy of depression (Dunbar,

1989); (Kuhs & Rudoff, 1989)(Rickels et al, 1989). Transaminases normalized after withdrawal of the drug in 1 patient (Kuhs & Rudoff, 1989).

3.3.6.A.4 Liver finding

a) Hepatitis and elevations of liver enzymes have been noted with paroxetine therapy. Deaths due to liver necrosis and severe hepatic dysfunction have been reported but without an established causal relationship to paroxetine therapy.

3.3.7 Immunologic Effects

3.3.7.A Paroxetine Hydrochloride

Anaphylaxis

Immune hypersensitivity reaction, Delayed

Immunology finding

3.3.7.A.1 Anaphylaxis

a) Summary

1) The occurrence of anaphylaxis has been documented in postmarketing paroxetine reports (Prod Info Paxil(R), 2002e); (Prod Info Paxil CR(TM), 2002).

3.3.7.A.2 Immune hypersensitivity reaction, Delayed

a) Summary

1) CASE REPORT - A 63-year-old woman, with a history of arterial hypertension and major depression, who was treated with atenolol and hydrochlorothiazide (for 3 years) and paroxetine (for 18 months), developed abdominal pain associated with intermittent fever, vomiting, and constipation. Laboratory tests showed leucocytosis, eosinophilia, monocytosis, lymphopenia, normocytic anemia, and hypoalbuminemia. Exploratory laparotomy revealed a gelatin-like abdominal fluid and a fibrotic omentum, which, on biopsy, showed massive infiltrates of eosinophils and mononuclear cells. During treatment with hydrocortisone 750 milligrams for 2 days, the fever, eosinophilia, and pain disappeared , only to recur. Atenolol and paroxetine were discontinued. Symptoms resolved with a 6-week course of oral prednisone. Three months later, drug hypersensitivity testing showed a positive reaction to paroxetine in the interferon-gamma release test in vitro and to atenolol in a histamine release test. At one year, there had been no relapse. The authors concluded that the delayed-type hypersensitivity was probably cause by paroxetine (Rozin et al, 2000).

3.3.7.A.3 Immunology finding

a) Anaphylaxis and delayed hypersensitivity have been reported with paroxetine therapy.

3.3.8 Musculoskeletal Effects

3.3.8.A Paroxetine Hydrochloride

Arthralgia

Arthritis

Arthropathy

Bursitis

Fracture of bone

Fracture of bone, Nonvertebral

Myositis

Osteoporosis

Spasm

Summary

Tenosynovitis

3.3.8.A.1 Arthralgia

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

b) Arthralgia was reported in at least 1% of patients exposed to multiple doses of paroxetine (n=9089) in clinical trials; a causal relationship cannot be determined (Prod Info PAXIL(R) oral tablets, suspension, 2009).

3.3.8.A.2 Arthritis

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

b) Arthritis was reported in 0.1 to 1% of patients exposed to multiple doses of paroxetine (n=9089) in clinical trials; a causal relationship cannot be determined (Prod Info PAXIL(R) oral tablets, suspension, 2009).

3.3.8.A.3 Arthropathy

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

b) Arthrosis was reported in 0.1 to 1% of patients exposed to multiple doses of paroxetine (n=9089) in clinical trials; a causal relationship cannot be determined (Prod Info PAXIL(R) oral tablets, suspension, 2009).

3.3.8.A.4 Bursitis

a) Incidence: less than 0.1% (Prod Info PAXIL(R) oral tablets, suspension, 2009)

b) Bursitis was reported in fewer than 0.1% of patients exposed to multiple doses of paroxetine (n=9089) in clinical trials; a causal relationship cannot be determined (Prod Info PAXIL(R) oral tablets, suspension, 2009).

3.3.8.A.5 Fracture of bone

a) In a case-control study including fracture cases (n=124,655) during the year 2000 and age- and gender-matched controls (n=373,962), there was an increased risk of any fracture in participants who were using an average standard daily dose of paroxetine (adjusted odds ratio (OR), 1.21; 95% CI, 1.1 to 1.33) compared to those who were not exposed to paroxetine. Paroxetine use was associated with an increased risk of hip fracture (adjusted OR, 1.39; 95% CI, 1.04 to 1.84) and forearm fracture (adjusted OR, 1.64; 95% CI, 1.28 to 2.11), but not spine fracture (adjusted OR, 1.38; CI, 0.8 to 2.4) (Vestergaard et al, 2008).

b) In a population-based, randomly selected, prospective cohort study adjusted for potential covariates, an increased risk of fragility fracture was reported at the 5-year follow-up in patients 50 years of age and older who used daily SSRIs (n=137; mean age of 65.1 years), including paroxetine, compared with those who did not use an SSRI (n=4871; mean age of 65.7 years). Daily SSRI use was associated with a significant 2.1-fold increased risk of fragility fracture (95% confidence interval (CI), 1.3 to 3.4). Daily dose of SSRI use was associated with a 1.5-fold increased risk of fragility fracture (95% CI, 1.1 to 2.1). Daily SSRI users who were recurrent (ie, treated with SSRIs at baseline and at 5-year follow-up) had a significant 2.1-fold increased risk of fragility fracture (95% CI, 1.1 to 4.0). Fractures were reported at the following sites: forearm (40%), ankle and foot (21%), hip (13%), rib (13%), femur (9%), and back (4%). None were reported at the skull, toes, or fingers (Richards et al, 2007).

3.3.8.A.6 Fracture of bone, Nonvertebral

a) In a prospective, population-based, cohort study (n=7983) with a mean follow-up of 8.4 years, there was an increased risk of nonvertebral fracture in adult participants older than 55 years of age (mean age of 77.5 years) who were currently using an SSRI (citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine, or sertraline) compared to those who were not exposed to antidepressants. Current SSRI use was associated with an increased risk of nonvertebral fracture (adjusted hazard ratio (HR), 2.35; 95% confidence interval (CI), 1.32 to 4.18) compared with no antidepressant use. Current SSRI use was also associated with an increased risk of nonvertebral fracture (adjusted HR, 2.07; 95% CI, 1.23 to 3.5) compared with past antidepressant use (n=1217). In addition, duration of SSRI use showed a 9% increase in fracture risk per extra month on an SSRI (95% CI, 3% to 16%; p for trend=0.004). Fractures of the hip (most frequent), wrist, humerus, and pelvis were reported (Ziere et al, 2008).

3.3.8.A.7 Myositis

a) Incidence: less than 0.1% (Prod Info PAXIL(R) oral tablets, suspension, 2009)

b) Myositis was reported in fewer than 0.1% of patients exposed to multiple doses of paroxetine (n=9089) in clinical trials; a causal relationship cannot be determined (Prod Info PAXIL(R) oral tablets,

suspension, 2009).

3.3.8.A.8 Osteoporosis

a) Incidence: less than 0.1% (Prod Info PAXIL(R) oral tablets, suspension, 2009)

b) Osteoporosis was reported in fewer than 0.1% of patients exposed to multiple doses of paroxetine (n=9089) in clinical trials; a causal relationship cannot be determined (Prod Info PAXIL(R) oral tablets, suspension, 2009).

3.3.8.A.9 Spasm

a) Incidence: less than 0.1% (Prod Info PAXIL(R) oral tablets, suspension, 2009)

b) Generalized spasm was reported in fewer than 0.1% of patients exposed to multiple doses of paroxetine (n=9089) in clinical trials; a causal relationship cannot be determined (Prod Info PAXIL(R) oral tablets, suspension, 2009).

3.3.8.A.10 Summary

a) Arthralgia, arthritis, arthrosis, bursitis, generalized spasm, myositis, osteoporosis, and tenosynovitis have been reported following paroxetine treatment (Prod Info PAXIL(R) oral tablets, suspension, 2009). Paroxetine use was associated with an increased risk of hip and forearm fracture, but not spine fracture in a case-control study (Vestergaard et al, 2008). An increased risk of fragility fracture has been reported in a prospective cohort study of SSRIs, including paroxetine (Richards et al, 2007). An increased risk of nonvertebral fracture has been reported in a prospective cohort study of SSRI use, including paroxetine, in adult participants older than 55 years of age (Ziere et al, 2008).

3.3.8.A.11 Tenosynovitis

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

b) Tenosynovitis was reported in 0.1 to 1% of patients exposed to multiple doses of paroxetine (n=9089) in clinical trials; a causal relationship cannot be determined (Prod Info PAXIL(R) oral tablets, suspension, 2009).

3.3.9 Neurologic Effects

Paroxetine

Paroxetine Hydrochloride

3.3.9.A Paroxetine

3.3.9.A.1 Seizure

See Drug Consult reference: COMPARATIVE INCIDENCE OF SEIZURES FROM ANTIDEPRESSANTS

3.3.9.B Paroxetine Hydrochloride

Akathisia

Central nervous system depression

Chorea

Cognitive function finding

Confusion

Decreased serotonin level

Dizziness

EEG finding

Extrapyramidal sign

Headache

Impaired psychomotor performance

Paresthesia

Parkinson's disease

Restless legs syndrome

Seizure

Sleep walking disorder

Somnolence

Summary

Tetany

Tremor

3.3.9.B.1 Akathisia

a) Summary

1) In a retrospective review of a series of patients treated with paroxetine, akathisia was reported to occur at an incidence of 4% (Baldassano et al, 1996). In two of the reported cases, akathisia occurred within a week of initiation of paroxetine therapy (20 milligrams/day) in which the patients described feelings of inner restlessness, insomnia, and the inability to stay still. Akathisia resolved in both cases following the addition of propranolol (40 to 80 milligrams/day) (Baldassano et al, 1996; Adler & Angrist, 1995).

b) LITERATURE REPORTS

1) A 38-year-old man who had been treated with paroxetine 70 milligrams (mg) once daily for 2 years for obsessive-compulsive disorder developed a subjective inner restlessness. Three years earlier, he had a similar reaction shortly after starting pimozide treatment; pimozide was discontinued. Because of that previous experience, the current episode was diagnosed as TARDIVE AKATHISIA and attributed to paroxetine. Treatment with lorazepam 1 mg 3 times daily eliminated, within 4 days, the restlessness without further changes in medication (Boffa & Lofchy, 2000).

2) A 33-year-old man treated for depression with paroxetine 20 milligrams (mg) daily developed an intense restlessness in both legs which began as he was falling asleep. Restlessness of the arms and hands also appeared. Only physical exercise helped in relieving the symptoms. Due to the restless leg syndrome, he stopped treatment, and symptoms disappeared within days. Two months later, he presented with a recurrence of depression. Paroxetine 20 mg was restarted and resulted in improvement in depression; however, the nocturnal leg restlessness occurred with greater intensity. Treatment with paroxetine was continued for 3 months and then stopped. Restlessness of the legs disappeared after stopping paroxetine. This patient reported worsening when alcohol was consumed and also reported that his mother had experienced similar symptoms (Sanz-Fuentenebro et al, 1996).

3) Akathisia developed in a 63-year-old man treated with paroxetine 20 milligrams/day (Adler & Angrist, 1995). The Adverse Drug Reactions Advisory Committee has received several reports of akathisia (restlessness, constant need to pace), including one case which began 5 months after starting paroxetine and resolved on discontinuation of the drug (Anon, 1996).

3.3.9.B.2 Central nervous system depression

a) Summary

1) TIREDNESS, LETHARGY, and difficulty concentrating are commonly reported adverse effects of paroxetine therapy (Feighner et al, 1993)(Dunbar et al, 1993a); (Calghorn et al, 1992)(Rickels et al, 1989); (Laurson et al, 1985).

b) LITERATURE REPORTS

1) Profound psychomotor retardation developed in a mentally retarded 67-year-old woman taking paroxetine 20 milligrams/day (Lewis et al, 1993).

3.3.9.B.3 Chorea

a) Summary

1) Of 246 suspected cases of extrapyramidal reactions submitted to the Committee on Safety of Medicines in the United Kingdom, only 3 described chorea associated with paroxetine. The manufacturer has received only 12 reports of chorea from all countries where paroxetine is available. None of the previously reported cases occurred after the first dose (Fox et al, 1997).

b) LITERATURE REPORTS

1) A 42-year-old woman presented with choreiform movements of all 4 limbs and an inability to communicate after taking 1 dose of paroxetine 20 milligrams for depression. On examination, she also had oculogyric crisis, hypertension (220/120 mmHg), and tachycardia. Three doses of procyclidine 5 milligrams relieved symptoms after 30 minutes (Fox et al, 1997).

3.3.9.B.4 Cognitive function finding

a) Summary

1) Use of FLUOXETINE or PAROXETINE was not associated with degradation of cognitive function in depressed non-demented elderly patients (Cassano et al, 2002).

b) LITERATURE REPORTS

1) A 1-year course of FLUOXETINE or PAROXETINE did NOT have detrimental effects on cognitive function in depressed non-demented elderly patients; in fact, tests of cognition showed improved results after 1 year of treatment compared with baseline, according to a randomized, double-blind trial (n=242; mean age 75.4 years). Both active treatments were well tolerated, and both significantly reduced symptoms of depression. Memory, learning, and attention improved over the year of therapy, and improved scores were seen on the Mini-Mental State Exam (MMSE), the Blessed Information and Memory Test (BIMT), the Cancellation Task Test (CTT), the Clifton Assessment Schedule (CLAS), and the Wechsler Paired Word Test (WPW). Some parameters on the Buschke Selective Reminding Test (BSRT) were better treatment. Daily doses of fluoxetine were in the range of 20 to 60 mg, and paroxetine dosages ranged from 20 to 40 mg/day (Cassano et al, 2002).

3.3.9.B.5 Confusion

a) Summary

1) CONFUSION (1%) was reported during clinical trials with paroxetine (Prod Info Paxil(R), 2002e); (Prod Info Paxil CR(TM), 2002)(Dunbar, 1989; Rickels et al, 1989).

3.3.9.B.6 Decreased serotonin level

a) Summary

1) Serum serotonin concentrations decreased in 3 healthy volunteers following 1 to 2 weeks of paroxetine 10 to 25 milligrams/day. Pretreatment levels were 0.3 micrograms/milliliter (mcg/mL) in one subject and 0.1 mcg/mL in the other two. Serotonin levels decreased to 0.02 to 0.04 mcg/mL following treatment with paroxetine. A drug-free period of 3 to 4 weeks was necessary to return to pretreatment serum serotonin concentrations (Lund et al, 1979).

3.3.9.B.7 Dizziness

a) Summary

1) Dizziness (11% to 14%) was reported during clinical trials with paroxetine (Prod Info Paxil(R), 2002e); (Prod Info Paxil CR(TM), 2002)(Dunbar, 1989; Rickels et al, 1989). The incidence of dizziness is lower after treatment with paroxetine than amitriptyline (Kuhs & Rudolf, 1989a); (Lund et al, 1985).

3.3.9.B.8 EEG finding

a) Summary

1) At therapeutic doses paroxetine induces a decrease in delta and theta activity, and in increase in beta activity (McClelland & Raptopoulos, 1984).

3.3.9.B.9 Extrapyramidal sign

a) Summary

1) Extrapyramidal reactions, particularly dystonic reactions involving the face or mouth, appear to occur more frequently with paroxetine than with other serotonin reuptake inhibitors (Gerber & Lynd, 1998; Romanelli et al, 1996); (Anon, 1996). The majority of extrapyramidal reactions (EPRs) occur within the first few days to month of treatment. Therefore, careful monitoring for EPRs is recommended weekly during the first 4 weeks of treatment with selective serotonin reuptake inhibitors (SSRIs) and periodically thereafter. EPRs generally resolve within a few days after reducing the dose or stopping the SSRI (Caley, 1997; Gill et al, 1997).

b) LITERATURE REPORTS

1) Orolingual movements (intermittent facial movements, initially involving the tongue and lips) have been described as an adverse effect of selective serotonin reuptake inhibitors (SSRIs), including paroxetine (Gerber & Lynd, 1998); (Anon, 1996). BRUXISM has also been described as an adverse effect of paroxetine (Gerber & Lynd, 1998; Romanelli et al, 1996).

2) Extrapyramidal reactions (EPRs) including acute DYSTONIC REACTIONS, PARKINSONISM, NEUROLEPTIC MALIGNANT SYNDROME, and DYSKINESIAS were reported with 1 or more selective serotonin reuptake inhibitors (SSRI). The majority of case reports involve fluoxetine; however, all of the SSRIs were implicated in at least 1 EPR (Caley, 1997; Gill et al, 1997). Reactions occurred primarily in women (about 75%) possibly due to use of SSRIs for treating mental disorders common to women (ie, depression). In many, but not all, case reports, the dose of the SSRI was increased to the maximum recommended dose within 7 days or near maximum doses were used. The majority of reactions occurred within the first week or during the second to fourth week of treatment. Possible mechanisms by which SSRIs cause EPRs include: (1) Central serotonergic activity which inhibits dopaminergic activity resulting in clinically significant effects; and (2) Concurrent use of an SSRI and antipsychotic may cause EPRs by a pharmacokinetic interaction, a pharmacodynamic interaction, or a combination of the two (Caley, 1997).
3) TREATMENT - In a limited number of case reports, propranolol and/or benzodiazepines were used to treat akathisia; the dose of propranolol ranged from 40 to 90 milligrams (mg) daily, and the dose of clonazepam was 1.5 mg daily (Gill et al, 1997). In single case reports, dystonic reactions responded to an unspecified dose of intramuscular trihexyphenidyl or diphenhydramine 50 mg. Parkinsonism characterized by increasing rigidity and tremor frequently occurred with high doses of the SSRI or during concomitant treatment with a neuroleptic agent. In all cases, symptoms disappeared after reducing the dose or stopping the SSRI. In contrast to neuroleptic-induced dyskinesias including tardive dyskinesia, SSRI-induced dyskinesias resolve spontaneously over days to weeks after the SSRI is stopped (Gill et al, 1997).
4) A 35-year-old woman with early-onset parkinsonism developed worsening symptoms (tremor, rigidity, postural instability) after taking paroxetine 20 milligrams/day. Symptoms returned to baseline after discontinuing paroxetine (Jimenez-Jimenez et al, 1994).

3.3.9.B.10 Headache

a) Summary

1) Headache is reported in (18%) of patients with therapeutic paroxetine doses (Prod Info Paxil(R), 2002e); (Ohrberg et al, 1992)(Dunbar, 1989; Mertens & Pintens, 1988b; Laursen et al, 1985b). In clinical trials with Paxil CR(TM), headache (27%) was reported at an incidence higher than placebo (Prod Info Paxil CR(TM), 2002).

3.3.9.B.11 Impaired psychomotor performance

a) Summary

1) No significant effects on psychomotor performance have been observed in single- or multiple-dose studies with paroxetine in healthy subjects (Warrington et al, 1989b; McClelland & Raptopoulos, 1985). In 1 study, a significant increase in cerebrospinal fluid (CSF) threshold was observed with paroxetine, suggesting an alerting effect of the drug. In this study, amitriptyline reduced the CSF threshold, indicative of sedation (Warrington et al, 1989b). Recently, in a large retrospective review, it was found that nursing home patients treated with fluoxetine and other selective serotonin-reuptake inhibitors (SSRIs) including paroxetine and sertraline have an increased 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 assessed the incidence of falls before and after the initiation of antidepressant therapy. Results were then compared to those not treated (n=847). Antidepressant treatment included tricyclic antidepressants (TCAs; n=665), selective serotonin reuptake inhibitors (SSRIs) (n=612), and trazodone (n=304). The rate of falls for treated patients was higher than that for patients who were not treated, both before and after the initiation of antidepressant therapy. This suggests that nursing home patients with depression or related conditions are at a greater risk of falls than those without such conditions Patients on TCAs had the highest rate of falls, with an adjusted rate ratio of 2 (95% confidence interval (CI), 1.8 to 2.2). Next were the SSRIs with an adjusted rate ratio of 1.8 (1.6 to 2, p=0.001) and trazodone with a ratio of 1.2 (1 to 1.4, p less than 0.001). No significant differences in incidence were seen within different medications of the same class. It was, however, noted that patients receiving a dose of 20 milligrams (mg) daily of fluoxetine, or an equivalent dose of another SSRI, had a statistically significant increase in the incidence of falls than those receiving lower doses (Thapa et al, 1998).

3.3.9.B.12 Paresthesia

a) Summary

1) Paresthesia were reported in 4% of patients during clinical trials with paroxetine (Prod Info Paxil (R), 2002e); (Prod Info Paxil CR(TM), 2002)(Dunbar, 1989; Rickels et al, 1989).

b) LITERATURE REPORTS

1) Three women 22 to 29 years of age reported electric shock-like paresthesias of the face and head shortly after taking the first several doses of paroxetine 20 milligrams (mg). Each paroxysm lasted 5 to 15 seconds and occurred repeatedly for up to 5 minutes. The paresthesias ceased after 5 days; 2 of 3 patients continued taking paroxetine. Paroxetine was the only medication used by each patient; none of the women had other medical or neurologic diseases which may have caused

the paresthesias. Another author reported similar shock-like paresthesias which radiated from one region to another often ending in the limbs; these cases were reported in young males when paroxetine was stopped. This report is intended to alert health care providers that paroxetine may cause shock-like paresthesias upon initiation or discontinuation of therapy (Berigan et al, 1997).

3.3.9.B.13 Parkinson's disease

a) Summary

1) Paroxetine 10 to 20 milligrams/day did not aggravate parkinsonian symptoms in most of the Parkinson's disease patients treated for depression in a small prospective study. Thirteen of 65 patients stopped paroxetine treatment within 1 to 30 days because of adverse reactions, but only 2 patients experienced exacerbation of parkinsonian tremor (Tesei et al, 2000).

b) LITERATURE REPORTS

1) A case report indicates that paroxetine exacerbated a 35- year-old woman's parkinsonism (Jimenez-Jimenez et al, 1994). Following one month of therapy with paroxetine 20 milligrams/day, the patient experienced increased tremor, mild rigidity and postural instability. Upon discontinuation of paroxetine, the patient experienced marked improvement in her Parkinson's disease symptoms.

3.3.9.B.14 Restless legs syndrome

a) In a prospective, naturalistic study of patients (median age, 46 years; range, 18 to 87 years) treated with antidepressants, 24 of 271 (9%) subjects experienced new-onset restless leg syndrome (RLS) or worsening of preexisting RLS as a side effect related to treatment. Antidepressants included fluoxetine, paroxetine, citalopram, sertraline, escitalopram, venlafaxine, duloxetine, reboxetine, and mirtazapine. Mirtazapine led to a marked decline of RLS in 28% of subjects compared with reboxetine which had none. The other antidepressants showed RLS symptoms (newly occurred or deteriorated) at the rate of 5% to 10%. Subjects stated symptoms occurred early in treatment (median of 2.5 days, range 1 to 23 days) (Rottach et al, 2008).

b) CASE REPORT - A 48-year-old woman with a history of major depressive disorder developed restless legs syndrome (RLS) immediately after receiving paroxetine. Paroxetine 20 milligrams (mg) daily was initiated after discontinuing clomipramine 60 mg daily (taken for 5 years). At that time, she began to experience an unpleasant sensation in her legs during the night which was relieved by movement. After 3 weeks of therapy, paroxetine was replaced by citalopram 20 mg daily (progressively increased to 60 mg daily in 1 week). At that time, the unpleasant sensation in the legs dramatically worsened with symptoms occurring during each period of inactivity, extending to the arms after 1 week. At a psychiatric emergency unit, she presented with motor restlessness, nocturnal worsening of symptoms, association between the desire to move the limbs and paresthesia or dysesthesia, and worsening of symptoms during rest and partial relief with activity. A diagnosis of RLS induced by paroxetine and citalopram was made; the International Restless Leg Syndrome Study Group (IRLSSG) rating scale score was 30 (the maximum score is 40). After the discontinuation of citalopram, her RLS symptoms started to diminish after 3 days of therapy with bupropion 150 mg daily and sertraline 50 mg daily. She recovered completely after 3 weeks of therapy. The authors suggested that RLS could be a possible "dopamine-dependent side effect" of selective serotonin reuptake inhibitors (SSRIs). Amongst SSRIs, sertraline may provide the least risk of RLS by blocking dopamine reuptake and bupropion may correct dopaminergic dysfunction in RLS (Nader et al, 2007).

3.3.9.B.15 Seizure

a) Summary

1) The occurrence of STATUS EPILEPTICUS has been documented in paroxetine postmarketing reports (Prod Info Paxil(R), 2002e); (Prod Info Paxil CR(TM), 2002).

b) Incidence: rare

3.3.9.B.16 Sleep walking disorder

a) Summary

1) A 34-year-old HIV-positive woman developed somnambulism while being treated with paroxetine, and later with sertraline, for anxiety and depression. The initial 10-milligram (mg) daily dose of paroxetine was gradually increased over 2 weeks to 20 mg daily. Three days after achieving 20 mg/day, the woman began to sleepwalk up to 3 times per night, according to witnesses. The somnambulism disappeared completely 1 week after the daily dose was reduced to 10 mg. However, at 10 mg/day, she had a relapse of depression. Upon again increasing the dose to 20 mg/day, the sleepwalking reappeared. Paroxetine was discontinued and sertraline 50 mg/day was substituted. Four days after the sertraline dose was increased to 100 mg/day, she again began to sleepwalk. Her symptoms of depression and anxiety improved at that dose. She therefore continued sertraline 100 mg/day despite continuing somnambulism (Alao et al, 1999).

3.3.9.B.17 Somnolence

a) Summary

1) Somnolence (19% to 24%) was reported during clinical trials with paroxetine (Prod Info Paxil(R), 2002e); (Prod Info Paxil CR(TM), 2002)(Dunbar, 1989; Rickels et al, 1989).

b) LITERATURE REPORTS

1) A 38-year-old woman developed NARCOLEPSY 4 weeks after beginning paroxetine 20 milligrams/day. Symptoms resolved after paroxetine was discontinued and returned when it was resumed at 10 milligrams/day (Owley & Flaherty, 1994).

3.3.9.B.18 Summary

a) Akathisia, chorea, extrapyramidal reactions, paresthesias, psychomotor impairments, confusion, lethargy, central nervous system depression, headache, dizziness, mild electroencephalogram changes, sleep disorders, somnolence, tetany, tremors, and seizure activity have been reported with paroxetine therapy (Prod Info Paxil(R), 2002e); (Prod Info Paxil CR(TM), 2002)(Dunbar, 1989; Rickels et al, 1989).

3.3.9.B.19 Tetany

a) Incidence: rare (Prod Info Paxil(R), 2002e)

b) Tetany was reported rarely during premarketing evaluation of paroxetine (Prod Info Paxil(R), 2002e).

3.3.9.B.20 Tremor

a) Summary

1) Tremor is a commonly reported side effect (8% to 11%) in patients during therapeutic paroxetine use (Prod Info Paxil(R), 2002e; Dunbar et al, 1993a); (Feighner et al, 1993; Ohrberg et al, 1992)(Claghorn et al, 1992a; Dunbar, 1989); (Laurson et al, 1985). In clinical trials with Paxil(R) CR(TM), tremor (7%) was reported at an incidence higher than placebo (Prod Info Paxil CR(TM), 2002).

3.3.10 Ophthalmic Effects

3.3.10.A Paroxetine Hydrochloride

Anisocoria

Eye / vision finding

Glaucoma

Optic neuritis

3.3.10.A.1 Anisocoria

a) Summary

1) CASE REPORT - Unevenly dilated pupils (anisocoria) was reported in a 33-year-old woman who had been taking paroxetine 50 milligrams/day for 4 weeks (Barrett, 1994). The patient's outcome was not disclosed.

3.3.10.A.2 Eye / vision finding

a) Summary

1) BLURRED VISION has occurred in 5% of patients treated with paroxetine (Dunbar, 1989). MYDRIASIS has been observed in some studies (Raptopoulos et al, 1989b).

b) Glaucoma, optic neuritis, anisocoria, blurred vision and mydriasis have occurred with paroxetine therapy.

3.3.10.A.3 Glaucoma

a) Summary

1) Several cases of glaucoma have been reported with therapeutic paroxetine use. The proposed mechanism is a direct effect on the iris or ciliary body muscle via serotonergic or anticholinergic effects. Careful monitoring of older patients for anticholinergic side effects may be prudent even when the newer antidepressants are used (Bennett & Wyllie, 1999; Eke & Bates, 1997; Kirwan et al, 1997).

b) LITERATURE REPORTS

1) On 2 different occasions, acute angle-closure glaucoma developed 1 to 3 days after starting paroxetine. With the first episode, paroxetine 20 milligrams (mg) daily was started 3 days before glaucoma developed; this episode resolved spontaneously after the patient stopped taking paroxetine. Ocular pain, browache, and blurred vision began 1 day after paroxetine was restarted. Ocular examination revealed conjunctival congestion, a mid-dilated pupil, and an intraocular pressure of 61 millimeters mercury. She was admitted to the hospital for medical therapy, and she underwent laser peripheral iridotomy. Her recovery was uneventful, and she required no topical treatment (Bennett & Wyllie, 1999).

2) A 91-year-old woman developed eye pain, blurred vision, and a dry mouth after taking the first dose of paroxetine (dose not specified) for depression. Evaluation in the ophthalmology clinic revealed similar symptoms, dilated pupils, and an intraocular pressure (IOP) of 70 millimeters of mercury (mmHg) in each eye. Treatment consisted of acetazolamide 500 milligrams (mg) intravenously, pilocarpine 4% every 15 minutes, and timoptic 0.5% twice daily. The IOP decreased over 5 hours. After performing bilateral laser peripheral iridotomies, the IOP was 14 mmHg in each eye. No previous eye diseases or symptoms had been reported. This patient had mild congestive heart failure and osteoarthritis which were treated with a diuretic and acetaminophen. The authors suggest careful monitoring of older patients for anticholinergic side effects even when the newer antidepressants are used (Kirwan et al, 1997).

3) Glaucoma occurred 13 days after paroxetine 10 milligrams (mg) increased to 20 mg was started in an 84-year-old woman with depression. Her presenting symptoms included eye pain and redness with blurring of vision; ophthalmic examination revealed an intraocular pressure (IOP) of 40 millimeters of mercury. Paroxetine was stopped, and the IOP responded to standard medical therapy followed by laser iridotomy. The proposed mechanism is a direct effect on the iris or ciliary body muscle via serotonergic or anticholinergic effects (Eke & Bates, 1997).

3.3.10.A.4 Optic neuritis

a) Summary

1) The occurrence of optic neuritis has been documented in post marketing paroxetine reports (Prod Info Paxil(R), 2002e); (Prod Info Paxil CR(TM), 2002).

3.3.12 Psychiatric Effects

3.3.12.A Paroxetine Hydrochloride

Delirium

Depression, exacerbation

Hallucinations

Hypomania

Inappropriate laughter

Mania

Psychiatric sign or symptom

Sleep disorder

Suicidal thoughts

3.3.12.A.1 Delirium

a) Summary

1) CASE REPORT - A 39-year-old male treated for severe depression with paroxetine 20 milligrams daily and phenothiazines (promethazine 250 milligrams daily and perazine 200 milligrams daily) developed a delirium syndrome on the second day of treatment, possibly due to the combination of a serotonin reuptake inhibitor and phenothiazine derivative. The delirium cleared after discontinuation of the phenothiazines and addition of diazepam 10 milligrams daily to the paroxetine (Koenig et al, 1993).

3.3.12.A.2 Depression, exacerbation

a) Adult and pediatric patients who experience symptoms of anxiety, agitation, panic attacks, insomnia, irritability, hostility (aggressiveness), impulsivity, akathisia (psychomotor restlessness), hypomania, or mania may be at risk of worsening of their depression. This same concern applies to treating patients with other psychiatric and nonpsychiatric disorders. If these symptoms are observed, therapy should be reevaluated and it may be necessary to discontinue medications when symptoms are severe, sudden in onset, or were not part of the patient's initial symptoms (Anon, 2004).

3.3.12.A.3 Hallucinations

a) Incidence: infrequent (Prod Info PAXIL(R) oral tablets, oral suspension, 2006)
b) Hallucinations have been reported in 22 of 9,089 patients receiving immediate-release paroxetine compared with 4 of 3,187 receiving placebo in pooled clinical trials (Prod Info PAXIL(R) oral tablets, oral suspension, 2006).

3.3.12.A.4 Hypomania
a) Incidence: 0.3 to 2.2% (Prod Info PAXIL(R) oral tablets, oral suspension, 2006)
b) Hypomania or mania occurred in approximately 1% unipolar patients receiving paroxetine compared with 0.3% unipolar patients receiving placebo during premarketing testing. In a subset of patients classified as bipolar, the rate of manic episodes was 2.2% for paroxetine and 11.6% for the combined active control groups (Prod Info PAXIL(R) oral tablets, oral suspension, 2006).

3.3.12.A.5 Inappropriate laughter
a) Summary
1) A 52-year-old woman manifested unmotivated compulsive laughing 3 days after starting paroxetine 20 milligrams (mg) per day to treat anxiety and depression. The woman had schizoaffective disorder, which was being treated with clozapine 200 mg/day, lithium 1320 mg/day, and lorazepam 1 mg/day. She also had type 2 diabetes, which was controlled with metformin and glimepiride. Toxic plasma levels of lithium were corrected by lowering the lithium dose, but depression symptoms continued for 3 weeks after the correction and were therefore treated with paroxetine. The pathologic laughing that began after initiation of paroxetine treatment could be induced at any time of day. On day 5, paroxetine was withdrawn, and the laughter was no longer inducible the next day (Zullino et al, 2002).

3.3.12.A.6 Mania
a) Incidence: rare
b) Hypomania or mania occurred in approximately 1% unipolar patients receiving paroxetine compared with 0.3% unipolar patients receiving placebo during premarketing testing. In a subset of patients classified as bipolar, the rate of manic episodes was 2.2% for paroxetine and 11.6% for the combined active control groups (Prod Info PAXIL(R) oral tablets, oral suspension, 2006).

3.3.12.A.7 Psychiatric sign or symptom
a) Summary
1) NERVOUSNESS (5% to 9%) and ANXIETY (5%) were reported during clinical trials with paroxetine (Prod Info Paxil(R), 2002e); (Prod Info Paxil CR(TM), 2002)(Dunbar, 1989; Rickels et al, 1989).
b) Paroxetine therapy has been associated with anxiety, nervousness, delirium and suicidal ideation.

3.3.12.A.8 Sleep disorder
a) Summary
1) Sleep disturbance is common with therapeutic paroxetine doses (Ohrberg et al, 1992)(Claghorn et al, 1992a; Laursen et al, 1985b). In clinical trials with Paxil CR(TM), INSOMNIA (17%) were reported at an incidence higher than placebo (Prod Info Paxil CR(TM), 2002).
b) LITERATURE REPORTS
1) In 12 volunteers paroxetine increased the time required to achieve rapid eye movement (REM) sleep, decreased the proportion of sleep spent as REM sleep, increased the number of awakenings and reduced total sleep (Oswald & Adam, 1986).

3.3.12.A.9 Suicidal thoughts
a) Summary
1) Adult and pediatric patients being treated with antidepressants for major depressive disorder who experience symptoms of anxiety, agitation, panic attacks, insomnia, irritability, hostility (aggressiveness), impulsivity, akathisia (psychomotor restlessness), hypomania, or mania may be at risk of suicidal ideation and behavior (suicidality). This same concern applies to treating patients with other psychiatric and nonpsychiatric disorders. If these symptoms are observed, therapy should be reevaluated and it may be necessary to discontinue medications when symptoms are severe, sudden in onset, or were not part of the patient's initial symptoms. Patients and their caregivers should be provided with the Medication Guide that is available for this drug (Anon, 2004; Anon, 2004).
2) A causal role for antidepressants in inducing suicidality has been established in pediatric patients. Anyone considering the use of antidepressants in a child or adolescent must balance this risk with the clinical need. In pooled analyses of 24 short-term, placebo-controlled trials of nine antidepressants (citalopram, fluoxetine, fluvoxamine, paroxetine, sertraline, bupropion, mirtazapine, nefazodone, and venlafaxine extended-release) including over 4400 pediatric patients with major depressive disorder, obsessive compulsive disorder, or other psychiatric disorders, a greater risk of suicidal behavior or ideation during the first few months of therapy was demonstrated in patients receiving antidepressants as compared with placebo (4% vs 2%, respectively). The risk of suicidality was most consistently observed in the trials that included patients with major depressive

disorder, but there were signs of risk emerging from trials in other psychiatric indications, such as obsessive compulsive disorder and social anxiety disorder. No suicides occurred in these trials. The risk of suicidality during longer-term use (ie, beyond several months) in pediatric patients is not known. It is also unknown whether this risk extends to adult patients (Anon, 2004).

b) Incidence: rare

3.3.13 Renal Effects

3.3.13.A Paroxetine Hydrochloride

Kidney finding

Renal failure

Urogenital finding

3.3.13.A.1 Kidney finding

a) Summary

1) URINARY HESITANCY (3%), URINARY FREQUENCY (3%), and URINARY TRACT INFECTION (2%) were reported during clinical trials (Prod Info Paxil(R), 2002e); (Prod Info Paxil CR(TM), 2002; Feighner et al, 1993; Ohrberg et al, 1992).

3.3.13.A.2 Renal failure

a) Summary

1) The occurrence of ACUTE RENAL FAILURE has been documented in postmarketing paroxetine reports (Prod Info Paxil(R), 2002e); (Prod Info Paxil CR(TM), 2002).

3.3.13.A.3 Urogenital finding

a) Urinary infections, frequency, hesitancy, sexual dysfunction, priapism and eclampsia have been noted with therapeutic paroxetine use. Acute renal failure has also been reported.

3.3.14 Reproductive Effects

Paroxetine

Paroxetine Hydrochloride

3.3.14.A Paroxetine

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 DYSFUNCTION

3.3.14.B Paroxetine Hydrochloride

Eclampsia

Priapism

Sexual dysfunction

3.3.14.B.1 Eclampsia

a) Summary

1) The occurrence of eclampsia has been documented in paroxetine postmarketing reports (Prod Info Paxil(R), 2002e); (Prod Info Paxil CR(TM), 2002).

3.3.14.B.2 Priapism

a) Summary

1) CASE REPORT - Priapism was reported in a 58-year-old man after receiving paroxetine 20

milligrams/day for depression. The length of therapy was not disclosed. The patient presented with a painful erection which lasted for 42 hours. Paroxetine was discontinued and the patient experienced complete recovery over the next 8 hours; rechallenge was not attempted (Ahmad, 1995).

3.3.14.B.3 Sexual dysfunction

a) Summary

1) EJACULATORY DISTURBANCES (13% to 28%) or ANORGASMIA (10%), ERECTILE DIFFICULTIES (10%), DELAYED ORGASM (10%), and IMPOTENCE (5% to 10%) were reported in males during clinical trials. Anorgasmia and difficulty reaching climax/orgasm were reported in 2% of women treated with paroxetine. Decreased libido was also reported in 3% to 12% of patients (Prod Info Paxil(R), 2002e); (Feighner et al, 1993)(Anon, 1993; Claghorn et al, 1992a). Abnormal ejaculation (26%), anorgasmia or delayed orgasm (in women; 10%), and decreased libido (7%) occurred at a higher incidence than placebo in clinical trials of Paxil CR(TM) (Prod Info Paxil CR (TM), 2002).

3.3.15 Respiratory Effects

3.3.15.A Paroxetine Hydrochloride

Lung finding

Pharyngitis

Respiratory finding

Yawning

3.3.15.A.1 Lung finding

a) Summary

1) The occurrence of PULMONARY HYPERTENSION and ALLERGIC ALVEOLITIS have been documented in postmarketing paroxetine reports (Prod Info Paxil(R), 2002e); (Prod Info Paxil CR (TM), 2002).

3.3.15.A.2 Pharyngitis

a) Summary

1) In data from the manufacturer involving 2683 paroxetine patients, pharyngitis and RHINITIS were each reported in 2% of patients treated (Dunbar, 1989).

3.3.15.A.3 Respiratory finding

a) Pharyngitis, rhinitis, pulmonary hypertension and allergic alveolitis have been noted with paroxetine therapy.

3.3.15.A.4 Yawning

a) Incidence: 4% (Prod Info Paxil(R), 2002e)

b) Yawning (4%) was reported during clinical trials with paroxetine (Prod Info Paxil(R), 2002e; Dunbar, 1989; Rickels et al, 1989).

1) Excessive daytime yawning, not associated with sedation or drowsiness, occurred in 2 women after starting paroxetine for panic disorder. In both cases they were well rested, the frequency was greatest in the morning, and the yawning completely resolved with a dose reduction or discontinuation of paroxetine. In the first case, a 21-year-old woman experienced excessive yawning, despite adequate sleep, 1 day after starting paroxetine 10 mg/day. The frequency of yawning decreased when the dose was reduced to 5 mg/day and completely resolved when paroxetine was discontinued. In the second case, a 43-year-old woman started on 10 mg/day and the dose was increased 2 weeks later to 20 mg/day. Within 1 day of increasing the dose the excessive yawning commenced. After 7 days, the dose was reduced to 10 mg/day and the yawning completely resolved (Harada, 2006)

3.3.16 Other

Paroxetine

Paroxetine Hydrochloride

3.3.16.A Paroxetine

3.3.16.A.1 Drug withdrawal

See Drug Consult reference: WITHDRAWAL SYNDROME OF SELECTIVE SEROTONIN REUPTAKE INHIBITORS

3.3.16.B Paroxetine Hydrochloride

Serotonin syndrome

Withdrawal sign or symptom

3.3.16.B.1 Serotonin syndrome

a) Summary

1) Serotonin syndrome, including life-threatening cases, or neuroleptic malignant syndrome (NMS)-like reactions have been reported with the use of paroxetine alone. Signs and symptoms of serotonin syndrome include mental status changes (eg, agitation, hallucination, coma), autonomic instability (eg, tachycardia, labile blood pressure, hyperthermia), neuromuscular aberrations (eg, hyperreflexia, incoordination) and/or gastrointestinal symptoms (eg, nausea, vomiting, diarrhea). Severe serotonin syndrome can resemble NMS with symptoms including hyperthermia, muscle rigidity, autonomic instability with possible rapid fluctuation of vital signs, and mental status changes. Serotonin syndrome occurs most commonly with the concomitant use of serotonergic drugs, including triptans, with drugs that impair metabolism of serotonin, including MAOIs, or with antipsychotics or other dopamine antagonists (Prod Info PEXEVA(R) oral tablets, 2009; Prod Info PAXIL(R) oral tablets, suspension, 2009; Prod Info PAXIL CR(R) controlled-release oral tablets, 2009). Serotonin syndrome is produced most often following the concurrent use of paroxetine (an SSRI) with another drug that enhances central nervous system serotonin activity. This syndrome is characterized by alterations in cognition, behavior, autonomic nervous system function, and neuromuscular activity. The difference between serotonin syndrome and the occurrence of adverse effects due to paroxetine alone is the clustering of the signs and symptoms, their severity, and duration (Lane & Baldwin, 1997). Some drugs that may enhance central nervous system serotonin activity include: moclobemide, selegiline, tramadol, nefazodone, trazodone, dextromethorphan, phentermine, fenfluramine, lithium, tryptophan, and irreversible monoamine oxidase inhibitors. Any of these drugs taken in combination with paroxetine may result in serotonin syndrome (Mitchell, 1997).

b) LITERATURE REPORTS

1) A patient with psychotic depression who received concomitant risperidone and paroxetine developed serotonin syndrome. Within 2 hours of increasing the dosage of paroxetine to 40 mg per day and risperidone to 6 mg per day, the patient developed ataxia, tremor, shivering, and bilateral jerking movements. He presented to the emergency department and was admitted to the hospital; he was difficult to arouse and had a depressed mood with prominent psychomotor agitation. He reported auditory hallucinations; he was oriented only to year and location. On neurologic examination, he was hyperreflexic and had involuntary jerking movements but had no muscular rigidity. Within 2 days of stopping both medicines, his sensorium was clear. After appropriate laboratory and diagnostic tests for neuromuscular malignant syndrome, recurrent psychotic depression, and drug overdose, the authors believed this case represented serotonin syndrome and was due to the combination of risperidone and paroxetine. The patient responded well to the combination of nortriptyline, haloperidol, and diphenhydramine and had no adverse effects (Hamilton & Malone, 2000a).

2) A 51-year-old woman with bipolar affective disorder developed a serotonin syndrome 2 days after a 6-month course of nefazodone was stopped and 1 day after paroxetine 20 mg was started. The patient became agitated and incoherent; family members found her unresponsive with shaking movements of her arms and legs. Upon admission to the hospital, the patient was in a coma and required mechanical ventilation; her temperature rose to 102.2 degrees F; muscle rigidity was present with an elevated creatine kinase value of 20,520 units/L. Treatment consisted of a cooling blanket, sedation with propofol up to 1.5 mg/kg/hour, and dantrolene 1.5 mg/kg. Symptoms resolved, and she was extubated on day 3. Medications started 1 day before this reaction included paroxetine 20 mg daily, valproic acid 250 mg three times a day, and zopiclone 7.5 mg daily, a short-acting sedative. Rechallenge 7 days after stopping nefazodone with paroxetine 20 mg daily did NOT result in recurrence of symptoms (John et al, 1997b).

3) A 29-year-old woman developed agitation, difficulty concentrating, hyperreflexia, tremor, choreiform movements, diaphoresis, shivering, and loose stools 24 hours after paroxetine 20 mg/day was added to her regimen of trazodone 50 mg at night (Reeves & Bullen, 1995b).

4) A 51-year-old man taking diltiazem, nitroglycerin, ticlopidine, piroxicam, ranitidine, diazepam

and paroxetine developed serotonin syndrome two days after beginning a cold medication containing acetaminophen, doxylamine succinate, pseudoephedrine and dextromethorphan. Effects included hypertension, headache, confusion, tachycardia, tachypnea, shortness of breath, vomiting, increased muscle tone, rigidity, clonus, and a metabolic acidosis. Clinical presentation was felt to be due to serotonin syndrome which was most likely induced by the combination of paroxetine and dextromethorphan (Skop et al, 1994b).

3.3.16.B.2 Withdrawal sign or symptom

a) Summary

1) It is recommended that paroxetine dosage be reduced gradually when treatment is going to be discontinued. In some clinical trials paroxetine was decreased by 10 milligrams (mg) per day at weekly intervals. When a daily dose of 20 mg/day was reached, patients were continued on this dose for 1 week before treatment was stopped. If intolerable symptoms occur following a reduction in dose or upon discontinuation of treatment, then resuming the previously prescribed dose maybe be considered. Decreasing the dose at a more gradual rate is then recommended (Prod Info Paxil (R), 2002e); (Prod Info Paxil CR(TM), 2002).

2) A hyposerotonergic state has been suggested to explain selective serotonin reuptake inhibitor (SSRI) withdrawal symptoms. These symptoms typically occur two days after the last dose taken and continue for an average of 10 days. The symptoms are nonspecific and include dizziness, paresthesia, tremor, anxiety, nausea, and emesis (Stiskal et al, 2001; Price et al, 1996)

3) Sweating, dizziness, insomnia, headache, anxiety, fatigue, delirium tremor, confusion and sensory disturbance have been reported after abrupt withdrawal of paroxetine (Hayakawa et al, 2004; Anon, 1993; Zajecka et al, 1997). Children may experience withdrawal symptoms within a shorter time after abruptly stopping paroxetine due to their higher rate of drug metabolism (Diler et al, 2000). Vertigo, nausea, vomiting, diarrhea, fatigue and gait instability have been reported in patients whose paroxetine dose was tapered over 7 to 10 days (Barr et al, 1994). Other effects reported after paroxetine withdrawal include anorexia, nausea, vomiting, diarrhea, shaking chills, agitation, abdominal discomfort, and sensations like electric shocks (Frost & Lal, 1995; Phillips, 1995; Pyke, 1995).

b) LITERATURE REPORTS

1) ADULT

a) A 73-year-old woman developed delirium following the abrupt cessation of paroxetine therapy. The patient had been taking paroxetine for 2 months at a daily dose of 40 milligrams (mg) when she abruptly stopped the medication prior to undergoing left-side donor nephrectomy. Two hours following surgery, the patient suddenly developed symptoms of thirst and dizziness and then gradually exhibited symptoms of disorderly behavior. Etizolam (1 mg) and alprazolam (0.8 mg) were administered; however, the patient remained agitated and reported visual hallucinations. The woman was referred to a psychiatrist the next morning and was unable to follow verbal commands and was not fully oriented. Psychotic symptoms resolved on postoperative day 2 following the administration of tiapride hydrochloride (75 mg) and chlorpromazine (15 mg). While the authors do not attribute this reaction to the preoperative (diazepam, ranitidine) or anesthetic (thiopental, sevoflurane) medications, it is possible that these agents contributed to the patient's symptoms (Hayakawa et al, 2004).

2) PEDIATRIC

a) Twenty-four hours following the abrupt discontinuation of paroxetine (20 milligrams (mg) per day), a 9-year-old boy developed emesis, dizziness, drowsiness, headache, and fatigue. Paroxetine was restarted at the former dose and the patient's discontinuation symptoms resolved within 24 hours. An 11-year-old boy experienced discontinuation symptoms of headache, poor concentration, nausea, dizziness, drowsiness, and fatigue, 30 hours after stopping paroxetine 10 mg/day. Reinstitution of paroxetine at 10 mg/day resulted in resolution of withdrawal symptoms within 12 hours. A 10-year-old girl who was taking paroxetine 15 mg twice daily developed mild discontinuation symptoms 48 hours after stopping her morning dose. Once the paroxetine morning dose was restarted her withdrawal symptoms lessened in 12 hours and resolved completely within 48 hours (Diler & Avci, 2002)

b) Signs of withdrawal in a healthy, premature infant on day 3 after birth were attributed to the paroxetine (40 milligrams per day) taken by her mother before and throughout pregnancy. Finnegan scores (a behavior scale for neonatal withdrawal reactions) from day 1 to day 10 were 0, 0, 2, 2, 9, 9, 6, 6, 7, and 7. The baby was lethargic, irritable, hypertonic, and jittery. There were no signs of infection, and screenings for opiates were negative. Cerebral ultrasound and electroencephalogram were normal. The baby improved spontaneously, with a Finnegan score of 0 at day 13. Follow-up at 4.5 months showed normal neurological maturity (Nijhuis et al, 2001).

c) Paroxetine exposure in utero, with maternal doses ranging from 20 to 120 milligrams per day, has resulted in a neonatal withdrawal syndrome. Effects included jitteriness, vomiting, irritability, hypoglycemia, and necrotizing enterocolitis. It was speculated that paroxetine, which causes inhibition of muscarinic-type cholinergic receptors, when withdrawn may result in cholinergic rebound in neonates (Stiskal et al, 2001).

d) Some investigators have speculated that neonates actually experience serotonin

syndrome, due to time course and symptoms, as opposed to a neonatal paroxetine withdrawal syndrome Ibister et al 2001.

3.4 Teratogenicity/Effects in Pregnancy/Breastfeeding

A) Teratogenicity/Effects in Pregnancy

1) U.S. Food and Drug Administration's Pregnancy Category: Category D (Prod Info PAXIL(R) oral tablets, suspension, 2008) (All Trimesters)

a) There is positive evidence of human fetal risk, but the benefits from use in pregnant women may be acceptable despite the risk (e.g., if the drug is needed in a life-threatening situation or for a serious disease for which safer drugs cannot be used or are ineffective).

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

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

See Drug Consult reference: PREGNANCY RISK CATEGORIES

3) Crosses Placenta: Yes

4) Clinical Management

a) When used in the third trimester, the incidence of complications, primarily respiratory distress, was significantly higher when compared to women who took paroxetine in early pregnancy and women who took nonteratogenic medications (Costei et al, 2002). The use of SSRIs, including paroxetine, after 20 weeks of gestation has been associated with an increased risk of persistent pulmonary hypertension of the newborn (Chambers et al, 2006). A study of prospectively collected data suggests antenatal use of selective serotonin-reuptake inhibitor (SSRI) antidepressants is associated with QTc interval prolongation in exposed neonates (Dubnov-Raz et al, 2008). A significantly greater risk of congenital malformations were observed in infants exposed to paroxetine compared to other antidepressants (Cole et al, 2007). There was no significant association between the use of SSRIs in early pregnancy and the risks of birth defects, including congenital heart defects, according to a later population-based case-control study (Alwan et al, 2007). One study found that first trimester paroxetine exposure was associated with major congenital and cardiac malformations in newborns only at doses greater than 25 mg/day (Berard et al, 2007). There is also evidence that paroxetine use during pregnancy is associated with neonatal withdrawal syndrome and convulsions in the neonate (Sanz et al, 2005). The manufacturer recommends either discontinuing paroxetine therapy or switching to another antidepressant unless the benefits of paroxetine to the mother justify continuing treatment. For women intending to become pregnant or those already in their first trimester, paroxetine should be initiated only after other treatment options have been given thorough consideration (Prod Info PAXIL(R) oral tablets, suspension, 2008; Prod Info PAXIL CR(R) controlled-release oral tablets, 2008).

5) Literature Reports

a) A study of prospectively collected data suggests antenatal use of selective serotonin-reuptake inhibitor (SSRI) antidepressants is associated with QTc interval prolongation in exposed neonates. Between January 2000 and December 2005, researchers compared 52 neonates exposed to SSRI antidepressants (paroxetine (n=25), citalopram (n=13), fluoxetine (n=12), fluvoxamine (n=1), and venlafaxine (n=1)) in the immediate antenatal period to 52 matched neonates with no exposure. Prolonged QTc is defined as an interval of greater than 460 milliseconds (msec) (the widely used upper limit cited by authorities in both pediatric cardiology and neonatology). A pediatric cardiologist blinded to drug exposure, interpreted all electrocardiograms (ECGs) using standard statistical analyses. ECG recordings revealed markedly prolonged mean QTc intervals in exposed neonates compared to unexposed neonates (mean; 409 +/- 42 msec versus 392 +/- 29 msec, p=0.02). The mean uncorrected QT interval was 7.5% longer among exposed neonates (mean; 280 +/- 31 msec versus 261 +/- 25 msec, p less than 0.001). Ten percent (n=5) of exposed neonates had a notable increase in QTc interval prolongation (greater than 460 msec) compared to none of the unexposed neonates. The longest QTc interval observed was 543 msec (Dubnov-Raz et al, 2008).

b) Data from the case-controlled National Birth Defects Prevention Study (NBDPS), which included data from 13,714 infants born between 1997 and 2002, indicated that early maternal exposure (defined as treatment with any SSRI from 1 month before to 3 months after conception) to SSRIs was associated with anencephaly in 9 exposed infants out of 214 (adjusted odds ratio (OR), 2.4; 95% confidence interval (CI), 1.1 to 5.1; P=0.02), craniosynostosis in 24 exposed infants out of 432 (adjusted OR 2.5; 95% CI, 1.5 to 4.0; P less than 0.001), and omphalocele in 11 exposed infants out of 181 (adjusted OR 2.8; 95% CI, 1.3 to 5.7; P=0.005). However, early exposure did not significantly increase the risks of congenital heart defects or most other birth defects. The most commonly used SSRIs reported by control mothers were sertraline, fluoxetine, paroxetine, and citalopram (Alwan et al, 2007).

c) First-trimester paroxetine exposure is not associated with an increase in infant cardiovascular defects, according to an international retrospective epidemiological study. In unpublished studies, cardiovascular malformations were reported in 0.7% of 1174 infants exposed to paroxetine and in 0.7% of 1174 infants with no exposure to antidepressants or teratogenic agents (95% confidence interval (CI), 0.36 to 2.78). In an analysis of 5 published database studies including 2061 cases, the rate of cardiovascular malformations in paroxetine-exposed infants was 1.5%. When combined, the mean cardiovascular malformation rate in paroxetine-exposed infants was 1.2% (95% CI, 1.1 to 2.1) (Einarson et al, 2008).

d) Paroxetine doses above 25 mg/day are associated with major congenital and cardiac malformations in

infants exposed during the first trimester of pregnancy, according to a population-based registry analysis including 1403 women. Based on results from 2 nested case-control studies of 101 infants with major congenital malformations (including 24 with cardiac malformations), exposure to paroxetine (95% confidence interval (CI), 0.49 to 3.92) or other SSRIs (95% CI, 0.28 to 2.84) did not increase the risk of malformations compared to non-SSRI antidepressants when given at doses less than 25 mg/day. Adjusted analysis showed that infants exposed to paroxetine during the first trimester at doses greater than 25 mg/day had a 3-fold greater risk of major cardiac malformations (95% CI, 1 to 9.42) and more than 2-fold greater risk of major congenital malformations (95% CI, 1.19 to 4.17) (Berard et al, 2007).

e) Fetal exposure to paroxetine during the first trimester resulted in a higher incidence of malformations compared with exposure to other antidepressants, according to a population-based cohort study including 815 infants among 791 women exposed to paroxetine monotherapy, 1020 infants among 989 women exposed to paroxetine mono- or polytherapy, 4198 infants among 4072 women exposed to other antidepressant monotherapy, and 4936 infants among 4767 women exposed to other antidepressant mono- or polytherapy. A significantly increased risk of all congenital malformations and a nonsignificantly increased risk of cardiovascular malformations were observed in infants exposed to paroxetine compared with other antidepressants in monotherapy (89% and 46%, respectively) and mono- or polytherapy groups (76% and 68%, respectively) (Cole et al, 2007).

f) A case-control study found that the use of SSRIs after 20 weeks of gestation was associated with an increased risk of persistent pulmonary hypertension of the newborn (PPHN). Fluoxetine, paroxetine, and sertraline were the specific SSRIs studied to carry this increased risk. A total of 377 women who had infants with PPHN were matched to 836 women and their infants. Assessment of exposure was determined by telephone interview within 6 months of birth. After adjusting for other covariates, SSRI use after 20 weeks of gestation was associated 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 during the pregnancy. SSRI use before 20 weeks of gestation and non-SSRI antidepressants use at any gestation time was not associated with increased risk of PPHN development. The incidence of PPHN in the general population is about 0.1 to 0.2%. According to this study, infants exposed to SSRIs after 20 weeks of gestation have a PPHN incidence of 0.6 to 1.2% (Chambers et al, 2006).

g) A population-based study of 1782 pregnant women exposed to SSRIs found no increased risk of adverse perinatal outcome except for treatment in the neonatal intensive or special care unit, particularly with third trimester exposure. Using 1996 to 2001 data derived from a government project involving 4 birth or medication registries in Finland, women who had at least one purchase (a 3-months supply) of an SSRI during the period of one month before pregnancy and the day pregnancy ended were compared to 1782 controls with no reimbursed drug purchases during the same peripartum period. The mean age of both cohorts was 30 years (+/-7). There were more than twice as many smokers and 6 times as many pregnancies induced by artificial reproductive techniques in the SSRI group compared to controls (p less than 0.001), and mean length of gestation and birth weight were lower (p less than 0.001) in the SSRI group. Malformations, however, were not more common in the SSRI group (p=0.4). Purchases of SSRIs (citalopram, fluoxetine, paroxetine, sertraline and fluvoxamine) were more common in the first trimester than later in pregnancy, with 152 women purchasing paroxetine during the first trimester, 54 during the second trimester, 64 during the third, and 28 throughout pregnancy. When compared to first trimester exposure, treatment in a special or intensive care unit was more common for the infants exposed during the third trimester (11.2% and 15.7%, respectively; p=0.009). Even after adjusting for confounding variables, this difference remained statistically significant (OR 1.6; 95% CI 1.1 to 2.2) (Malm et al, 2005).

h) Data recorded through the Swedish national registry included infants of 6896 women treated with antidepressants in early pregnancy, 5123 of whom were exposed to SSRIs. Paroxetine exposure occurred in 815, and these infants had an increased risk of cardiovascular malformations (primarily ventral and atrial septal defects) compared to the aggregate registry population (OR 1.8; 95% CI: 1.1 to 2.8). The corresponding rate of cardiovascular complications in these infants was 2%, compared to 1% in the aggregate registry population. Using data supplied by the US United Healthcare, a separate retrospective study evaluated 5956 infants of women dispensed paroxetine (n=815) or other antidepressants during the first trimester. Compared to other antidepressants, the data trended towards an increased risk for cardiovascular malformations for paroxetine (OR 1.5; 95% CI: 0.8 to 2.9). Following first trimester dispensing, the prevalence of cardiovascular malformations was 1.5% for paroxetine (9 of 12 infants with ventral septal defects) compared to 1% for the other antidepressants. Compared to other antidepressants, there appeared to be an increased risk of overall major congenital malformations, including cardiovascular defects, for paroxetine (OR 1.8; 95% CI: 1.2 to 2.8). With first trimester exposure, the prevalence of all congenital malformations was 4% for paroxetine and 2% for other antidepressants (Prod Info PAXIL(R) oral tablets, suspension, 2008; Prod Info PAXIL CR(R) controlled-release oral tablets, 2008).

i) Third-trimester paroxetine exposure is associated with neonatal distress, according to a prospective, controlled cohort study including 55 neonates. The pregnant women studied were taking between 10 mg and 60 mg of paroxetine daily. Data showed that 12 of 55 neonates exposed to paroxetine in late gestation had complications necessitating intensive treatment and prolonged hospitalization. A comparison group of 27 women treated with paroxetine (10 mg to 40 mg/day) in their first or second trimester and 27 women exposed to nonteratogenic agents (eg, acetaminophen or dental x-rays) were matched for maternal age, gravity, parity, social drug use, and nonteratogenic drug use. Of the 12 infants experiencing complications, 9 had respiratory distress, 2 had hypoglycemia, and 1 had jaundice. Only 3 infants in the comparison group experienced complications, 2 with respiratory distress and 1 with jaundice (Costei et al, 2002).

B) Breastfeeding

1) American Academy of Pediatrics Rating: Drugs for which the effect on nursing infants is unknown but may be of concern. (American Academy of Pediatrics Committee on Drugs, 2001)

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 risk to the infant when used during breastfeeding.

3) Clinical Management

a) Paroxetine is excreted into the breast milk of lactating women. Case reports suggest that the dose available to the infant through breast milk may be low and not of clinical significance (Hendrick et al, 2001; Begg et al, 1999; Ohman et al, 1999). However, the long-term effects on neuro behavior and development from exposure to paroxetine during a period of rapid CNS development have not been evaluated.

4) Literature Reports

a) Paroxetine is excreted in human milk. Caution is advised when administering paroxetine to a nursing woman (Prod Info PAXIL(R) oral tablets, suspension, 2008; Prod Info PAXIL CR(R) controlled-release oral tablets, 2008).

b) From a study of 75 lactating women exposed to antidepressants, 108 samples of paroxetine in breast milk were obtained and analyzed with a new assay system for determining antidepressant concentrations in breast milk. Concentrations of paroxetine ranged from less than 5 to 101 nanograms/mL; the assay system had a 2 nanograms/mL limit of detection (LOD) for paroxetine. The assay system used in this study is reported to be more accurate than existing systems because it minimizes the intra- and inter-sample variability in the composition of human breast milk (Hostetter et al, 2004).

c) Normal infant weight gain was reported in a study of 78 breast-feeding mothers treated with venlafaxine or SSRIs, 15 of whom took paroxetine doses of approximately 20 mg/day. The mean weight gain reported with paroxetine did not significantly differ from that of other SSRIs used in the study (data not reported) or from normative growth data. Infants of mothers who relapsed to a major depressive episode, defined as an episode lasting 2 months or more despite antidepressant treatment, weighed significantly less at 6 months (p=0.002) when compared to infants of mothers who relapsed to a brief episode and to infants of mothers who did not relapse to depression. The absence of a control group and the maternal use of other medications (56 women used antidepressants during pregnancy and 6 women took psychotropics such as benzodiazepines or tricyclic antidepressants during the study) potentially confound the results of this study (Hendrick et al, 2003).

d) A study of 16 breast-feeding women taking paroxetine at a mean dose of 23.1 mg/day reported paroxetine concentrations ranging from 2 to 101 nanograms/mL in 108 breast milk samples. Samples were obtained from both fore and hind milk for all women. Hind milk had greater paroxetine concentrations than fore milk. A sub-sample of 8 women who gave more than 3 samples over 24 hours was used in an attempt to determine the time course of paroxetine excretion into milk. No time course relationship was observed, although a relationship between maternal daily paroxetine dose and breast milk peak and trough paroxetine concentrations was evident. Mothers did not report any observable adverse effects on the infants (Stowe et al, 2000).

e) Using data from 2 studies, the mean infant dose of paroxetine was 1.13% and 1.25% of the weight adjusted maternal dose. Based on the 10% rule (infant concentrations less than 10% of maternal concentrations), data from these studies suggest that paroxetine may be safe during breast-feeding. In the first study (n=6), milk and plasma concentrations were measured during a 24-hour period; whereas, in the second study (n=4), single prefeed and postfeed milk and plasma concentrations were obtained. Plasma paroxetine concentrations were undetectable in 7 of 8 infants, and 1 infant had a concentration below the level of quantification. Blood samples were not allowed in the remaining infants. No adverse behavioral or physical effects were noted in the infants (Begg et al, 1999).

f) In a study of 7 breast-feeding women, the mean relative dose to the infant ranged from 0.7% to 2.9% of the weight-adjusted maternal dose. In 6 women, serum and breast milk samples were obtained immediately before the morning dose and 4 to 7 hours after the morning dose (time corresponding to the maximum concentration). In the remaining woman, 8 serum and milk samples were drawn. The milk and serum paroxetine concentrations ranged from 18 to 92 nanograms/mL and 17 to 164 nanograms/mL, respectively. No samples were obtained from the infants although there were no changes in infant behavior or adverse effects (Ohman et al, 1999).

g) One study determined that paroxetine was not detectable in infant serum following exposure through breast milk. Samples were obtained from 16 infants whose mothers were treated with 5 mg to 30 mg per day of paroxetine. The infants were 2 to 26 weeks of age at the time of sampling and weighed an average of 5.5 kg (Hendrick et al, 2001). Similarly, paroxetine was not detectable in the serum of 6 nursing infants whose mothers were treated with the drug. There was no evidence of adverse effects in the infants as reported by the mothers. The authors suggest that breast-feeding should generally not be discouraged in mothers treated with serotonin reuptake inhibitor antidepressants (Berle et al, 2004).

3.5 Drug Interactions

Drug-Drug Combinations

Drug-Food Combinations

3.5.1 Drug-Drug Combinations

Abciximab

Aceclofenac

Acemetacin

Acenocoumarol

Alclofenac

Almotriptan

Amitriptyline

Amoxapine

Anagrelide

Ancrod

Anisindione

Antithrombin III Human

Aprepitant

Ardeparin

Aripiprazole

Aspirin

Atomoxetine

Benoxaprofen

Bivalirudin

Bromfenac

Bufexamac

Bupropion

Cannabis

Carprofen

Celecoxib

Certoparin

Cilostazol

Cimetidine

Clarithromycin

Clomipramine

Clonixin

Clopidogrel

Clorgyline

Clozapine

Cyproheptadine

Dalteparin

Danaparoid

Darunavir

Defibrotide

Dehydroepiandrosterone

Dermatan Sulfate

Desipramine

Desirudin

Desvenlafaxine

Dexfenfluramine

Dexketoprofen

Dextromethorphan

Diclofenac

Dicumarol

Diflunisal

Dipyridamole

Dipyrone

Dothiepin

Doxepin

Droperidol

Droxicam

Duloxetine

Eletriptan

Encainide

Enoxaparin

Epoprostenol

Eptifibatide

Etodolac

Etofenamate

Etoricoxib

Felbinac

Fenbufen

Fenfluramine

Fenoprofen

Fentiazac

Flecainide

Floctafenine

Flufenamic Acid

Fluoxetine

Fluphenazine

Flurbiprofen

Fondaparinux

Fosamprenavir

Fosaprepitant

Fosphenytoin

Frovatriptan

Furazolidone

Galantamine

Ginkgo

Heparin

Hydroxytryptophan

Ibuprofen

Iloperidone

Iloprost

Imipramine

Indomethacin

Indoprofen

Iproniazid

Isocarboxazid

Isoxicam

Ketoprofen

Ketorolac

Lamifiban

Lexipafant

Linezolid

Lithium

Lofepramine

Lornoxicam

Meclofenamate

Mefenamic Acid

Meloxicam

Methylphenidate

Metoprolol

Milnacipran

Moclobemide

Morniflumate

Nabumetone

Nadroparin

Naproxen

Naratriptan

Nebivolol

Nefazodone

Nialamide

Niflumic Acid

Nimesulide

Nortriptyline

Oxaprozin

Paliperidone

Parecoxib

Pargyline

Parnaparin

Pentosan Polysulfate Sodium

Perhexiline

Perphenazine

Phenelzine

Phenindione

Phenobarbital

Phenprocoumon

Phenylbutazone

Phenytoin

Pimozide

Pirazolac

Piroxicam

Pirprofen

Procarbazine

Procyclidine

Propafenone

Propyphenazone

Proquazone

Protriptyline

Quinidine

Ranolazine

Rasagiline

Reviparin

Risperidone

Ritonavir

Rizatriptan

Rofecoxib

Selegiline

Sibrafiban

Sibutramine

St John's Wort

Sulfinpyrazone

Sulindac

Sulodexide

Sumatriptan

Suprofen

Tamoxifen

Tapentadol

Tenidap

Tenoxicam

Tetrabenazine

Theophylline

Thioridazine

Tiaprofenic Acid

Ticlopidine

Tinzaparin

Tipranavir

Tirofiban

Tolmetin

Toloxatone

Tramadol

Tranylcypromine

Trazodone

Trimipramine

Tryptophan

Valdecoxib

Warfarin

Xemilofiban

Zolmitriptan

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 cohort studies have shown that the combined use of SSRIs and antiplatelet agents has been associated with an increased risk of bleeding. Bleeding events reported have included epistaxis, ecchymosis, hematoma, petechiae, and life-threatening hemorrhages (Prod Info PAXIL(R) oral 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 signs of increased bleeding (Prod Info PAXIL(R) oral tablets, suspension, 2008; Prod Info 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 cohort studies have shown that the combined use of SSRIs and NSAIDs has been associated with an increased risk of bleeding. Bleeding events have included epistaxis, ecchymosis, hematoma, petechiae, and life-threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension, 2008) (Prod Info Lexapro(TM),

2003; Dalton et al, 2003a; Prod Info CELEXA (R) oral tablet, solution, 2005).
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 increased bleeding.
7) Probable Mechanism: unknown
8) Literature Reports
a) SSRIs increase the risk of upper gastrointestinal bleeding and this effect is potentiated by concurrent use of NSAIDs or low-dose aspirin. Hospitalizations for upper gastrointestinal bleeding were searched among 26,005 users of antidepressant medications and compared with the number of hospitalizations in those patients who did not receive prescriptions for antidepressants. The amount of upper GI bleeding episodes was 3.6 times more than expected (95% confidence interval, 2.7 to 4.7). Combined use of an SSRI and NSAIDs or low-dose aspirin increased the risk to 12.2 (95% confidence interval, 7.1 to 19.5) and 5.2 (95% confidence interval, 3.2 to 8), respectively. The findings of this study demonstrate an increased risk of upper GI bleeding during the use of SSRIs. Combined use of SSRIs and NSAIDs or low-dose aspirin increased the risk even further (Dalton et al, 2003).
b) Coadministration of ketorolac with psychoactive drugs (such as fluoxetine) has been associated with hallucinations in some patients (Prod Info TORADOL(R) oral tablets, 2007).

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 cohort studies have shown that the combined use of SSRIs and NSAIDs has been associated with an increased risk of bleeding. Bleeding events have included epistaxis, ecchymosis, hematoma, petechiae, and life-threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension, 2008) (Prod Info Lexapro(TM), 2003; Dalton et al, 2003a; Prod Info CELEXA (R) oral tablet, solution, 2005).
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 increased bleeding.
7) Probable Mechanism: unknown
8) Literature Reports
a) SSRIs increase the risk of upper gastrointestinal bleeding and this effect is potentiated by concurrent use of NSAIDs or low-dose aspirin. Hospitalizations for upper gastrointestinal bleeding were searched among 26,005 users of antidepressant medications and compared with the number of hospitalizations in those patients who did not receive prescriptions for antidepressants. The amount of upper GI bleeding episodes was 3.6 times more than expected (95% confidence interval, 2.7 to 4.7). Combined use of an SSRI and NSAIDs or low-dose aspirin increased the risk to 12.2 (95% confidence interval, 7.1 to 19.5) and 5.2 (95% confidence interval, 3.2 to 8), respectively. The findings of this study demonstrate an increased risk of upper GI bleeding during the use of SSRIs. Combined use of SSRIs and NSAIDs or low-dose aspirin increased the risk even further (Dalton et al, 2003).
b) Coadministration of ketorolac with psychoactive drugs (such as fluoxetine) has been associated with hallucinations in some patients (Prod Info TORADOL(R) oral tablets, 2007).

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 cohort studies have shown that the combined use of SSRIs and anticoagulants has been associated with an increased risk of bleeding (Wallerstedt et al, 2009; Schalekamp et al, 2008; Prod Info PAXIL(R) oral tablets, suspension, 2008). Bleeding events reported have included epistaxis, ecchymosis, hematoma, petechiae, and life-threatening hemorrhages. Altered anticoagulant effects (including increased bleeding) have been reported with the coadministration of SSRIs with warfarin (Schalekamp et al, 2008; Prod Info PAXIL(R) oral tablets, suspension, 2008).
3) Severity: major
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: When paroxetine and an anticoagulant are given concurrently, monitor patients for signs of increased bleeding. Patients who are taking warfarin should be monitored closely for altered anticoagulant effects, including increased bleeding, when paroxetine therapy is initiated or discontinued (Prod Info PAXIL(R) oral tablets, suspension, 2008).
7) Probable Mechanism: unknown
8) Literature Reports
a) According to a retrospective cohort study (n=234), there was an increased risk of clinically relevant bleeding (hospital admission due to bleeding) in patients receiving warfarin for atrial fibrillation during concomitant SSRI therapy or within 2 weeks following SSRI therapy termination. Patients with a mean age of 72 +/- 7 years receiving warfarin plus SSRI (n=117) were matched with randomly selected

patients who received warfarin only (n=117). SSRI included fluoxetine, citalopram, paroxetine, sertraline, fluvoxamine, or escitalopram. Nine patients experienced 11 bleeding episodes during 213.9 treatment years in the warfarin plus SSRI group, and 10 patients experienced 14 bleedings during 586.4 treatment years in the warfarin-only group. The corresponding total incidences of bleedings were 51.4 and 23.9 per 1000 treatment years, respectively. The hazard ratio for first bleedings during treatment with warfarin plus SSRI was 3.49 (95% CI; 1.37 to 8.91, p=0.009) compared with warfarin only. The SSRI implicated in patients experiencing bleeding at the time of concomitant administration were sertraline or citalopram. The addition of an SSRI was not associated with a change in warfarin dose or INR (p=0.48 and p=0.31 respectively). The results of the study may be limited by earlier bleeding events, unknown patient adherence, and exclusion of clopidogrel, dipyridamol, corticosteroids and anticoagulants other than warfarin in the model (Wallerstedt et al, 2009).

b) A population-based, case-controlled study of new coumarin users (acenocoumarol and phenprocoumon) with concomitant selective serotonin reuptake inhibitors (SSRIs) resulted in an increased risk of hospitalization due to nongastrointestinal bleeding. Using national pharmacy and hospitalization records, Netherlands researchers identified 1848 cases that were admitted for abnormal bleeding and compared them with 5818 control subjects also taking coumarins. Median duration of treatment in patients was 220 days (range, 1 to 4690 days). Patients on SSRIs showed greater risk for hospitalization for nongastrointestinal bleeding (adjusted odds ratio (OR) 1.7, 95% confidence interval (CI), 1.1 to 2.5), however, the rate of gastrointestinal bleeding (adjusted OR 0.8, 95% CI, 0.4 to 1.5) was not significantly different (Schalekamp et al, 2008).

c) Preliminary data suggest that there may be a pharmacodynamic interaction (that causes an increased bleeding diathesis with unaltered prothrombin time) between paroxetine and warfarin. The concomitant use of paroxetine and warfarin should be undertaken with caution (Prod Info PAXIL(R) oral tablets, suspension, 2008).

d) In a multiple-dose study, several days of combined therapy with warfarin and paroxetine resulted in mild but clinically significant bleeding in 5 of 27 subjects. This effect occurred in the absence of a significant enhancement in warfarin-induced hypoprothrombinemia or changes in either paroxetine or warfarin disposition (Bannister et al, 1989b).

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 cohort studies have shown that the combined use of SSRIs and NSAIDs has been associated with an increased risk of bleeding. Bleeding events have included epistaxis, ecchymosis, hematoma, petechiae, and life-threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension, 2008) (Prod Info Lexapro(TM), 2003; Dalton et al, 2003a; Prod Info CELEXA (R) oral tablet, solution, 2005).

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 increased bleeding.

7) Probable Mechanism: unknown

8) Literature Reports

a) SSRIs increase the risk of upper gastrointestinal bleeding and this effect is potentiated by concurrent use of NSAIDs or low-dose aspirin. Hospitalizations for upper gastrointestinal bleeding were searched among 26,005 users of antidepressant medications and compared with the number of hospitalizations in those patients who did not receive prescriptions for antidepressants. The amount of upper GI bleeding episodes was 3.6 times more than expected (95% confidence interval, 2.7 to 4.7). Combined use of an SSRI and NSAIDs or low-dose aspirin increased the risk to 12.2 (95% confidence interval, 7.1 to 19.5) and 5.2 (95% confidence interval, 3.2 to 8), respectively. The findings of this study demonstrate an increased risk of upper GI bleeding during the use of SSRIs. Combined use of SSRIs and NSAIDs or low-dose aspirin increased the risk even further (Dalton et al, 2003).

b) Coadministration of ketorolac with psychoactive drugs (such as fluoxetine) has been associated with hallucinations in some patients (Prod Info TORADOL(R) oral tablets, 2007).

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 reported to cause weakness, hyperreflexia, and incoordination (Prod Info Axert(TM), 2001). Concurrent use of a triptan and an SSRI may result in serotonin syndrome which may be life-threatening. Symptoms of serotonin syndrome may include restlessness, hallucinations, loss of coordination, fast heart beat, rapid changes in blood pressure, increased body temperature, overreactive reflexes, nausea, vomiting, and diarrhea. Clinicians should be aware that triptans may be commonly used intermittently and that either the triptan or the SSRI may be prescribed by a different physician. Discuss the risks of serotonin syndrome with patients who are prescribed this combination and monitor them closely for symptoms of serotonin syndrome (US Food and Drug Administration, 2006).

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-threatening condition called serotonin syndrome. Be aware that triptans may be commonly used intermittently and that either the triptan or the SSRI may be prescribed by a different physician. If these agents are used together, discuss the risks of serotonin syndrome with the patient and monitor closely for symptoms of serotonin syndrome (restlessness, hyperthermia, hyperreflexia, incoordination).
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 modest effect on almotriptan maximum plasma concentration (Cmax). Other almotriptan pharmacokinetics are not significantly affected. A randomized, open-label, two-way crossover study involving 14 healthy volunteers has been conducted. Subjects received each of the following treatments with a minimum 3-week washout between periods: (1) three 20 mg fluoxetine capsules on day 1 to 8 and one dose almotriptan 12.5 mg on day 8, (2) one dose of almotriptan 12.5 mg on day 8 with no treatment on days 1 through 7. Peak almotriptan concentrations were 18% higher following concomitant administration of fluoxetine than after almotriptan administration alone. This difference was statistically significant (p equal 0.023). Mean almotriptan area under the concentration-time curve (AUC) and oral clearance were borderline statistically different between treatment groups. Mean half-life was not statistically different between the treatment groups. During fluoxetine coadministration, Tmax was shorter, suggesting that the absorption rate of almotriptan may have been increased by fluoxetine. The author concludes that based on the results of this study and the lack of effect of fluoxetine on almotriptan pharmacokinetics, almotriptan and fluoxetine can be safely used concomitantly in migraine management (Fleishaker et al, 2001).

3.5.1.G Amitriptyline

1) Interaction Effect: amitriptyline toxicity (dry mouth, sedation, urinary retention)
2) Summary: Paroxetine coadministered with desipramine or imipramine produced higher serum concentrations of the tricyclic antidepressant (TCA) in some patients (Brosen et al, 1993r). Although not reported specifically with amitriptyline, a similar interaction could be expected to occur. Paroxetine's effect on tricyclic antidepressants may resemble that of fluoxetine (another selective serotonin reuptake inhibitor), which is known to inhibit TCA metabolism (Aranow et al, 1989g; Vaughan, 1988g; Goodnick, 1989g). With coadministration, monitor patients for amitriptyline toxicity (Prod Info Paxil(R), 2002c). Amitriptyline doses may need to be reduced.
3) Severity: moderate
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: When paroxetine is coadministered with amitriptyline, monitor patients for signs and symptoms of amitriptyline toxicity (dry mouth, sedation, urinary retention, blurred vision). Amitriptyline doses may need to be reduced.
7) Probable Mechanism: decreased cytochrome P450 2D6-mediated amitriptyline metabolism
8) Literature Reports
a) The effect of paroxetine on desipramine metabolism was studied in 9 extensive metabolizers (EM) and 8 poor metabolizers (PM) of desipramine (Brosen et al, 1993q). Subjects took a single oral dose of desipramine before starting paroxetine and a second dose after 11 days of paroxetine use. After the addition of paroxetine, extensive metabolizers experienced a 5-fold decrease in clearance of desipramine, indicating that paroxetine inhibits oxidation reactions catalyzed by CYP2D6. Poor metabolizers had a slight increase in clearance of desipramine with paroxetine. With concurrent administration of desipramine and paroxetine, interaction of the two drugs may result in a need for dosage adjustments, especially in extensive metabolizers of desipramine.

3.5.1.H Amoxapine

1) Interaction Effect: amoxapine toxicity (dry mouth, sedation, urinary retention)
2) Summary: Paroxetine coadministered with desipramine or imipramine produced higher serum concentrations of the tricyclic antidepressant (TCA) in some patients (Hartter et al, 1994b; Brosen et al, 1993g). Although not reported specifically with amoxapine, a similar interaction could be expected to occur. Paroxetine's effect on TCAs may resemble that of fluoxetine (another selective serotonin reuptake inhibitor), which is known to inhibit TCA metabolism (Aranow et al, 1989b; Vaughan, 1988b; Goodnick, 1989b). With coadministration, monitor patients for amoxapine toxicity. Amoxapine doses may need to be reduced (Prod Info Paxil CR(TM), 2003f).
3) Severity: moderate
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: When paroxetine is coadministered with amoxapine, monitor patients for signs and symptoms of amoxapine toxicity (dry mouth, sedation, urinary retention, blurred vision). Amoxapine doses may need to be reduced.
7) Probable Mechanism: decreased amoxapine metabolism
8) Literature Reports
a) The effect of paroxetine on desipramine metabolism was studied in 9 extensive metabolizers (EM)

and 8 poor metabolizers (PM) of desipramine (Brosen et al, 1993f). Subjects took a single oral dose of desipramine before starting paroxetine and a second dose after 11 days of paroxetine use. After the addition of paroxetine, EMs experienced a 5-fold decrease in clearance of desipramine, indicating that paroxetine inhibits oxidation reactions catalyzed by CYP2D6. PMs had a slight increase in clearance of desipramine with paroxetine. With concurrent administration of desipramine and paroxetine, interaction of the two drugs may result in a need for dosage adjustments, especially in extensive metabolizers of desipramine.

3.5.1.I Anagrelide

1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs and antiplatelet agents has been associated with an increased risk of bleeding. Bleeding events reported have included epistaxis, ecchymosis, hematoma, petechiae, and life-threatening hemorrhages (Prod Info PAXIL(R) oral 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 signs of increased bleeding (Prod Info PAXIL(R) oral tablets, suspension, 2008; Prod Info PROZAC(R) oral capsules, delayed-release capsules, solution, 2008)
7) Probable Mechanism: unknown

3.5.1.J Ancrod

1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs and anticoagulants has been associated with an increased risk of bleeding (Wallerstedt et al, 2009; Schalekamp et al, 2008; Prod Info PAXIL(R) oral tablets, suspension, 2008). Bleeding events reported have included epistaxis, ecchymosis, hematoma, petechiae, and life-threatening hemorrhages. Altered anticoagulant effects (including increased bleeding) have been reported with the coadministration of SSRIs with warfarin (Schalekamp et al, 2008; Prod Info PAXIL(R) oral tablets, suspension, 2008).
3) Severity: major
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: When paroxetine and an anticoagulant are given concurrently, monitor patients for signs of increased bleeding. Patients who are taking warfarin should be monitored closely for altered anticoagulant effects, including increased bleeding, when paroxetine therapy is initiated or discontinued (Prod Info PAXIL(R) oral tablets, suspension, 2008).
7) Probable Mechanism: unknown
8) Literature Reports

a) According to a retrospective cohort study (n=234), there was an increased risk of clinically relevant bleeding (hospital admission due to bleeding) in patients receiving warfarin for atrial fibrillation during concomitant SSRI therapy or within 2 weeks following SSRI therapy termination. Patients with a mean age of 72 +/- 7 years receiving warfarin plus SSRI (n=117) were matched with randomly selected patients who received warfarin only (n=117). SSRI included fluoxetine, citalopram, paroxetine, sertraline, fluvoxamine, or escitalopram. Nine patients experienced 11 bleeding episodes during 213.9 treatment years in the warfarin plus SSRI group, and 10 patients experienced 14 bleedings during 586.4 treatment years in the warfarin-only group. The corresponding total incidences of bleedings were 51.4 and 23.9 per 1000 treatment years, respectively. The hazard ratio for first bleedings during treatment with warfarin plus SSRI was 3.49 (95% CI; 1.37 to 8.91, p=0.009) compared with warfarin only. The SSRI implicated in patients experiencing bleeding at the time of concomitant administration were sertraline or citalopram. The addition of an SSRI was not associated with a change in warfarin dose or INR (p=0.48 and p=0.31 respectively). The results of the study may be limited by earlier bleeding events, unknown patient adherence, and exclusion of clopidogrel, dipyridamol, corticosteroids and anticoagulants other than warfarin in the model (Wallerstedt et al, 2009).

b) A population-based, case-controlled study of new coumarin users (acenocoumarol and phenprocoumon) with concomitant selective serotonin reuptake inhibitors (SSRIs) resulted in an increased risk of hospitalization due to nongastrointestinal bleeding. Using national pharmacy and hospitalization records, Netherlands researchers identified 1848 cases that were admitted for abnormal bleeding and compared them with 5818 control subjects also taking coumarins. Median duration of treatment in patients was 220 days (range, 1 to 4690 days). Patients on SSRIs showed greater risk for hospitalization for nongastrointestinal bleeding (adjusted odds ratio (OR) 1.7, 95% confidence interval (CI), 1.1 to 2.5), however, the rate of gastrointestinal bleeding (adjusted OR 0.8, 95% CI, 0.4 to 1.5) was not significantly different (Schalekamp et al, 2008).

c) Preliminary data suggest that there may be a pharmacodynamic interaction (that causes an increased bleeding diathesis with unaltered prothrombin time) between paroxetine and warfarin. The concomitant use of paroxetine and warfarin should be undertaken with caution (Prod Info PAXIL(R) oral

tablets, suspension, 2008).

d) In a multiple-dose study, several days of combined therapy with warfarin and paroxetine resulted in mild but clinically significant bleeding in 5 of 27 subjects. This effect occurred in the absence of a significant enhancement in warfarin-induced hypoprothrombinemia or changes in either paroxetine or warfarin disposition (Bannister et al, 1989b).

3.5.1.K Anisindione

1) Interaction Effect: an increased risk of bleeding

2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs and anticoagulants has been associated with an increased risk of bleeding (Wallerstedt et al, 2009; Schalekamp et al, 2008; Prod Info PAXIL(R) oral tablets, suspension, 2008). Bleeding events reported have included epistaxis, ecchymosis, hematoma, petechiae, and life-threatening hemorrhages. Altered anticoagulant effects (including increased bleeding) have been reported with the coadministration of SSRIs with warfarin (Schalekamp et al, 2008; Prod Info PAXIL(R) oral tablets, suspension, 2008).

3) Severity: major

4) Onset: delayed

5) Substantiation: probable

6) Clinical Management: When paroxetine and an anticoagulant are given concurrently, monitor patients for signs of increased bleeding. Patients who are taking warfarin should be monitored closely for altered anticoagulant effects, including increased bleeding, when paroxetine therapy is initiated or discontinued (Prod Info PAXIL(R) oral tablets, suspension, 2008).

7) Probable Mechanism: unknown

8) Literature Reports

a) According to a retrospective cohort study (n=234), there was an increased risk of clinically relevant bleeding (hospital admission due to bleeding) in patients receiving warfarin for atrial fibrillation during concomitant SSRI therapy or within 2 weeks following SSRI therapy termination. Patients with a mean age of 72 +/- 7 years receiving warfarin plus SSRI (n=117) were matched with randomly selected patients who received warfarin only (n=117). SSRI included fluoxetine, citalopram, paroxetine, sertraline, fluvoxamine, or escitalopram. Nine patients experienced 11 bleeding episodes during 213.9 treatment years in the warfarin plus SSRI group, and 10 patients experienced 14 bleedings during 586.4 treatment years in the warfarin-only group. The corresponding total incidences of bleedings were 51.4 and 23.9 per 1000 treatment years, respectively. The hazard ratio for first bleedings during treatment with warfarin plus SSRI was 3.49 (95% CI; 1.37 to 8.91, p=0.009) compared with warfarin only. The SSRI implicated in patients experiencing bleeding at the time of concomitant administration were sertraline or citalopram. The addition of an SSRI was not associated with a change in warfarin dose or INR (p=0.48 and p=0.31 respectively). The results of the study may be limited by earlier bleeding events, unknown patient adherence, and exclusion of clopidogrel, dipyridamol, corticosteroids and anticoagulants other than warfarin in the model (Wallerstedt et al, 2009).

b) A population-based, case-controlled study of new coumarin users (acenocoumarol and phenprocoumon) with concomitant selective serotonin reuptake inhibitors (SSRIs) resulted in an increased risk of hospitalization due to nongastrointestinal bleeding. Using national pharmacy and hospitalization records, Netherlands researchers identified 1848 cases that were admitted for abnormal bleeding and compared them with 5818 control subjects also taking coumarins. Median duration of treatment in patients was 220 days (range, 1 to 4690 days). Patients on SSRIs showed greater risk for hospitalization for nongastrointestinal bleeding (adjusted odds ratio (OR) 1.7, 95% confidence interval (CI), 1.1 to 2.5), however, the rate of gastrointestinal bleeding (adjusted OR 0.8, 95% CI, 0.4 to 1.5) was not significantly different (Schalekamp et al, 2008).

c) Preliminary data suggest that there may be a pharmacodynamic interaction (that causes an increased bleeding diathesis with unaltered prothrombin time) between paroxetine and warfarin. The concomitant use of paroxetine and warfarin should be undertaken with caution (Prod Info PAXIL(R) oral tablets, suspension, 2008).

d) In a multiple-dose study, several days of combined therapy with warfarin and paroxetine resulted in mild but clinically significant bleeding in 5 of 27 subjects. This effect occurred in the absence of a significant enhancement in warfarin-induced hypoprothrombinemia or changes in either paroxetine or warfarin disposition (Bannister et al, 1989b).

3.5.1.L 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 cohort studies have shown that the combined use of SSRIs and anticoagulants has been associated with an increased risk of bleeding (Wallerstedt et al, 2009; Schalekamp et al, 2008; Prod Info PAXIL(R) oral tablets, suspension, 2008). Bleeding events reported have included epistaxis, ecchymosis, hematoma, petechiae, and life-threatening hemorrhages. Altered anticoagulant effects (including increased bleeding) have been reported with the coadministration of SSRIs with warfarin (Schalekamp et al, 2008; Prod Info PAXIL(R) oral tablets, suspension, 2008).

3) Severity: major

4) Onset: delayed

5) Substantiation: probable
6) Clinical Management: When paroxetine and an anticoagulant are given concurrently, monitor patients for signs of increased bleeding. Patients who are taking warfarin should be monitored closely for altered anticoagulant effects, including increased bleeding, when paroxetine therapy is initiated or discontinued (Prod Info PAXIL(R) oral tablets, suspension, 2008).
7) Probable Mechanism: unknown
8) Literature Reports
a) According to a retrospective cohort study (n=234), there was an increased risk of clinically relevant bleeding (hospital admission due to bleeding) in patients receiving warfarin for atrial fibrillation during concomitant SSRI therapy or within 2 weeks following SSRI therapy termination. Patients with a mean age of 72 +/- 7 years receiving warfarin plus SSRI (n=117) were matched with randomly selected patients who received warfarin only (n=117). SSRI included fluoxetine, citalopram, paroxetine, sertraline, fluvoxamine, or escitalopram. Nine patients experienced 11 bleeding episodes during 213.9 treatment years in the warfarin plus SSRI group, and 10 patients experienced 14 bleedings during 586.4 treatment years in the warfarin-only group. The corresponding total incidences of bleedings were 51.4 and 23.9 per 1000 treatment years, respectively. The hazard ratio for first bleedings during treatment with warfarin plus SSRI was 3.49 (95% CI; 1.37 to 8.91, p=0.009) compared with warfarin only. The SSRI implicated in patients experiencing bleeding at the time of concomitant administration were sertraline or citalopram. The addition of an SSRI was not associated with a change in warfarin dose or INR (p=0.48 and p=0.31 respectively). The results of the study may be limited by earlier bleeding events, unknown patient adherence, and exclusion of clopidogrel, dipyridamol, corticosteroids and anticoagulants other than warfarin in the model (Wallerstedt et al, 2009).
b) A population-based, case-controlled study of new coumarin users (acenocoumarol and phenprocoumon) with concomitant selective serotonin reuptake inhibitors (SSRIs) resulted in an increased risk of hospitalization due to nongastrointestinal bleeding. Using national pharmacy and hospitalization records, Netherlands researchers identified 1848 cases that were admitted for abnormal bleeding and compared them with 5818 control subjects also taking coumarins. Median duration of treatment in patients was 220 days (range, 1 to 4690 days). Patients on SSRIs showed greater risk for hospitalization for nongastrointestinal bleeding (adjusted odds ratio (OR) 1.7, 95% confidence interval (CI), 1.1 to 2.5), however, the rate of gastrointestinal bleeding (adjusted OR 0.8, 95% CI, 0.4 to 1.5) was not significantly different (Schalekamp et al, 2008).
c) Preliminary data suggest that there may be a pharmacodynamic interaction (that causes an increased bleeding diathesis with unaltered prothrombin time) between paroxetine and warfarin. The concomitant use of paroxetine and warfarin should be undertaken with caution (Prod Info PAXIL(R) oral tablets, suspension, 2008).
d) In a multiple-dose study, several days of combined therapy with warfarin and paroxetine resulted in mild but clinically significant bleeding in 5 of 27 subjects. This effect occurred in the absence of a significant enhancement in warfarin-induced hypoprothrombinemia or changes in either paroxetine or warfarin disposition (Bannister et al, 1989b).

3.5.1.M Aprepitant

1) Interaction Effect: decreased AUC and Cmax of aprepitant and paroxetine
2) Summary: Once daily doses of aprepitant, as a tablet formulation comparable to 85 mg or 170 mg of the capsule formulation, co-administered with paroxetine 20 mg once daily, resulted in a decrease in AUC by approximately 25% and Cmax by approximately 20% of both aprepitant and paroxetine (Prod Info EMEND (R) oral capsules, 2008).
3) Severity: moderate
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: Coadministration of aprepitant and paroxetine may result in a decrease in AUC and Cmax of aprepitant and paroxetine (Prod Info EMEND(R) oral capsules, 2008).
7) Probable Mechanism: unknown

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 cohort studies have shown that the combined use of SSRIs and anticoagulants has been associated with an increased risk of bleeding (Wallerstedt et al, 2009; Schalekamp et al, 2008; Prod Info PAXIL(R) oral tablets, suspension, 2008). Bleeding events reported have included epistaxis, ecchymosis, hematoma, petechiae, and life-threatening hemorrhages. Altered anticoagulant effects (including increased bleeding) have been reported with the coadministration of SSRIs with warfarin (Schalekamp et al, 2008; Prod Info PAXIL(R) oral tablets, suspension, 2008).
3) Severity: major
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: When paroxetine and an anticoagulant are given concurrently, monitor patients for signs of increased bleeding. Patients who are taking warfarin should be monitored closely for altered anticoagulant effects, including increased bleeding, when paroxetine therapy is initiated or discontinued

(Prod Info PAXIL(R) oral tablets, suspension, 2008).
7) Probable Mechanism: unknown
8) Literature Reports
a) According to a retrospective cohort study (n=234), there was an increased risk of clinically relevant bleeding (hospital admission due to bleeding) in patients receiving warfarin for atrial fibrillation during concomitant SSRI therapy or within 2 weeks following SSRI therapy termination. Patients with a mean age of 72 +/- 7 years receiving warfarin plus SSRI (n=117) were matched with randomly selected patients who received warfarin only (n=117). SSRI included fluoxetine, citalopram, paroxetine, sertraline, fluvoxamine, or escitalopram. Nine patients experienced 11 bleeding episodes during 213.9 treatment years in the warfarin plus SSRI group, and 10 patients experienced 14 bleedings during 586.4 treatment years in the warfarin-only group. The corresponding total incidences of bleedings were 51.4 and 23.9 per 1000 treatment years, respectively. The hazard ratio for first bleedings during treatment with warfarin plus SSRI was 3.49 (95% CI; 1.37 to 8.91, p=0.009) compared with warfarin only. The SSRI implicated in patients experiencing bleeding at the time of concomitant administration were sertraline or citalopram. The addition of an SSRI was not associated with a change in warfarin dose or INR (p=0.48 and p=0.31 respectively). The results of the study may be limited by earlier bleeding events, unknown patient adherence, and exclusion of clopidogrel, dipyridamol, corticosteroids and anticoagulants other than warfarin in the model (Wallerstedt et al, 2009).
b) A population-based, case-controlled study of new coumarin users (acenocoumarol and phenprocoumon) with concomitant selective serotonin reuptake inhibitors (SSRIs) resulted in an increased risk of hospitalization due to nongastrointestinal bleeding. Using national pharmacy and hospitalization records, Netherlands researchers identified 1848 cases that were admitted for abnormal bleeding and compared them with 5818 control subjects also taking coumarins. Median duration of treatment in patients was 220 days (range, 1 to 4690 days). Patients on SSRIs showed greater risk for hospitalization for nongastrointestinal bleeding (adjusted odds ratio (OR) 1.7, 95% confidence interval (CI), 1.1 to 2.5), however, the rate of gastrointestinal bleeding (adjusted OR 0.8, 95% CI, 0.4 to 1.5) was not significantly different (Schalekamp et al, 2008).
c) Preliminary data suggest that there may be a pharmacodynamic interaction (that causes an increased bleeding diathesis with unaltered prothrombin time) between paroxetine and warfarin. The concomitant use of paroxetine and warfarin should be undertaken with caution (Prod Info PAXIL(R) oral tablets, suspension, 2008).
d) In a multiple-dose study, several days of combined therapy with warfarin and paroxetine resulted in mild but clinically significant bleeding in 5 of 27 subjects. This effect occurred in the absence of a significant enhancement in warfarin-induced hypoprothrombinemia or changes in either paroxetine or warfarin disposition (Bannister et al, 1989b).

3.5.1.O Aripiprazole
1) Interaction Effect: increased aripiprazole levels
2) Summary: Aripiprazole is partly metabolized by cytochrome P450 2D6 (CYP2D6) enzymes. Coadministration with CYP2D6 inhibitors, such as paroxetine, may inhibit aripiprazole elimination causing increased blood concentrations. Consider a dosage reduction for aripiprazole when these agents are coadministered. If therapy with paroxetine is discontinued, the dose of aripiprazole should then be increased (Prod Info ABILIFY(R) oral tablets, oral solution, 2005).
3) Severity: moderate
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: Increased aripiprazole plasma levels may result if used concomitantly with paroxetine. Consider a dosage reduction for aripiprazole when these agents are coadministered. If therapy with paroxetine is discontinued, the dose of aripiprazole should then be increased.
7) Probable Mechanism: inhibition of cytochrome P450 2D6-mediated metabolism of aripiprazole

3.5.1.P 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 cohort studies have shown that the combined use of SSRIs and antiplatelet agents has been associated with an increased risk of bleeding. Bleeding events reported have included epistaxis, ecchymosis, hematoma, petechiae, and life-threatening hemorrhages (Prod Info PAXIL(R) oral 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 signs of increased bleeding (Prod Info PAXIL(R) oral tablets, suspension, 2008; Prod Info PROZAC(R) oral capsules, delayed-release capsules, solution, 2008)
7) Probable Mechanism: unknown

3.5.1.Q Atomoxetine
1) Interaction Effect: an increase in atomoxetine steady-state plasma concentrations

2) Summary: Atomoxetine is primarily metabolized by the cytochrome P450 2D6 (CYP 2D6) pathway to 4-hydroxyatomoxetine. In extensive metabolizers, atomoxetine steady-state plasma concentrations are increased with selective inhibitors of CYP2D6, such as paroxetine. The exposure is similar to that observed in poor metabolizers. In extensive metabolizers treated with paroxetine, the area under the concentration-time curve of atomoxetine is approximately 6- to 8-fold greater, and maximum plasma concentration at steady-state is about 3- to 4-fold greater than atomoxetine alone (Prod Info Strattera(TM), 2002).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Dosage adjustment of atomoxetine may be necessary when coadministered with paroxetine.
7) Probable Mechanism: inhibition of cytochrome P450 2D6-mediated metabolism of atomoxetine by paroxetine

3.5.1.R 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 cohort studies have shown that the combined use of SSRIs and NSAIDs has been associated with an increased risk of bleeding. Bleeding events have included epistaxis, ecchymosis, hematoma, petechiae, and life-threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension, 2008) (Prod Info Lexapro(TM), 2003; Dalton et al, 2003a; Prod Info CELEXA (R) oral tablet, solution, 2005).
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 increased bleeding.
7) Probable Mechanism: unknown
8) Literature Reports
a) SSRIs increase the risk of upper gastrointestinal bleeding and this effect is potentiated by concurrent use of NSAIDs or low-dose aspirin. Hospitalizations for upper gastrointestinal bleeding were searched among 26,005 users of antidepressant medications and compared with the number of hospitalizations in those patients who did not receive prescriptions for antidepressants. The amount of upper GI bleeding episodes was 3.6 times more than expected (95% confidence interval, 2.7 to 4.7). Combined use of an SSRI and NSAIDs or low-dose aspirin increased the risk to 12.2 (95% confidence interval, 7.1 to 19.5) and 5.2 (95% confidence interval, 3.2 to 8), respectively. The findings of this study demonstrate an increased risk of upper GI bleeding during the use of SSRIs. Combined use of SSRIs and NSAIDs or low-dose aspirin increased the risk even further (Dalton et al, 2003).
b) Coadministration of ketorolac with psychoactive drugs (such as fluoxetine) has been associated with hallucinations in some patients (Prod Info TORADOL(R) oral tablets, 2007).

3.5.1.S 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 cohort studies have shown that the combined use of SSRIs and anticoagulants has been associated with an increased risk of bleeding (Wallerstedt et al, 2009; Schalekamp et al, 2008; Prod Info PAXIL(R) oral tablets, suspension, 2008). Bleeding events reported have included epistaxis, ecchymosis, hematoma, petechiae, and life-threatening hemorrhages. Altered anticoagulant effects (including increased bleeding) have been reported with the coadministration of SSRIs with warfarin (Schalekamp et al, 2008; Prod Info PAXIL(R) oral tablets, suspension, 2008).
3) Severity: major
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: When paroxetine and an anticoagulant are given concurrently, monitor patients for signs of increased bleeding. Patients who are taking warfarin should be monitored closely for altered anticoagulant effects, including increased bleeding, when paroxetine therapy is initiated or discontinued (Prod Info PAXIL(R) oral tablets, suspension, 2008).
7) Probable Mechanism: unknown
8) Literature Reports
a) According to a retrospective cohort study (n=234), there was an increased risk of clinically relevant bleeding (hospital admission due to bleeding) in patients receiving warfarin for atrial fibrillation during concomitant SSRI therapy or within 2 weeks following SSRI therapy termination. Patients with a mean age of 72 +/- 7 years receiving warfarin plus SSRI (n=117) were matched with randomly selected patients who received warfarin only (n=117). SSRI included fluoxetine, citalopram, paroxetine, sertraline, fluvoxamine, or escitalopram. Nine patients experienced 11 bleeding episodes during 213.9 treatment years in the warfarin plus SSRI group, and 10 patients experienced 14 bleedings during 586.4 treatment years in the warfarin-only group. The corresponding total incidences of bleedings were 51.4 and 23.9 per 1000 treatment years, respectively. The hazard ratio for first bleedings during treatment with warfarin plus SSRI was 3.49 (95% CI; 1.37 to 8.91, p=0.009) compared with warfarin only. The

SSRI implicated in patients experiencing bleeding at the time of concomitant administration were sertraline or citalopram. The addition of an SSRI was not associated with a change in warfarin dose or INR (p=0.48 and p=0.31 respectively). The results of the study may be limited by earlier bleeding events, unknown patient adherence, and exclusion of clopidogrel, dipyridamol, corticosteroids and anticoagulants other than warfarin in the model (Wallerstedt et al, 2009).

b) A population-based, case-controlled study of new coumarin users (acenocoumarol and phenprocoumon) with concomitant selective serotonin reuptake inhibitors (SSRIs) resulted in an increased risk of hospitalization due to nongastrointestinal bleeding. Using national pharmacy and hospitalization records, Netherlands researchers identified 1848 cases that were admitted for abnormal bleeding and compared them with 5818 control subjects also taking coumarins. Median duration of treatment in patients was 220 days (range, 1 to 4690 days). Patients on SSRIs showed greater risk for hospitalization for nongastrointestinal bleeding (adjusted odds ratio (OR) 1.7, 95% confidence interval (CI), 1.1 to 2.5), however, the rate of gastrointestinal bleeding (adjusted OR 0.8, 95% CI, 0.4 to 1.5) was not significantly different (Schalekamp et al, 2008).

c) Preliminary data suggest that there may be a pharmacodynamic interaction (that causes an increased bleeding diathesis with unaltered prothrombin time) between paroxetine and warfarin. The concomitant use of paroxetine and warfarin should be undertaken with caution (Prod Info PAXIL(R) oral tablets, suspension, 2008).

d) In a multiple-dose study, several days of combined therapy with warfarin and paroxetine resulted in mild but clinically significant bleeding in 5 of 27 subjects. This effect occurred in the absence of a significant enhancement in warfarin-induced hypoprothrombinemia or changes in either paroxetine or warfarin disposition (Bannister et al, 1989b).

3.5.1.T 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 cohort studies have shown that the combined use of SSRIs and NSAIDs has been associated with an increased risk of bleeding. Bleeding events have included epistaxis, ecchymosis, hematoma, petechiae, and life-threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension, 2008) (Prod Info Lexapro(TM), 2003; Dalton et al, 2003a; Prod Info CELEXA (R) oral tablet, solution, 2005).

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 increased bleeding.

7) Probable Mechanism: unknown

8) Literature Reports

a) SSRIs increase the risk of upper gastrointestinal bleeding and this effect is potentiated by concurrent use of NSAIDs or low-dose aspirin. Hospitalizations for upper gastrointestinal bleeding were searched among 26,005 users of antidepressant medications and compared with the number of hospitalizations in those patients who did not receive prescriptions for antidepressants. The amount of upper GI bleeding episodes was 3.6 times more than expected (95% confidence interval, 2.7 to 4.7). Combined use of an SSRI and NSAIDs or low-dose aspirin increased the risk to 12.2 (95% confidence interval, 7.1 to 19.5) and 5.2 (95% confidence interval, 3.2 to 8), respectively. The findings of this study demonstrate an increased risk of upper GI bleeding during the use of SSRIs. Combined use of SSRIs and NSAIDs or low-dose aspirin increased the risk even further (Dalton et al, 2003).

b) Coadministration of ketorolac with psychoactive drugs (such as fluoxetine) has been associated with hallucinations in some patients (Prod Info TORADOL(R) oral tablets, 2007).

3.5.1.U 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 cohort studies have shown that the combined use of SSRIs and NSAIDs has been associated with an increased risk of bleeding. Bleeding events have included epistaxis, ecchymosis, hematoma, petechiae, and life-threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension, 2008) (Prod Info Lexapro(TM), 2003; Dalton et al, 2003a; Prod Info CELEXA (R) oral tablet, solution, 2005).

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 increased bleeding.

7) Probable Mechanism: unknown

8) Literature Reports

a) SSRIs increase the risk of upper gastrointestinal bleeding and this effect is potentiated by concurrent use of NSAIDs or low-dose aspirin. Hospitalizations for upper gastrointestinal bleeding were searched among 26,005 users of antidepressant medications and compared with the number of hospitalizations in those patients who did not receive prescriptions for antidepressants. The amount of upper GI bleeding episodes was 3.6 times more than expected (95% confidence interval, 2.7 to 4.7). Combined

use of an SSRI and NSAIDs or low-dose aspirin increased the risk to 12.2 (95% confidence interval, 7.1 to 19.5) and 5.2 (95% confidence interval, 3.2 to 8), respectively. The findings of this study demonstrate an increased risk of upper GI bleeding during the use of SSRIs. Combined use of SSRIs and NSAIDs or low-dose aspirin increased the risk even further (Dalton et al, 2003).

b) Coadministration of ketorolac with psychoactive drugs (such as fluoxetine) has been associated with hallucinations in some patients (Prod Info TORADOL(R) oral tablets, 2007).

3.5.1.V Bupropion

1) Interaction Effect: increased plasma levels of paroxetine

2) Summary: It is recommended that paroxetine, an antidepressant metabolized by the cytochrome P450 2D6 isoenzyme, be initiated at the lower end of the dose range when administered concomitantly with bupropion (Prod Info Zyban(R), 2000).

3) Severity: moderate

4) Onset: delayed

5) Substantiation: probable

6) Clinical Management: Coadministration of bupropion and paroxetine should be approached with caution and should be initiated at the lower end of the dose range of paroxetine. If bupropion is added to the treatment regimen of a patient already receiving paroxetine, consider decreasing the dose of paroxetine.

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

3.5.1.W Cannabis

1) Interaction Effect: manic symptoms

2) Summary: One case of mania following use of marijuana with fluoxetine therapy has been reported (Stoll et al, 1991a). Although an interaction is proposed, the authors also state the manic symptoms could have resulted from the fluoxetine or marijuana alone. Caution is advised for patients using marijuana and taking fluoxetine or other serotonin reuptake inhibitors.

3) Severity: moderate

4) Onset: rapid

5) Substantiation: theoretical

6) Clinical Management: Caution patients taking selective serotonin reuptake inhibitors to avoid concomitant use of marijuana.

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 marijuana with fluoxetine therapy. She had been taking fluoxetine 20 mg daily for 4 weeks and reported smoking 2 "joints" during a 36-hour period. Over the next 24 hours, she developed increased energy, hypersexuality, pressured speech, and grandiose delusions. Lorazepam and perphenazine were given for agitation and excitement which gradually resolved over 4 days. She remained hospitalized for 36 days. Fluoxetine 20 mg every other day was reintroduced one week prior to discharge. One week after discharge, she discontinued fluoxetine due to insomnia and feeling "hyper". These symptoms resolved rapidly upon discontinuation of fluoxetine. Due to the rapid switch to mania after smoking marijuana with fluoxetine, the manic symptoms were associated with the concomitant use of fluoxetine and marijuana, though mania could have developed from either fluoxetine or marijuana alone (Stoll et al, 1991).

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 cohort studies have shown that the combined use of SSRIs and NSAIDs has been associated with an increased risk of bleeding. Bleeding events have included epistaxis, ecchymosis, hematoma, petechiae, and life-threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension, 2008) (Prod Info Lexapro(TM), 2003; Dalton et al, 2003a; Prod Info CELEXA (R) oral tablet, solution, 2005).

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 increased bleeding.

7) Probable Mechanism: unknown

8) Literature Reports

a) SSRIs increase the risk of upper gastrointestinal bleeding and this effect is potentiated by concurrent use of NSAIDs or low-dose aspirin. Hospitalizations for upper gastrointestinal bleeding were searched among 26,005 users of antidepressant medications and compared with the number of hospitalizations in those patients who did not receive prescriptions for antidepressants. The amount of upper GI bleeding episodes was 3.6 times more than expected (95% confidence interval, 2.7 to 4.7). Combined use of an SSRI and NSAIDs or low-dose aspirin increased the risk to 12.2 (95% confidence interval, 7.1 to 19.5) and 5.2 (95% confidence interval, 3.2 to 8), respectively. The findings of this study demonstrate an increased risk of upper GI bleeding during the use of SSRIs. Combined use of SSRIs and NSAIDs or low-dose aspirin increased the risk even further (Dalton et al, 2003).

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

hallucinations in some patients (Prod Info TORADOL(R) oral tablets, 2007).

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 cohort studies have shown that the combined use of SSRIs and NSAIDs has been associated with an increased risk of bleeding. Bleeding events have included epistaxis, ecchymosis, hematoma, petechiae, and life-threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension, 2008) (Prod Info Lexapro(TM), 2003; Dalton et al, 2003a; Prod Info CELEXA (R) oral tablet, solution, 2005).

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 increased bleeding.

7) Probable Mechanism: unknown

8) Literature Reports

a) SSRIs increase the risk of upper gastrointestinal bleeding and this effect is potentiated by concurrent use of NSAIDs or low-dose aspirin. Hospitalizations for upper gastrointestinal bleeding were searched among 26,005 users of antidepressant medications and compared with the number of hospitalizations in those patients who did not receive prescriptions for antidepressants. The amount of upper GI bleeding episodes was 3.6 times more than expected (95% confidence interval, 2.7 to 4.7). Combined use of an SSRI and NSAIDs or low-dose aspirin increased the risk to 12.2 (95% confidence interval, 7.1 to 19.5) and 5.2 (95% confidence interval, 3.2 to 8), respectively. The findings of this study demonstrate an increased risk of upper GI bleeding during the use of SSRIs. Combined use of SSRIs and NSAIDs or low-dose aspirin increased the risk even further (Dalton et al, 2003).

b) Coadministration of ketorolac with psychoactive drugs (such as fluoxetine) has been associated with hallucinations in some patients (Prod Info TORADOL(R) oral tablets, 2007).

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 cohort studies have shown that the combined use of SSRIs and anticoagulants has been associated with an increased risk of bleeding (Wallerstedt et al, 2009; Schalekamp et al, 2008; Prod Info PAXIL(R) oral tablets, suspension, 2008). Bleeding events reported have included epistaxis, ecchymosis, hematoma, petechiae, and life-threatening hemorrhages. Altered anticoagulant effects (including increased bleeding) have been reported with the coadministration of SSRIs with warfarin (Schalekamp et al, 2008; Prod Info PAXIL(R) oral tablets, suspension, 2008).

3) Severity: major

4) Onset: delayed

5) Substantiation: probable

6) Clinical Management: When paroxetine and an anticoagulant are given concurrently, monitor patients for signs of increased bleeding. Patients who are taking warfarin should be monitored closely for altered anticoagulant effects, including increased bleeding, when paroxetine therapy is initiated or discontinued (Prod Info PAXIL(R) oral tablets, suspension, 2008).

7) Probable Mechanism: unknown

8) Literature Reports

a) According to a retrospective cohort study (n=234), there was an increased risk of clinically relevant bleeding (hospital admission due to bleeding) in patients receiving warfarin for atrial fibrillation during concomitant SSRI therapy or within 2 weeks following SSRI therapy termination. Patients with a mean age of 72 +/- 7 years receiving warfarin plus SSRI (n=117) were matched with randomly selected patients who received warfarin only (n=117). SSRI included fluoxetine, citalopram, paroxetine, sertraline, fluvoxamine, or escitalopram. Nine patients experienced 11 bleeding episodes during 213.9 treatment years in the warfarin plus SSRI group, and 10 patients experienced 14 bleedings during 586.4 treatment years in the warfarin-only group. The corresponding total incidences of bleedings were 51.4 and 23.9 per 1000 treatment years, respectively. The hazard ratio for first bleedings during treatment with warfarin plus SSRI was 3.49 (95% CI; 1.37 to 8.91, p=0.009) compared with warfarin only. The SSRI implicated in patients experiencing bleeding at the time of concomitant administration were sertraline or citalopram. The addition of an SSRI was not associated with a change in warfarin dose or INR (p=0.48 and p=0.31 respectively). The results of the study may be limited by earlier bleeding events, unknown patient adherence, and exclusion of clopidogrel, dipyridamol, corticosteroids and anticoagulants other than warfarin in the model (Wallerstedt et al, 2009).

b) A population-based, case-controlled study of new coumarin users (acenocoumarol and phenprocoumon) with concomitant selective serotonin reuptake inhibitors (SSRIs) resulted in an increased risk of hospitalization due to nongastrointestinal bleeding. Using national pharmacy and hospitalization records, Netherlands researchers identified 1848 cases that were admitted for abnormal bleeding and compared them with 5818 control subjects also taking coumarins. Median duration of treatment in patients was 220 days (range, 1 to 4690 days). Patients on SSRIs showed greater risk for hospitalization for nongastrointestinal bleeding (adjusted odds ratio (OR) 1.7, 95% confidence interval

(CI), 1.1 to 2.5), however, the rate of gastrointestinal bleeding (adjusted OR 0.8, 95% CI, 0.4 to 1.5) was not significantly different (Schalekamp et al, 2008).

c) Preliminary data suggest that there may be a pharmacodynamic interaction (that causes an increased bleeding diathesis with unaltered prothrombin time) between paroxetine and warfarin. The concomitant use of paroxetine and warfarin should be undertaken with caution (Prod Info PAXIL(R) oral tablets, suspension, 2008).

d) In a multiple-dose study, several days of combined therapy with warfarin and paroxetine resulted in mild but clinically significant bleeding in 5 of 27 subjects. This effect occurred in the absence of a significant enhancement in warfarin-induced hypoprothrombinemia or changes in either paroxetine or warfarin disposition (Bannister et al, 1989b).

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 cohort studies have shown that the combined use of SSRIs and antiplatelet agents has been associated with an increased risk of bleeding. Bleeding events reported have included epistaxis, ecchymosis, hematoma, petechiae, and life-threatening hemorrhages (Prod Info PAXIL(R) oral 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 signs of increased bleeding (Prod Info PAXIL(R) oral tablets, suspension, 2008; Prod Info PROZAC(R) oral capsules, delayed-release capsules, solution, 2008)

7) Probable Mechanism: unknown

3.5.1.AB Cimetidine

1) Interaction Effect: increased paroxetine serum concentrations and possibly paroxetine toxicity (dizziness, somnolence, nausea, headache)

2) Summary: Coadministered cimetidine may increase serum concentrations of paroxetine by as much as 50% to 80% in some patients (Greb et al, 1989a; Bannister et al, 1989a). The clinical significance of this interaction is unclear. In one study, no adverse clinical effects were reported. In another study, tiredness, dizziness, headache, muscle tension, and GI distress were observed; these effects were also reported with paroxetine alone, but to a lesser extent. The mechanism of this interaction is thought to be inhibition by cimetidine of P450 isoenzymes responsible for paroxetine metabolism. Dosage adjustment of paroxetine after the 20 mg starting dose should be guided by clinical effect. The effect of paroxetine on cimetidine's pharmacokinetics has not been studied (Prod Info Paxil CR(TM), 2004).

3) Severity: moderate

4) Onset: delayed

5) Substantiation: probable

6) Clinical Management: If cimetidine and paroxetine are coadministered, observe the patient for signs and symptoms of paroxetine toxicity (dizziness, somnolence, nausea, headache). Lower doses of paroxetine may be required. An alternative H-2 blocker that has less impact on hepatic isoenzymes (such as famotidine or ranitidine) might be considered.

7) Probable Mechanism: inhibition of paroxetine cytochrome P450 metabolism by cimetidine

8) Literature Reports

a) In a multiple-dose study in 11 healthy volunteers, concurrent administration of oral cimetidine and paroxetine resulted in a mean increase of 51% in the area under the concentration-time curve (AUC) for paroxetine. Maximum concentration (Cmax) of paroxetine increased by 45%. Volunteers received paroxetine 30 mg once a day for 28 days, with cimetidine 300 mg three times daily given during the last 7 days. No changes in half-life or elimination rate constant occurred. The increases in the paroxetine AUC and maximum concentration were attributed to inhibition of first-pass metabolism of paroxetine by cimetidine. No adverse clinical effects were observed during the study (Bannister et al, 1989).

b) Effects of cimetidine on a single dose of paroxetine were studied in 10 healthy male subjects (Greb et al, 1989). Subjects received 8 days of cimetidine 200 mg four times daily followed by a 30 mg dose of paroxetine. Pharmacokinetic values were compared with those of the same dose of paroxetine given before initiation of the H-2 blocker. The mean AUC of paroxetine increased from 195.98 to 308.36 ng-h/mL (a 57% increase), but, due to high interindividual variation, this increase did not attain statistical significance. In two subjects, the increases were 55% and 81%, respectively.

3.5.1.AC Clarithromycin

1) Interaction Effect: an increased risk of serotonin syndrome (hypertension, hyperthermia, myoclonus, mental status changes)

2) Summary: Concurrent use of clarithromycin and paroxetine may increase the risk of serotonin syndrome (hypertension, hyperthermia, myoclonus, mental status changes) (Jaber et al, 2006).

3) Severity: moderate

4) Onset: delayed

5) Substantiation: probable

6) Clinical Management: Concurrent use of clarithromycin and paroxetine may result in serotonin syndrome. Monitor patients for serotonin syndrome effects including restlessness, tremors, blushing, diaphoresis, and hyperpyrexia. Consider reducing the dose of paroxetine.
7) Probable Mechanism: unknown
8) Literature Reports
a) A 36-year-old-woman experienced acute ocular clonus, akathisia, and fever after 2 days of clarithromycin 500 milligrams twice daily despite stopping paroxetine 3 days prior to starting clarithromycin. She was on paroxetine 10 milligrams daily for 3 months prior to stopping it. Clarithromycin was discontinued. She was treated with intravenous fluids and lorazepam and within 24 hours symptoms resolved (Jaber et al, 2006).

3.5.1.AD Clomipramine
1) Interaction Effect: clomipramine toxicity (dry mouth, sedation, urinary retention)
2) Summary: Concurrent use of paroxetine with drugs that are metabolized by cytochrome P450 2D6, such as clomipramine, should be approached with caution (Prod Info Paxil(R), 2003i).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When paroxetine is coadministered with clomipramine, monitor patients for signs and symptoms of clomipramine toxicity (dry mouth, sedation, urinary retention, blurred vision). Clomipramine doses may need to be reduced.
7) Probable Mechanism: decreased cytochrome P450 2D6-mediated clomipramine metabolism

3.5.1.AE 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 cohort studies have shown that the combined use of SSRIs and NSAIDs has been associated with an increased risk of bleeding. Bleeding events have included epistaxis, ecchymosis, hematoma, petechiae, and life-threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension, 2008) (Prod Info Lexapro(TM), 2003; Dalton et al, 2003a; Prod Info CELEXA (R) oral tablet, solution, 2005).
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 increased bleeding.
7) Probable Mechanism: unknown
8) Literature Reports
a) SSRIs increase the risk of upper gastrointestinal bleeding and this effect is potentiated by concurrent use of NSAIDs or low-dose aspirin. Hospitalizations for upper gastrointestinal bleeding were searched among 26,005 users of antidepressant medications and compared with the number of hospitalizations in those patients who did not receive prescriptions for antidepressants. The amount of upper GI bleeding episodes was 3.6 times more than expected (95% confidence interval, 2.7 to 4.7). Combined use of an SSRI and NSAIDs or low-dose aspirin increased the risk to 12.2 (95% confidence interval, 7.1 to 19.5) and 5.2 (95% confidence interval, 3.2 to 8), respectively. The findings of this study demonstrate an increased risk of upper GI bleeding during the use of SSRIs. Combined use of SSRIs and NSAIDs or low-dose aspirin increased the risk even further (Dalton et al, 2003).
b) Coadministration of ketorolac with psychoactive drugs (such as fluoxetine) has been associated with hallucinations in some patients (Prod Info TORADOL(R) oral tablets, 2007).

3.5.1.AF 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 cohort studies have shown that the combined use of SSRIs and antiplatelet agents has been associated with an increased risk of bleeding. Bleeding events reported have included epistaxis, ecchymosis, hematoma, petechiae, and life-threatening hemorrhages (Prod Info PAXIL(R) oral 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 signs of increased bleeding (Prod Info PAXIL(R) oral tablets, suspension, 2008; Prod Info PROZAC(R) oral capsules, delayed-release capsules, solution, 2008)
7) Probable Mechanism: unknown

3.5.1.AG Clorgyline
1) Interaction Effect: CNS toxicity or serotonin syndrome (hypertension, hyperthermia, myoclonus, mental status changes)
2) Summary: Concurrent administration or overlapping therapy with paroxetine and a monoamine oxidase

(MAO) inhibitor may result in CNS toxicity or serotonin syndrome, a hyperserotonergic state characterized by symptoms such as restlessness, myoclonus, changes in mental status, hyperreflexia, diaphoresis, shivering, and tremor. Serious, even fatal, reactions have been reported with concomitant use of serotonin specific reuptake inhibitors and MAO inhibitors (Prod Info Paxil(R), 2003c; Lappin & Auchincloss, 1994g; Graber et al, 1994g; Suchowersky & de Vries, 1990g). Concomitant use is contraindicated.
3) Severity: contraindicated
4) Onset: rapid
5) Substantiation: probable
6) Clinical Management: Concurrent use of paroxetine and an MAO inhibitor is contraindicated. Wait at least two weeks after discontinuing an MAO inhibitor before initiating paroxetine, and at least two weeks after discontinuing paroxetine before initiating therapy with an MAOI.
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 serotonin syndrome (Sternbach, 1991h). Serotonin syndrome is a condition of serotonergic hyperstimulation and manifests as restlessness, myoclonus, changes in mental status, hyperreflexia, diaphoresis, shivering, and tremor (Sternbach, 1991h). If the syndrome is not recognized and correctly treated, fatality can result.
b) A 26-year old woman who had been taking isocarboxazid for eight weeks stopped taking the drug for 11 days before beginning therapy with sertraline. After a single 100 mg sertraline dose, the patient became restless and developed leg twitches. The patients was later admitted to the emergency room with diaphoresis, tachycardia, hyperreflexia, and various neuromuscular disturbances. After treatment with diazepam and propranolol the patient did not improve. The patient was then given two 4 mg doses of cyproheptadine an hour apart, with notable improvement in 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 added to a regimen of lithium, phenelzine, thioridazine, and doxepin. Three hours after taking the first sertraline dose, the patient was found in a semicomatose state, with elevated body temperature, increased pulse, increased respiration rate, and a blood pressure of 140/110 mm Hg. After transportation to the hospital, the patient was misdiagnosed as having neuroleptic malignant syndrome (NMS) which was later changed to serotonin syndrome due to a reaction between sertraline and phenelzine. The authors suggest that monoamine oxidase inhibitor (MAOI) therapy should be discontinued for at least two weeks before initiation of therapy with a selective serotonin reuptake inhibitor (SSRI) and that before starting a MAOI, SSRI therapy should be discontinued for at least five half-lives of the parent drug and any active metabolites (Graber et al, 1994f).
d) Two cases reports suggested a possible interaction between fluoxetine and selegiline (Suchowersky & de Vries, 1990f). One case involved a first episode of mania being observed approximately one month after adding selegiline to fluoxetine. The patient improved two months after both drugs were discontinued, and no further details were provided. The second case involved diaphoresis, vasoconstriction, and cyanosis of the hands which occurred in close temporal relationship to adding fluoxetine to selegiline. Both drugs were discontinued, with relatively quick resolution of symptoms. Rechallenge with fluoxetine alone occurred without incident.

3.5.1.AH Clozapine
1) Interaction Effect: an increased risk of clozapine toxicity (sedation, seizures, hypotension)
2) Summary: Increased serum concentrations of clozapine and its metabolites have been observed when it is given with serotonin reuptake inhibitors; however, other published reports describe paroxetine having no effect on serum concentrations of clozapine or its metabolites (Prod Info Clozaril(R), 2002; Centorrino et al, 1996a; Wetzel et al, 1998a).
3) Severity: moderate
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: Monitor for signs of clozapine toxicity or serum concentrations when paroxetine is given concomitantly.
7) Probable Mechanism: decreased clozapine metabolism
8) Literature Reports
a) Paroxetine had no significant effect on serum levels of clozapine in 14 patients with schizophrenia. Clozapine 2.5 to 3 mg/kg/day was given for 14 days, then paroxetine 20 mg daily was added for 14 days. Serum concentrations of clozapine and two metabolites were measured on days 1, 7, and 14. Over the course of this study there was no significant difference in serum concentrations of clozapine or its metabolites (Wetzel et al, 1998).
b) Serum concentrations of clozapine and norclozapine, the major metabolite, were evaluated when given in combination with the selective serotonin reuptake inhibitors (SSRIs) fluoxetine, paroxetine, and sertraline. Eighty outpatients receiving clozapine all had been diagnosed with schizophrenia or major affective disorder, and 40 of these patients were receiving an SSRI in combination with clozapine. Of these 40 patients, 14 were receiving fluoxetine, 10 were receiving sertraline, and 16 were receiving paroxetine therapy. Among the patients on SSRI therapy, serum concentrations of clozapine and norclozapine were 41.1% and 44.8% higher, respectively, than in matched patients who were not

receiving an SSRI. The ratio of clozapine plus norclozapine concentration to dose was also 37.7% higher in patients receiving SSRIs, indicating clozapine impaired clearance. The differences between the three SSRIs were minor, and the study groups were too limited for an accurate statistical comparison between the individual SSRIs (Centorrino et al, 1996).

3.5.1.AI Cyproheptadine

1) Interaction Effect: reduced paroxetine efficacy

2) Summary: Coadministration of cyproheptadine with paroxetine may result in reduced paroxetine effectiveness (Christensen, 1995a). Cyproheptadine acts to antagonize postsynaptic serotonin. Concomitant use of cyproheptadine with drugs that possess serotonin-enhancing properties (such as the selective serotonin reuptake inhibitors) might be expected to result in a pharmacodynamic interaction. Lack of antidepressant efficacy was also reported when cyproheptadine was given concomitantly with fluoxetine (Katz & Rosenthal, 1994; Feder, 1991; Goldbloom & Kennedy, 1991).

3) Severity: moderate

4) Onset: delayed

5) Substantiation: probable

6) Clinical Management: Monitor patients for reduced paroxetine efficacy. When cyproheptadine is coadministered with paroxetine, paroxetine doses may need to be adjusted upward. In some cases, it may be necessary to withdraw cyproheptadine therapy.

7) Probable Mechanism: unknown; because cyproheptadine is a serotonin antagonist, it may oppose effects of agents that inhibit serotonin uptake

8) Literature Reports

a) A 54-year-old woman was using paroxetine 20 mg per day for the treatment of nonpsychotic major depression. Cyproheptadine 2 mg twice a day was added to her therapy. Two days later, her depression worsened and she experienced confusion and paranoid delusions. Her psychotic symptoms resolved two days after cyproheptadine was discontinued. She declined to be rechallenged (Christensen, 1995).

3.5.1.AJ 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 cohort studies have shown that the combined use of SSRIs and anticoagulants has been associated with an increased risk of bleeding (Wallerstedt et al, 2009; Schalekamp et al, 2008; Prod Info PAXIL(R) oral tablets, suspension, 2008). Bleeding events reported have included epistaxis, ecchymosis, hematoma, petechiae, and life-threatening hemorrhages. Altered anticoagulant effects (including increased bleeding) have been reported with the coadministration of SSRIs with warfarin (Schalekamp et al, 2008; Prod Info PAXIL(R) oral tablets, suspension, 2008).

3) Severity: major

4) Onset: delayed

5) Substantiation: probable

6) Clinical Management: When paroxetine and an anticoagulant are given concurrently, monitor patients for signs of increased bleeding. Patients who are taking warfarin should be monitored closely for altered anticoagulant effects, including increased bleeding, when paroxetine therapy is initiated or discontinued (Prod Info PAXIL(R) oral tablets, suspension, 2008).

7) Probable Mechanism: unknown

8) Literature Reports

a) According to a retrospective cohort study (n=234), there was an increased risk of clinically relevant bleeding (hospital admission due to bleeding) in patients receiving warfarin for atrial fibrillation during concomitant SSRI therapy or within 2 weeks following SSRI therapy termination. Patients with a mean age of 72 +/- 7 years receiving warfarin plus SSRI (n=117) were matched with randomly selected patients who received warfarin only (n=117). SSRI included fluoxetine, citalopram, paroxetine, sertraline, fluvoxamine, or escitalopram. Nine patients experienced 11 bleeding episodes during 213.9 treatment years in the warfarin plus SSRI group, and 10 patients experienced 14 bleedings during 586.4 treatment years in the warfarin-only group. The corresponding total incidences of bleedings were 51.4 and 23.9 per 1000 treatment years, respectively. The hazard ratio for first bleedings during treatment with warfarin plus SSRI was 3.49 (95% CI; 1.37 to 8.91, p=0.009) compared with warfarin only. The SSRI implicated in patients experiencing bleeding at the time of concomitant administration were sertraline or citalopram. The addition of an SSRI was not associated with a change in warfarin dose or INR (p=0.48 and p=0.31 respectively). The results of the study may be limited by earlier bleeding events, unknown patient adherence, and exclusion of clopidogrel, dipyridamol, corticosteroids and anticoagulants other than warfarin in the model (Wallerstedt et al, 2009).

b) A population-based, case-controlled study of new coumarin users (acenocoumarol and phenprocoumon) with concomitant selective serotonin reuptake inhibitors (SSRIs) resulted in an increased risk of hospitalization due to nongastrointestinal bleeding. Using national pharmacy and hospitalization records, Netherlands researchers identified 1848 cases that were admitted for abnormal bleeding and compared them with 5818 control subjects also taking coumarins. Median duration of treatment in patients was 220 days (range, 1 to 4690 days). Patients on SSRIs showed greater risk for hospitalization for nongastrointestinal bleeding (adjusted odds ratio (OR) 1.7, 95% confidence interval

(CI), 1.1 to 2.5), however, the rate of gastrointestinal bleeding (adjusted OR 0.8, 95% CI, 0.4 to 1.5) was not significantly different (Schalekamp et al, 2008).

c) Preliminary data suggest that there may be a pharmacodynamic interaction (that causes an increased bleeding diathesis with unaltered prothrombin time) between paroxetine and warfarin. The concomitant use of paroxetine and warfarin should be undertaken with caution (Prod Info PAXIL(R) oral tablets, suspension, 2008).

d) In a multiple-dose study, several days of combined therapy with warfarin and paroxetine resulted in mild but clinically significant bleeding in 5 of 27 subjects. This effect occurred in the absence of a significant enhancement in warfarin-induced hypoprothrombinemia or changes in either paroxetine or warfarin disposition (Bannister et al, 1989b).

3.5.1.AK 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 cohort studies have shown that the combined use of SSRIs and anticoagulants has been associated with an increased risk of bleeding (Wallerstedt et al, 2009; Schalekamp et al, 2008; Prod Info PAXIL(R) oral tablets, suspension, 2008). Bleeding events reported have included epistaxis, ecchymosis, hematoma, petechiae, and life-threatening hemorrhages. Altered anticoagulant effects (including increased bleeding) have been reported with the coadministration of SSRIs with warfarin (Schalekamp et al, 2008; Prod Info PAXIL(R) oral tablets, suspension, 2008).

3) Severity: major

4) Onset: delayed

5) Substantiation: probable

6) Clinical Management: When paroxetine and an anticoagulant are given concurrently, monitor patients for signs of increased bleeding. Patients who are taking warfarin should be monitored closely for altered anticoagulant effects, including increased bleeding, when paroxetine therapy is initiated or discontinued (Prod Info PAXIL(R) oral tablets, suspension, 2008).

7) Probable Mechanism: unknown

8) Literature Reports

a) According to a retrospective cohort study (n=234), there was an increased risk of clinically relevant bleeding (hospital admission due to bleeding) in patients receiving warfarin for atrial fibrillation during concomitant SSRI therapy or within 2 weeks following SSRI therapy termination. Patients with a mean age of 72 +/- 7 years receiving warfarin plus SSRI (n=117) were matched with randomly selected patients who received warfarin only (n=117). SSRI included fluoxetine, citalopram, paroxetine, sertraline, fluvoxamine, or escitalopram. Nine patients experienced 11 bleeding episodes during 213.9 treatment years in the warfarin plus SSRI group, and 10 patients experienced 14 bleedings during 586.4 treatment years in the warfarin-only group. The corresponding total incidences of bleedings were 51.4 and 23.9 per 1000 treatment years, respectively. The hazard ratio for first bleedings during treatment with warfarin plus SSRI was 3.49 (95% CI; 1.37 to 8.91, p=0.009) compared with warfarin only. The SSRI implicated in patients experiencing bleeding at the time of concomitant administration were sertraline or citalopram. The addition of an SSRI was not associated with a change in warfarin dose or INR (p=0.48 and p=0.31 respectively). The results of the study may be limited by earlier bleeding events, unknown patient adherence, and exclusion of clopidogrel, dipyridamol, corticosteroids and anticoagulants other than warfarin in the model (Wallerstedt et al, 2009).

b) A population-based, case-controlled study of new coumarin users (acenocoumarol and phenprocoumon) with concomitant selective serotonin reuptake inhibitors (SSRIs) resulted in an increased risk of hospitalization due to nongastrointestinal bleeding. Using national pharmacy and hospitalization records, Netherlands researchers identified 1848 cases that were admitted for abnormal bleeding and compared them with 5818 control subjects also taking coumarins. Median duration of treatment in patients was 220 days (range, 1 to 4690 days). Patients on SSRIs showed greater risk for hospitalization for nongastrointestinal bleeding (adjusted odds ratio (OR) 1.7, 95% confidence interval (CI), 1.1 to 2.5), however, the rate of gastrointestinal bleeding (adjusted OR 0.8, 95% CI, 0.4 to 1.5) was not significantly different (Schalekamp et al, 2008).

c) Preliminary data suggest that there may be a pharmacodynamic interaction (that causes an increased bleeding diathesis with unaltered prothrombin time) between paroxetine and warfarin. The concomitant use of paroxetine and warfarin should be undertaken with caution (Prod Info PAXIL(R) oral tablets, suspension, 2008).

d) In a multiple-dose study, several days of combined therapy with warfarin and paroxetine resulted in mild but clinically significant bleeding in 5 of 27 subjects. This effect occurred in the absence of a significant enhancement in warfarin-induced hypoprothrombinemia or changes in either paroxetine or warfarin disposition (Bannister et al, 1989b).

3.5.1.AL Darunavir

1) Interaction Effect: decreased paroxetine exposure and plasma concentrations

2) Summary: Coadministration of darunavir/ritonavir with paroxetine has resulted in significantly decreased paroxetine exposure and plasma concentrations. If these agents are coadministered, the paroxetine dose should be carefully titrated based on clinical response. When darunavir/ritonavir is initiated in patients who are on a stable dose of paroxetine, monitor antidepressant response to paroxetine (Prod Info PREZISTA

(TM) oral tablets, 2006).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: established
6) Clinical Management: Concurrent administration of paroxetine with darunavir/ritonavir decreased paroxetine exposure and plasma concentrations. If these agents are coadministered, carefully titrate the paroxetine dose based on clinical response. When darunavir/ritonavir is initiated in patients who are on a stable dose of paroxetine, monitor antidepressant response to paroxetine.
7) Probable Mechanism: unknown
8) Literature Reports
a) In a pharmacokinetics study, concurrent administration of paroxetine and darunavir/ritonavir decreased paroxetine exposure and plasma concentrations. Subjects (n=16) were administered paroxetine 20 mg orally once daily concurrently with darunavir 400 mg/ritonavir 100 mg orally twice daily. Results indicated a 36% decrease in paroxetine Cmax (least squares (LS) mean ratio % 0.64; 90% confidence interval (CI), 0.59 to 0.71), a 39% decreased in paroxetine AUC (LS mean ratio % 0.61; 90% CI, 0.56 to 0.66), and a 37% decrease in paroxetine Cmin (LS mean ratio % 0.63; 90% CI, 0.55 to 0.73). Darunavir pharmacokinetics were not significantly altered (Prod Info PREZISTA(TM) oral tablets, 2006).

3.5.1.AM 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 cohort studies have shown that the combined use of SSRIs and anticoagulants has been associated with an increased risk of bleeding (Wallerstedt et al, 2009; Schalekamp et al, 2008; Prod Info PAXIL(R) oral tablets, suspension, 2008). Bleeding events reported have included epistaxis, ecchymosis, hematoma, petechiae, and life-threatening hemorrhages. Altered anticoagulant effects (including increased bleeding) have been reported with the coadministration of SSRIs with warfarin (Schalekamp et al, 2008; Prod Info PAXIL(R) oral tablets, suspension, 2008).
3) Severity: major
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: When paroxetine and an anticoagulant are given concurrently, monitor patients for signs of increased bleeding. Patients who are taking warfarin should be monitored closely for altered anticoagulant effects, including increased bleeding, when paroxetine therapy is initiated or discontinued (Prod Info PAXIL(R) oral tablets, suspension, 2008).
7) Probable Mechanism: unknown
8) Literature Reports
a) According to a retrospective cohort study (n=234), there was an increased risk of clinically relevant bleeding (hospital admission due to bleeding) in patients receiving warfarin for atrial fibrillation during concomitant SSRI therapy or within 2 weeks following SSRI therapy termination. Patients with a mean age of 72 +/- 7 years receiving warfarin plus SSRI (n=117) were matched with randomly selected patients who received warfarin only (n=117). SSRI included fluoxetine, citalopram, paroxetine, sertraline, fluvoxamine, or escitalopram. Nine patients experienced 11 bleeding episodes during 213.9 treatment years in the warfarin plus SSRI group, and 10 patients experienced 14 bleedings during 586.4 treatment years in the warfarin-only group. The corresponding total incidences of bleedings were 51.4 and 23.9 per 1000 treatment years, respectively. The hazard ratio for first bleedings during treatment with warfarin plus SSRI was 3.49 (95% CI; 1.37 to 8.91, p=0.009) compared with warfarin only. The SSRI implicated in patients experiencing bleeding at the time of concomitant administration were sertraline or citalopram. The addition of an SSRI was not associated with a change in warfarin dose or INR (p=0.48 and p=0.31 respectively). The results of the study may be limited by earlier bleeding events, unknown patient adherence, and exclusion of clopidogrel, dipyridamol, corticosteroids and anticoagulants other than warfarin in the model (Wallerstedt et al, 2009).
b) A population-based, case-controlled study of new coumarin users (acenocoumarol and phenprocoumon) with concomitant selective serotonin reuptake inhibitors (SSRIs) resulted in an increased risk of hospitalization due to nongastrointestinal bleeding. Using national pharmacy and hospitalization records, Netherlands researchers identified 1848 cases that were admitted for abnormal bleeding and compared them with 5818 control subjects also taking coumarins. Median duration of treatment in patients was 220 days (range, 1 to 4690 days). Patients on SSRIs showed greater risk for hospitalization for nongastrointestinal bleeding (adjusted odds ratio (OR) 1.7, 95% confidence interval (CI), 1.1 to 2.5), however, the rate of gastrointestinal bleeding (adjusted OR 0.8, 95% CI, 0.4 to 1.5) was not significantly different (Schalekamp et al, 2008).
c) Preliminary data suggest that there may be a pharmacodynamic interaction (that causes an increased bleeding diathesis with unaltered prothrombin time) between paroxetine and warfarin. The concomitant use of paroxetine and warfarin should be undertaken with caution (Prod Info PAXIL(R) oral tablets, suspension, 2008).
d) In a multiple-dose study, several days of combined therapy with warfarin and paroxetine resulted in mild but clinically significant bleeding in 5 of 27 subjects. This effect occurred in the absence of a significant enhancement in warfarin-induced hypoprothrombinemia or changes in either paroxetine or

warfarin disposition (Bannister et al, 1989b).

3.5.1.AN Dehydroepiandrosterone

1) Interaction Effect: development of manic symptoms

2) Summary: A case has been reported in which concomitant dehydroepiandrosterone (DHEA) and sertraline use was suggested to precipitate a manic episode in a patient with a history of bipolar disorder (Dean, 2000a). DHEA was also noted to cause mania in a patient with no previous personal or family history of bipolar disorder (Markowitz et al, 1999). Elevated DHEA levels have been found in patients with mental disorders; DHEA suppression has lead to improvement in psychotic symptoms (Howard, 1992). DHEA possesses proserotonergic activity which may predispose patients to manic episodes (Majewska, 1995). DHEA is a precursor to androgenic steroids, which in high doses may precipitate mania (Markowitz et al, 1999). Patients taking medication for bipolar disorder or patients with a personal and/or family history of bipolar disorder should not take DHEA until further data is available to characterize this drug-herb interaction. Concomitant use of DHEA with selective 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 reuptake inhibitors. If patients present with manic symptoms (i.e. agitation, anger, irritability, aggressive behavior), determine if the patient is using DHEA and discontinue DHEA.

7) Probable Mechanism: serotonergic activity of dehydroepiandrosterone, possibly increased androgen levels

8) Literature Reports

a) A 31-year-old male was admitted following threats to commit suicide and injure family members. He had self-initiated sertraline 100 milligrams (mg) daily for the previous 2 to 3 weeks for depression. Sertraline had been prescribed 3 years prior when he was diagnosed with bipolar disorder, which he discontinued after 2 weeks. He had also taken dehydroepiandrosterone (DHEA) 300 mg to 500 mg daily for the previous 2 months apparently for weight training. Following use of DHEA for a short time, he became more irritable, was not sleeping well, and began threatening a female friend and family members. He also drank alcohol occasionally and reportedly had difficulty controlling his anger when intoxicated. Sertraline was stopped and the patient was treated with valproic acid with the dose titrated to 500 mg twice daily. The combination of DHEA, sertraline, and alcohol was suggested responsible for the developing of the manic episode (Dean, 2000).

3.5.1.AO 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 cohort studies have shown that the combined use of SSRIs and anticoagulants has been associated with an increased risk of bleeding (Wallerstedt et al, 2009; Schalekamp et al, 2008; Prod Info PAXIL(R) oral tablets, suspension, 2008). Bleeding events reported have included epistaxis, ecchymosis, hematoma, petechiae, and life-threatening hemorrhages. Altered anticoagulant effects (including increased bleeding) have been reported with the coadministration of SSRIs with warfarin (Schalekamp et al, 2008; Prod Info PAXIL(R) oral tablets, suspension, 2008).

3) Severity: major

4) Onset: delayed

5) Substantiation: probable

6) Clinical Management: When paroxetine and an anticoagulant are given concurrently, monitor patients for signs of increased bleeding. Patients who are taking warfarin should be monitored closely for altered anticoagulant effects, including increased bleeding, when paroxetine therapy is initiated or discontinued (Prod Info PAXIL(R) oral tablets, suspension, 2008).

7) Probable Mechanism: unknown

8) Literature Reports

a) According to a retrospective cohort study (n=234), there was an increased risk of clinically relevant bleeding (hospital admission due to bleeding) in patients receiving warfarin for atrial fibrillation during concomitant SSRI therapy or within 2 weeks following SSRI therapy termination. Patients with a mean age of 72 +/- 7 years receiving warfarin plus SSRI (n=117) were matched with randomly selected patients who received warfarin only (n=117). SSRI included fluoxetine, citalopram, paroxetine, sertraline, fluvoxamine, or escitalopram. Nine patients experienced 11 bleeding episodes during 213.9 treatment years in the warfarin plus SSRI group, and 10 patients experienced 14 bleedings during 586.4 treatment years in the warfarin-only group. The corresponding total incidences of bleedings were 51.4 and 23.9 per 1000 treatment years, respectively. The hazard ratio for first bleedings during treatment with warfarin plus SSRI was 3.49 (95% CI; 1.37 to 8.91, p=0.009) compared with warfarin only. The SSRI implicated in patients experiencing bleeding at the time of concomitant administration were sertraline or citalopram. The addition of an SSRI was not associated with a change in warfarin dose or INR (p=0.48 and p=0.31 respectively). The results of the study may be limited by earlier bleeding events, unknown patient adherence, and exclusion of clopidogrel, dipyridamol, corticosteroids and anticoagulants other than warfarin in the model (Wallerstedt et al, 2009).

b) A population-based, case-controlled study of new coumarin users (acenocoumarol and phenprocoumon) with concomitant selective serotonin reuptake inhibitors (SSRIs) resulted in an increased risk of hospitalization due to nongastrointestinal bleeding. Using national pharmacy and hospitalization records, Netherlands researchers identified 1848 cases that were admitted for abnormal bleeding and compared them with 5818 control subjects also taking coumarins. Median duration of treatment in patients was 220 days (range, 1 to 4690 days). Patients on SSRIs showed greater risk for hospitalization for nongastrointestinal bleeding (adjusted odds ratio (OR) 1.7, 95% confidence interval (CI), 1.1 to 2.5), however, the rate of gastrointestinal bleeding (adjusted OR 0.8, 95% CI, 0.4 to 1.5) was not significantly different (Schalekamp et al, 2008).
c) Preliminary data suggest that there may be a pharmacodynamic interaction (that causes an increased bleeding diathesis with unaltered prothrombin time) between paroxetine and warfarin. The concomitant use of paroxetine and warfarin should be undertaken with caution (Prod Info PAXIL(R) oral tablets, suspension, 2008).
d) In a multiple-dose study, several days of combined therapy with warfarin and paroxetine resulted in mild but clinically significant bleeding in 5 of 27 subjects. This effect occurred in the absence of a significant enhancement in warfarin-induced hypoprothrombinemia or changes in either paroxetine or warfarin disposition (Bannister et al, 1989b).

3.5.1.AP Desipramine

1) Interaction Effect: an increase in the plasma concentrations of desipramine and in related side effects (dry mouth, sedation)
2) Summary: Paroxetine may increase desipramine exposure when the two are coadministered, and associated clinical toxicity (agitation, tremor, hyperreflexia, tachycardia) has been reported (Prod Info Paxil (R), 2002b; Chan et al, 1998a). Citalopram was successfully substituted for paroxetine when desipramine toxicity occurred with paroxetine coadministration (Ashton, 2000a). Paroxetine is metabolized by the cytochrome P450 2D6 isozyme, saturating it early during paroxetine dosing; desipramine is also metabolized by CYP2D6, and its metabolism is inhibited by the enzyme saturation caused by paroxetine (Prod Info Paxil(R), 2002b).
3) Severity: moderate
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: Monitor desipramine concentrations when there is a change in therapy or dose of paroxetine. Monitor for evidence of increased plasma levels of desipramine, such as dry mouth and sedation, with concurrent therapy. Lower desipramine doses may be required in some clinical situations.
7) Probable Mechanism: decreased cytochrome P450 2D6-mediated desipramine metabolism
8) Literature Reports

a) The effect of paroxetine on desipramine metabolism was studied in 9 extensive metabolizers (EM) and 8 poor metabolizers (PM) of desipramine (Brosen et al, 1993p). Subjects took a single oral dose of desipramine before starting paroxetine and a second dose after 11 days of paroxetine use. After the addition of paroxetine, EMs experienced a 5-fold decrease in clearance of desipramine, indicating that paroxetine inhibits oxidation reactions catalyzed by CYP2D6. PMs had only a slight increase in clearance of desipramine with paroxetine. With concurrent administration of desipramine and paroxetine, interaction of the two drugs may result in a need for dosage adjustments, especially in extensive metabolizers of desipramine.
b) A 21 year-old man experienced agitation, hyperreflexia, tremor, and tachycardia after taking a single dose of paroxetine one day after discontinuing desipramine therapy. The authors recommend at least a two-week washout period between use of selective serotonin reuptake inhibitors (SSRIs) and other classes of antidepressants such as monoamine oxidase inhibitors (MAOIs), tricyclic antidepressants (TCAs), and selective noradrenaline reuptake inhibitors (SNRIs) (Chan et al, 1998).
c) A 45-year-old white female with major depressive disorder and dysthymia failed several trials of antidepressants from all available drug classes, as well as electroconvulsive therapy. The patient's medications included pindolol, desipramine, clonazepam, and olanzapine. Paroxetine was initiated and titration to 40 mg/day occurred over 3 months. The patient developed lightheadedness, ataxia, and increased confusion after the titration. Desipramine serum levels were 1810 ng/mL (therapeutic range 75-300 ng/mL). After decreasing the daily desipramine 200 mg, the serum desipramine level was still 1665 ng/mL. The reduction in side effects were evident when the paroxetine dose was decreased to 30 mg/day and desipramine dose was decreased to 150 mg/day. Despite the dosage reduction of both drugs the patient's serum desipramine level was 1153 ng/mL. Paroxetine was discontinued and desipramine dose was decreased to 100 mg/day in divided doses. Citalopram was initiated and titrated to 40 mg/day. Over the next two months the patient's desipramine level decreased to 195 ng/mL. Depressive symptoms also improved. Desipramine toxicity is presumed to be caused by hepatic cytochrome P450 2D6 (CYP2D6) isoenzyme blockade from paroxetine. The author concludes that the switch to citalopram likely is responsible for diminished desipramine serum levels, although alternative explanations should not be discounted (Ashton, 2000).
d) One study looked at the effects on the pharmacokinetics of single-dose desipramine and concomitant paroxetine therapy. Paroxetine given daily (20 mg/day) under steady-state conditions increased single dose desipramine (100mg) Cmax, AUC, and T1/2 by an average of approximately 2, 5, and 3-fold, respectively (Prod Info PAXIL(R) oral tablets and oral suspension, 2005).

3.5.1.AQ 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 cohort studies have shown that the combined use of SSRIs and anticoagulants has been associated with an increased risk of bleeding (Wallerstedt et al, 2009; Schalekamp et al, 2008; Prod Info PAXIL(R) oral tablets, suspension, 2008). Bleeding events reported have included epistaxis, ecchymosis, hematoma, petechiae, and life-threatening hemorrhages. Altered anticoagulant effects (including increased bleeding) have been reported with the coadministration of SSRIs with warfarin (Schalekamp et al, 2008; Prod Info PAXIL(R) oral tablets, suspension, 2008).

3) Severity: major

4) Onset: delayed

5) Substantiation: probable

6) Clinical Management: When paroxetine and an anticoagulant are given concurrently, monitor patients for signs of increased bleeding. Patients who are taking warfarin should be monitored closely for altered anticoagulant effects, including increased bleeding, when paroxetine therapy is initiated or discontinued (Prod Info PAXIL(R) oral tablets, suspension, 2008).

7) Probable Mechanism: unknown

8) Literature Reports

a) According to a retrospective cohort study (n=234), there was an increased risk of clinically relevant bleeding (hospital admission due to bleeding) in patients receiving warfarin for atrial fibrillation during concomitant SSRI therapy or within 2 weeks following SSRI therapy termination. Patients with a mean age of 72 +/- 7 years receiving warfarin plus SSRI (n=117) were matched with randomly selected patients who received warfarin only (n=117). SSRI included fluoxetine, citalopram, paroxetine, sertraline, fluvoxamine, or escitalopram. Nine patients experienced 11 bleeding episodes during 213.9 treatment years in the warfarin plus SSRI group, and 10 patients experienced 14 bleedings during 586.4 treatment years in the warfarin-only group. The corresponding total incidences of bleedings were 51.4 and 23.9 per 1000 treatment years, respectively. The hazard ratio for first bleedings during treatment with warfarin plus SSRI was 3.49 (95% CI; 1.37 to 8.91, p=0.009) compared with warfarin only. The SSRI implicated in patients experiencing bleeding at the time of concomitant administration were sertraline or citalopram. The addition of an SSRI was not associated with a change in warfarin dose or INR (p=0.48 and p=0.31 respectively). The results of the study may be limited by earlier bleeding events, unknown patient adherence, and exclusion of clopidogrel, dipyridamol, corticosteroids and anticoagulants other than warfarin in the model (Wallerstedt et al, 2009).

b) A population-based, case-controlled study of new coumarin users (acenocoumarol and phenprocoumon) with concomitant selective serotonin reuptake inhibitors (SSRIs) resulted in an increased risk of hospitalization due to nongastrointestinal bleeding. Using national pharmacy and hospitalization records, Netherlands researchers identified 1848 cases that were admitted for abnormal bleeding and compared them with 5818 control subjects also taking coumarins. Median duration of treatment in patients was 220 days (range, 1 to 4690 days). Patients on SSRIs showed greater risk for hospitalization for nongastrointestinal bleeding (adjusted odds ratio (OR) 1.7, 95% confidence interval (CI), 1.1 to 2.5), however, the rate of gastrointestinal bleeding (adjusted OR 0.8, 95% CI, 0.4 to 1.5) was not significantly different (Schalekamp et al, 2008).

c) Preliminary data suggest that there may be a pharmacodynamic interaction (that causes an increased bleeding diathesis with unaltered prothrombin time) between paroxetine and warfarin. The concomitant use of paroxetine and warfarin should be undertaken with caution (Prod Info PAXIL(R) oral tablets, suspension, 2008).

d) In a multiple-dose study, several days of combined therapy with warfarin and paroxetine resulted in mild but clinically significant bleeding in 5 of 27 subjects. This effect occurred in the absence of a significant enhancement in warfarin-induced hypoprothrombinemia or changes in either paroxetine or warfarin disposition (Bannister et al, 1989b).

3.5.1.AR Desvenlafaxine

1) Interaction Effect: increased risk of serotonin syndrome (hypertension, hyperthermia, myoclonus, mental status changes)

2) Summary: Concurrent use of desvenlafaxine and a selective serotonin reuptake inhibitor (SSRI) may result in serotonin syndrome, which may be life-threatening. Symptoms of serotonin syndrome may include restlessness, hallucinations, loss of coordination, fast heart beat, rapid changes in blood pressure, increased body temperature, overreactive reflexes, nausea, vomiting, and diarrhea (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 condition called serotonin syndrome. If these agents are used together, discuss the risks of serotonin syndrome with the patient and monitor closely for symptoms of serotonin syndrome (restlessness, hyperthermia, hyperreflexia, incoordination), especially during treatment initiation and dose increases (Prod Info PRISTIQ(TM) oral extended-release tablets, 2008).

7) Probable Mechanism: additive serotonergic effect

3.5.1.AS 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 and inhibits serotonin reuptake. Combination therapy with dexfenfluramine and another selective serotonin reuptake inhibitor, such as paroxetine, has the potential to cause serotonin syndrome (Schenck & Mahowald, 1996). Serotonin syndrome is a hyperserotonergic state characterized by symptoms such as restlessness, myoclonus, changes in mental status, hyperreflexia, diaphoresis, shivering, and tremor. Serious, even fatal, reactions have been reported (Sternbach, 1991o). Dexfenfluramine should not be used in combination with paroxetine (Prod Info Redux(R), 1997).
3) Severity: major
4) Onset: rapid
5) Substantiation: theoretical
6) Clinical Management: Concurrent use of dexfenfluramine and paroxetine may result in an additive increase in serotonin levels in the central nervous system, and could result in serotonin syndrome (hypertension, hyperthermia, myoclonus, mental status changes). Dexfenfluramine should not be used in combination with paroxetine or other serotonin specific reuptake inhibitors.
7) Probable Mechanism: additive serotonergic effects

3.5.1.AT Dexketoprofen

1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs and NSAIDs has been associated with an increased risk of bleeding. Bleeding events have included epistaxis, ecchymosis, hematoma, petechiae, and life-threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension, 2008) (Prod Info Lexapro(TM), 2003; Dalton et al, 2003a; Prod Info CELEXA (R) oral tablet, solution, 2005).
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 increased bleeding.
7) Probable Mechanism: unknown
8) Literature Reports
a) SSRIs increase the risk of upper gastrointestinal bleeding and this effect is potentiated by concurrent use of NSAIDs or low-dose aspirin. Hospitalizations for upper gastrointestinal bleeding were searched among 26,005 users of antidepressant medications and compared with the number of hospitalizations in those patients who did not receive prescriptions for antidepressants. The amount of upper GI bleeding episodes was 3.6 times more than expected (95% confidence interval, 2.7 to 4.7). Combined use of an SSRI and NSAIDs or low-dose aspirin increased the risk to 12.2 (95% confidence interval, 7.1 to 19.5) and 5.2 (95% confidence interval, 3.2 to 8), respectively. The findings of this study demonstrate an increased risk of upper GI bleeding during the use of SSRIs. Combined use of SSRIs and NSAIDs or low-dose aspirin increased the risk even further (Dalton et al, 2003).
b) Coadministration of ketorolac with psychoactive drugs (such as fluoxetine) has been associated with hallucinations in some patients (Prod Info TORADOL(R) oral tablets, 2007).

3.5.1.AU Dextromethorphan

1) Interaction Effect: possible dextromethorphan toxicity (nausea, vomiting, blurred vision, hallucinations) or serotonin syndrome (hypertension, hyperthermia, myoclonus, mental status changes)
2) Summary: Coadministration of paroxetine with dextromethorphan has been implicated in two cases of serotonin syndrome (hypertension, hyperthermia, myoclonus, mental status changes) (Skop et al, 1994a; Harvey & Burke, 1995). Paroxetine is known to inhibit cytochrome P450IID6 (CYP2D6), the same enzyme which catalyzes dextromethorphan metabolism, and is itself metabolized by this enzyme (Prod Info Paxil(R), 1999e; Murray, 1992a). With concomitant administration, both agents may competitively inhibit each others metabolism. Thus, serum levels of both medications would be expected to increase.
3) Severity: major
4) Onset: rapid
5) Substantiation: probable
6) Clinical Management: Caution patients taking paroxetine that an interaction could occur with dextromethorphan. A reduction in the dextromethorphan dose may be necessary.
7) Probable Mechanism: competitively inhibited metabolism of both agents
8) Literature Reports
a) A 51-year old male patient with vascular disease developed serotonin syndrome following concurrent use of dextromethorphan and paroxetine. Two days after self-medication with a dextromethorphan-containing cold product, the patient experienced shortness of breath, nausea, headache, and confusion. Upon arrival to the hospital, the patient presented with diaphoresis, tremor, confusion, abdominal pain, and severe shortness of breath. After administration of benzodiazepines and discontinuation of paroxetine, the patient's condition improved and no further complications were seen

(Skop et al, 1994).

3.5.1.AV Diclofenac

1) Interaction Effect: an increased risk of bleeding

2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs and NSAIDs has been associated with an increased risk of bleeding. Bleeding events have included epistaxis, ecchymosis, hematoma, petechiae, and life-threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension, 2008) (Prod Info Lexapro(TM), 2003; Dalton et al, 2003a; Prod Info CELEXA (R) oral tablet, solution, 2005).

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 increased bleeding.

7) Probable Mechanism: unknown

8) Literature Reports

a) SSRIs increase the risk of upper gastrointestinal bleeding and this effect is potentiated by concurrent use of NSAIDs or low-dose aspirin. Hospitalizations for upper gastrointestinal bleeding were searched among 26,005 users of antidepressant medications and compared with the number of hospitalizations in those patients who did not receive prescriptions for antidepressants. The amount of upper GI bleeding episodes was 3.6 times more than expected (95% confidence interval, 2.7 to 4.7). Combined use of an SSRI and NSAIDs or low-dose aspirin increased the risk to 12.2 (95% confidence interval, 7.1 to 19.5) and 5.2 (95% confidence interval, 3.2 to 8), respectively. The findings of this study demonstrate an increased risk of upper GI bleeding during the use of SSRIs. Combined use of SSRIs and NSAIDs or low-dose aspirin increased the risk even further (Dalton et al, 2003).

b) Coadministration of ketorolac with psychoactive drugs (such as fluoxetine) has been associated with hallucinations in some patients (Prod Info TORADOL(R) oral tablets, 2007).

3.5.1.AW 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 cohort studies have shown that the combined use of SSRIs and anticoagulants has been associated with an increased risk of bleeding (Wallerstedt et al, 2009; Schalekamp et al, 2008; Prod Info PAXIL(R) oral tablets, suspension, 2008). Bleeding events reported have included epistaxis, ecchymosis, hematoma, petechiae, and life-threatening hemorrhages. Altered anticoagulant effects (including increased bleeding) have been reported with the coadministration of SSRIs with warfarin (Schalekamp et al, 2008; Prod Info PAXIL(R) oral tablets, suspension, 2008).

3) Severity: major

4) Onset: delayed

5) Substantiation: probable

6) Clinical Management: When paroxetine and an anticoagulant are given concurrently, monitor patients for signs of increased bleeding. Patients who are taking warfarin should be monitored closely for altered anticoagulant effects, including increased bleeding, when paroxetine therapy is initiated or discontinued (Prod Info PAXIL(R) oral tablets, suspension, 2008).

7) Probable Mechanism: unknown

8) Literature Reports

a) According to a retrospective cohort study (n=234), there was an increased risk of clinically relevant bleeding (hospital admission due to bleeding) in patients receiving warfarin for atrial fibrillation during concomitant SSRI therapy or within 2 weeks following SSRI therapy termination. Patients with a mean age of 72 +/- 7 years receiving warfarin plus SSRI (n=117) were matched with randomly selected patients who received warfarin only (n=117). SSRI included fluoxetine, citalopram, paroxetine, sertraline, fluvoxamine, or escitalopram. Nine patients experienced 11 bleeding episodes during 213.9 treatment years in the warfarin plus SSRI group, and 10 patients experienced 14 bleedings during 586.4 treatment years in the warfarin-only group. The corresponding total incidences of bleedings were 51.4 and 23.9 per 1000 treatment years, respectively. The hazard ratio for first bleedings during treatment with warfarin plus SSRI was 3.49 (95% CI; 1.37 to 8.91, p=0.009) compared with warfarin only. The SSRI implicated in patients experiencing bleeding at the time of concomitant administration were sertraline or citalopram. The addition of an SSRI was not associated with a change in warfarin dose or INR (p=0.48 and p=0.31 respectively). The results of the study may be limited by earlier bleeding events, unknown patient adherence, and exclusion of clopidogrel, dipyridamol, corticosteroids and anticoagulants other than warfarin in the model (Wallerstedt et al, 2009).

b) A population-based, case-controlled study of new coumarin users (acenocoumarol and phenprocoumon) with concomitant selective serotonin reuptake inhibitors (SSRIs) resulted in an increased risk of hospitalization due to nongastrointestinal bleeding. Using national pharmacy and hospitalization records, Netherlands researchers identified 1848 cases that were admitted for abnormal bleeding and compared them with 5818 control subjects also taking coumarins. Median duration of treatment in patients was 220 days (range, 1 to 4690 days). Patients on SSRIs showed greater risk for hospitalization for nongastrointestinal bleeding (adjusted odds ratio (OR) 1.7, 95% confidence interval

(CI), 1.1 to 2.5), however, the rate of gastrointestinal bleeding (adjusted OR 0.8, 95% CI, 0.4 to 1.5) was not significantly different (Schalekamp et al, 2008).
c) Preliminary data suggest that there may be a pharmacodynamic interaction (that causes an increased bleeding diathesis with unaltered prothrombin time) between paroxetine and warfarin. The concomitant use of paroxetine and warfarin should be undertaken with caution (Prod Info PAXIL(R) oral tablets, suspension, 2008).
d) In a multiple-dose study, several days of combined therapy with warfarin and paroxetine resulted in mild but clinically significant bleeding in 5 of 27 subjects. This effect occurred in the absence of a significant enhancement in warfarin-induced hypoprothrombinemia or changes in either paroxetine or warfarin disposition (Bannister et al, 1989b).

3.5.1.AX 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 cohort studies have shown that the combined use of SSRIs and NSAIDs has been associated with an increased risk of bleeding. Bleeding events have included epistaxis, ecchymosis, hematoma, petechiae, and life-threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension, 2008) (Prod Info Lexapro(TM), 2003; Dalton et al, 2003a; Prod Info CELEXA (R) oral tablet, solution, 2005).
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 increased bleeding.
7) Probable Mechanism: unknown
8) Literature Reports
a) SSRIs increase the risk of upper gastrointestinal bleeding and this effect is potentiated by concurrent use of NSAIDs or low-dose aspirin. Hospitalizations for upper gastrointestinal bleeding were searched among 26,005 users of antidepressant medications and compared with the number of hospitalizations in those patients who did not receive prescriptions for antidepressants. The amount of upper GI bleeding episodes was 3.6 times more than expected (95% confidence interval, 2.7 to 4.7). Combined use of an SSRI and NSAIDs or low-dose aspirin increased the risk to 12.2 (95% confidence interval, 7.1 to 19.5) and 5.2 (95% confidence interval, 3.2 to 8), respectively. The findings of this study demonstrate an increased risk of upper GI bleeding during the use of SSRIs. Combined use of SSRIs and NSAIDs or low-dose aspirin increased the risk even further (Dalton et al, 2003).
b) Coadministration of ketorolac with psychoactive drugs (such as fluoxetine) has been associated with hallucinations in some patients (Prod Info TORADOL(R) oral tablets, 2007).

3.5.1.AY 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 cohort studies have shown that the combined use of SSRIs and antiplatelet agents has been associated with an increased risk of bleeding. Bleeding events reported have included epistaxis, ecchymosis, hematoma, petechiae, and life-threatening hemorrhages (Prod Info PAXIL(R) oral 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 signs of increased bleeding (Prod Info PAXIL(R) oral tablets, suspension, 2008; Prod Info PROZAC(R) oral capsules, delayed-release capsules, solution, 2008)
7) Probable Mechanism: unknown

3.5.1.AZ 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 cohort studies have shown that the combined use of SSRIs and NSAIDs has been associated with an increased risk of bleeding. Bleeding events have included epistaxis, ecchymosis, hematoma, petechiae, and life-threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension, 2008) (Prod Info Lexapro(TM), 2003; Dalton et al, 2003a; Prod Info CELEXA (R) oral tablet, solution, 2005).
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 increased bleeding.
7) Probable Mechanism: unknown
8) Literature Reports
a) SSRIs increase the risk of upper gastrointestinal bleeding and this effect is potentiated by concurrent use of NSAIDs or low-dose aspirin. Hospitalizations for upper gastrointestinal bleeding were searched

among 26,005 users of antidepressant medications and compared with the number of hospitalizations in those patients who did not receive prescriptions for antidepressants. The amount of upper GI bleeding episodes was 3.6 times more than expected (95% confidence interval, 2.7 to 4.7). Combined use of an SSRI and NSAIDs or low-dose aspirin increased the risk to 12.2 (95% confidence interval, 7.1 to 19.5) and 5.2 (95% confidence interval, 3.2 to 8), respectively. The findings of this study demonstrate an increased risk of upper GI bleeding during the use of SSRIs. Combined use of SSRIs and NSAIDs or low-dose aspirin increased the risk even further (Dalton et al, 2003).

b) Coadministration of ketorolac with psychoactive drugs (such as fluoxetine) has been associated with hallucinations in some patients (Prod Info TORADOL(R) oral tablets, 2007).

3.5.1.BA Dothiepin

1) Interaction Effect: dothiepin toxicity (dry mouth, sedation, urinary retention)

2) Summary: Paroxetine coadministered with desipramine or imipramine produced higher serum concentrations of the tricyclic antidepressant (TCA) in some patients (Hartter et al, 1994c; Brosen et al, 1993i) because paroxetine may inhibit dothiepin metabolism (Prod Info Paxil CR(TM), 2003g). Although not reported specifically with dothiepin, a similar interaction could be expected to occur. The effect of paroxetine on TCA metabolism may resemble that of fluoxetine (another selective serotonin reuptake inhibitor), which is known to inhibit TCA metabolism (Aranow et al, 1989c; Vaughan, 1988c; Goodnick, 1989c).

3) Severity: moderate

4) Onset: delayed

5) Substantiation: probable

6) Clinical Management: When paroxetine is coadministered with dothiepin, monitor patients for signs and symptoms of dothiepin toxicity (dry mouth, sedation, urinary retention, blurred vision). Dothiepin doses may need to be reduced.

7) Probable Mechanism: decreased dothiepin metabolism

8) Literature Reports

a) The effect of paroxetine on desipramine metabolism was studied in 9 extensive metabolizers (EM) and 8 poor metabolizers (PM) of desipramine. Subjects took a single oral dose of desipramine before starting paroxetine and a second dose after 11 days of paroxetine use. After the addition of paroxetine, extensive metabolizers experienced a 5-fold decrease in clearance of desipramine, indicating that paroxetine inhibits oxidation reactions catalyzed by CYP2D6. Poor metabolizers had a slight increase in clearance of desipramine during paroxetine coadministration. With concurrent administration of desipramine and paroxetine, interaction of the two drugs may result in a need for dosage adjustments, especially in extensive metabolizers of desipramine (Brosen et al, 1993h).

3.5.1.BB Doxepin

1) Interaction Effect: doxepin toxicity (dry mouth, sedation, urinary retention)

2) Summary: Paroxetine coadministered with desipramine or imipramine produced higher serum concentrations of the tricyclic antidepressant (TCA) in some patients (Hartter et al, 1994f; Brosen et al, 1993o). Although not reported specifically with doxepin, a similar interaction could be expected to occur. Paroxetine's effect on TCAs may resemble that of fluoxetine (another selective serotonin reuptake inhibitor), which is known to inhibit TCA metabolism (Aranow et al, 1989f; Vaughan, 1988f; Goodnick, 1989f). With coadministration, monitor patients for doxepin toxicity. Doxepin doses may need to be reduced (Prod Info Paxil CR(TM), 2003n).

3) Severity: moderate

4) Onset: delayed

5) Substantiation: probable

6) Clinical Management: When doxepin is coadministered with paroxetine, monitor patients for signs and symptoms of doxepin toxicity (dry mouth, sedation, urinary retention, blurred vision). Doxepin doses may need to be reduced.

7) Probable Mechanism: decreased doxepin metabolism

8) Literature Reports

a) The effect of paroxetine on desipramine metabolism was studied in 9 extensive metabolizers (EM) and 8 poor metabolizers (PM) of desipramine. Subjects took a single oral dose of desipramine before starting paroxetine and a second dose after 11 days of paroxetine use. After the addition of paroxetine, EMs experienced a 5-fold decrease in clearance of desipramine, indicating that paroxetine inhibits oxidation reactions catalyzed by CYP2D6. PMs had a slight increase in clearance of desipramine with paroxetine. With concurrent administration of desipramine and paroxetine, interaction of the two drugs may result in a need for dosage adjustments, especially in extensive metabolizers of desipramine (Brosen et al, 1993n).

3.5.1.BC 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 with droperidol. Possible pharmacodynamic interactions can occur between droperidol and potentially arrhythmogenic agents such as antidepressants that prolong the QT interval (Prod Info Inapsine(R), 2002).

3) Severity: major

4) Onset: rapid
5) Substantiation: theoretical
6) Clinical Management: Droperidol should be administered with extreme caution in the presence of risk factors for development of prolonged QT syndrome, such as treatment with antidepressants.
7) Probable Mechanism: additive cardiac effects

3.5.1.BD 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 cohort studies have shown that the combined use of SSRIs and NSAIDs has been associated with an increased risk of bleeding. Bleeding events have included epistaxis, ecchymosis, hematoma, petechiae, and life-threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension, 2008) (Prod Info Lexapro(TM), 2003; Dalton et al, 2003a; Prod Info CELEXA (R) oral tablet, solution, 2005).
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 increased bleeding.
7) Probable Mechanism: unknown
8) Literature Reports
a) SSRIs increase the risk of upper gastrointestinal bleeding and this effect is potentiated by concurrent use of NSAIDs or low-dose aspirin. Hospitalizations for upper gastrointestinal bleeding were searched among 26,005 users of antidepressant medications and compared with the number of hospitalizations in those patients who did not receive prescriptions for antidepressants. The amount of upper GI bleeding episodes was 3.6 times more than expected (95% confidence interval, 2.7 to 4.7). Combined use of an SSRI and NSAIDs or low-dose aspirin increased the risk to 12.2 (95% confidence interval, 7.1 to 19.5) and 5.2 (95% confidence interval, 3.2 to 8), respectively. The findings of this study demonstrate an increased risk of upper GI bleeding during the use of SSRIs. Combined use of SSRIs and NSAIDs or low-dose aspirin increased the risk even further (Dalton et al, 2003).
b) Coadministration of ketorolac with psychoactive drugs (such as fluoxetine) has been associated with hallucinations in some patients (Prod Info TORADOL(R) oral tablets, 2007).

3.5.1.BE Duloxetine

1) Interaction Effect: increased duloxetine serum concentrations and an increased risk of serotonin syndrome
2) Summary: Duloxetine is a selective serotonin and norepinephrine reuptake inhibitor (SNRI). The concomitant use of duloxetine with paroxetine, an SSRI, is not recommended due to the potential for serotonin syndrome. In addition, coadministration of paroxetine, a potent CYP2D6 inhibitor, at a dose of 20 mg once daily with duloxetine 40 mg once daily resulted in a 60% increase in duloxetine serum concentration (Prod Info CYMBALTA(R) delayed-release oral capsules, 2008).
3) Severity: major
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: The concomitant use of duloxetine and paroxetine is not recommended due to the potential for development of serotonin syndrome. Additionally, concomitant use has resulted in significantly increased duloxetine serum levels (Prod Info CYMBALTA(R) delayed-release oral capsules, 2008).
7) Probable Mechanism: paroxetine inhibition of CYP2D6-mediated duloxetine metabolism; additive serotonergic effects

3.5.1.BF Eletriptan

1) Interaction Effect: an increased risk of serotonin syndrome
2) Summary: There have been case reports of weakness, hyperreflexia, and incoordination following concomitant use of sumatriptan, a 5-hydroxytryptamine-1 (5HT-1) agonist, and a serotonin specific reuptake inhibitor (SSRI) (Prod Info Imitrex(R) Nasal Spray, 2003). Because eletriptan is a 5HT 1B/1D agonist, a similar interaction between SSRIs and eletriptan may occur (Prod Info Relpax(R), 2003). Concurrent use of a triptan and an SSRI may result in serotonin syndrome which may be life-threatening. Symptoms of serotonin syndrome may include restlessness, hallucinations, loss of coordination, fast heart beat, rapid changes in blood pressure, increased body temperature, overreactive reflexes, nausea, vomiting, and diarrhea. Clinicians should be aware that triptans may be commonly used intermittently and that either the triptan or the SSRI may be prescribed by a different physician. Discuss the risks of serotonin syndrome with patients who are prescribed this combination and monitor them closely for symptoms of serotonin syndrome (US Food and Drug Administration, 2006).
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-threatening condition called serotonin syndrome. Be aware that triptans may be commonly used intermittently and that either the triptan or the SSRI may be prescribed by a different physician. If these

agents are used together, discuss the risks of serotonin syndrome with the patient and monitor closely for symptoms of serotonin syndrome (restlessness, hyperthermia, hyperreflexia, incoordination).
7) Probable Mechanism: additive pharmacologic effects resulting in excessive serotonergic stimulation

3.5.1.BG Encainide
1) Interaction Effect: an increased risk of encainide toxicity (cardiac arrhythmia)
2) Summary: Coadministration of paroxetine with other drugs that are metabolized by the cytochrome P4502D6 enzyme, such as encainide, should be approached with caution (Prod Info Paxil CR(TM), 2003k).
3) Severity: moderate
4) Onset: rapid
5) Substantiation: probable
6) Clinical Management: Monitor heart rate and the EKG in patients receiving concurrent paroxetine and encainide. Doses may need to be reduced. Coadministration of these agents should be approached with caution.
7) Probable Mechanism: inhibition of encainide metabolism

3.5.1.BH 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 cohort studies have shown that the combined use of SSRIs and anticoagulants has been associated with an increased risk of bleeding (Wallerstedt et al, 2009; Schalekamp et al, 2008; Prod Info PAXIL(R) oral tablets, suspension, 2008). Bleeding events reported have included epistaxis, ecchymosis, hematoma, petechiae, and life-threatening hemorrhages. Altered anticoagulant effects (including increased bleeding) have been reported with the coadministration of SSRIs with warfarin (Schalekamp et al, 2008; Prod Info PAXIL(R) oral tablets, suspension, 2008).
3) Severity: major
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: When paroxetine and an anticoagulant are given concurrently, monitor patients for signs of increased bleeding. Patients who are taking warfarin should be monitored closely for altered anticoagulant effects, including increased bleeding, when paroxetine therapy is initiated or discontinued (Prod Info PAXIL(R) oral tablets, suspension, 2008).
7) Probable Mechanism: unknown
8) Literature Reports
a) According to a retrospective cohort study (n=234), there was an increased risk of clinically relevant bleeding (hospital admission due to bleeding) in patients receiving warfarin for atrial fibrillation during concomitant SSRI therapy or within 2 weeks following SSRI therapy termination. Patients with a mean age of 72 +/- 7 years receiving warfarin plus SSRI (n=117) were matched with randomly selected patients who received warfarin only (n=117). SSRI included fluoxetine, citalopram, paroxetine, sertraline, fluvoxamine, or escitalopram. Nine patients experienced 11 bleeding episodes during 213.9 treatment years in the warfarin plus SSRI group, and 10 patients experienced 14 bleedings during 586.4 treatment years in the warfarin-only group. The corresponding total incidences of bleedings were 51.4 and 23.9 per 1000 treatment years, respectively. The hazard ratio for first bleedings during treatment with warfarin plus SSRI was 3.49 (95% CI; 1.37 to 8.91, p=0.009) compared with warfarin only. The SSRI implicated in patients experiencing bleeding at the time of concomitant administration were sertraline or citalopram. The addition of an SSRI was not associated with a change in warfarin dose or INR (p=0.48 and p=0.31 respectively). The results of the study may be limited by earlier bleeding events, unknown patient adherence, and exclusion of clopidogrel, dipyridamol, corticosteroids and anticoagulants other than warfarin in the model (Wallerstedt et al, 2009).
b) A population-based, case-controlled study of new coumarin users (acenocoumarol and phenprocoumon) with concomitant selective serotonin reuptake inhibitors (SSRIs) resulted in an increased risk of hospitalization due to nongastrointestinal bleeding. Using national pharmacy and hospitalization records, Netherlands researchers identified 1848 cases that were admitted for abnormal bleeding and compared them with 5818 control subjects also taking coumarins. Median duration of treatment in patients was 220 days (range, 1 to 4690 days). Patients on SSRIs showed greater risk for hospitalization for nongastrointestinal bleeding (adjusted odds ratio (OR) 1.7, 95% confidence interval (CI), 1.1 to 2.5), however, the rate of gastrointestinal bleeding (adjusted OR 0.8, 95% CI, 0.4 to 1.5) was not significantly different (Schalekamp et al, 2008).
c) Preliminary data suggest that there may be a pharmacodynamic interaction (that causes an increased bleeding diathesis with unaltered prothrombin time) between paroxetine and warfarin. The concomitant use of paroxetine and warfarin should be undertaken with caution (Prod Info PAXIL(R) oral tablets, suspension, 2008).
d) In a multiple-dose study, several days of combined therapy with warfarin and paroxetine resulted in mild but clinically significant bleeding in 5 of 27 subjects. This effect occurred in the absence of a significant enhancement in warfarin-induced hypoprothrombinemia or changes in either paroxetine or warfarin disposition (Bannister et al, 1989b).

3.5.1.BI 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 cohort studies have shown that the combined use of SSRIs and antiplatelet agents has been associated with an increased risk of bleeding. Bleeding events reported have included epistaxis, ecchymosis, hematoma, petechiae, and life-threatening hemorrhages (Prod Info PAXIL(R) oral 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 signs of increased bleeding (Prod Info PAXIL(R) oral tablets, suspension, 2008; Prod Info PROZAC(R) oral capsules, delayed-release capsules, solution, 2008)
7) Probable Mechanism: unknown

3.5.1.BJ 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 cohort studies have shown that the combined use of SSRIs and antiplatelet agents has been associated with an increased risk of bleeding. Bleeding events reported have included epistaxis, ecchymosis, hematoma, petechiae, and life-threatening hemorrhages (Prod Info PAXIL(R) oral 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 signs of increased bleeding (Prod Info PAXIL(R) oral tablets, suspension, 2008; Prod Info PROZAC(R) oral capsules, delayed-release capsules, solution, 2008)
7) Probable Mechanism: unknown

3.5.1.BK 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 cohort studies have shown that the combined use of SSRIs and NSAIDs has been associated with an increased risk of bleeding. Bleeding events have included epistaxis, ecchymosis, hematoma, petechiae, and life-threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension, 2008) (Prod Info Lexapro(TM), 2003; Dalton et al, 2003a; Prod Info CELEXA (R) oral tablet, solution, 2005).
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 increased bleeding.
7) Probable Mechanism: unknown
8) Literature Reports
a) SSRIs increase the risk of upper gastrointestinal bleeding and this effect is potentiated by concurrent use of NSAIDs or low-dose aspirin. Hospitalizations for upper gastrointestinal bleeding were searched among 26,005 users of antidepressant medications and compared with the number of hospitalizations in those patients who did not receive prescriptions for antidepressants. The amount of upper GI bleeding episodes was 3.6 times more than expected (95% confidence interval, 2.7 to 4.7). Combined use of an SSRI and NSAIDs or low-dose aspirin increased the risk to 12.2 (95% confidence interval, 7.1 to 19.5) and 5.2 (95% confidence interval, 3.2 to 8), respectively. The findings of this study demonstrate an increased risk of upper GI bleeding during the use of SSRIs. Combined use of SSRIs and NSAIDs or low-dose aspirin increased the risk even further (Dalton et al, 2003).
b) Coadministration of ketorolac with psychoactive drugs (such as fluoxetine) has been associated with hallucinations in some patients (Prod Info TORADOL(R) oral tablets, 2007).

3.5.1.BL 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 cohort studies have shown that the combined use of SSRIs and NSAIDs has been associated with an increased risk of bleeding. Bleeding events have included epistaxis, ecchymosis, hematoma, petechiae, and life-threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension, 2008) (Prod Info Lexapro(TM), 2003; Dalton et al, 2003a; Prod Info CELEXA (R) oral tablet, solution, 2005).
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 increased bleeding.
7) Probable Mechanism: unknown

8) Literature Reports

a) SSRIs increase the risk of upper gastrointestinal bleeding and this effect is potentiated by concurrent use of NSAIDs or low-dose aspirin. Hospitalizations for upper gastrointestinal bleeding were searched among 26,005 users of antidepressant medications and compared with the number of hospitalizations in those patients who did not receive prescriptions for antidepressants. The amount of upper GI bleeding episodes was 3.6 times more than expected (95% confidence interval, 2.7 to 4.7). Combined use of an SSRI and NSAIDs or low-dose aspirin increased the risk to 12.2 (95% confidence interval, 7.1 to 19.5) and 5.2 (95% confidence interval, 3.2 to 8), respectively. The findings of this study demonstrate an increased risk of upper GI bleeding during the use of SSRIs. Combined use of SSRIs and NSAIDs or low-dose aspirin increased the risk even further (Dalton et al, 2003).

b) Coadministration of ketorolac with psychoactive drugs (such as fluoxetine) has been associated with hallucinations in some patients (Prod Info TORADOL(R) oral tablets, 2007).

3.5.1.BM 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 cohort studies have shown that the combined use of SSRIs and NSAIDs has been associated with an increased risk of bleeding. Bleeding events have included epistaxis, ecchymosis, hematoma, petechiae, and life-threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension, 2008) (Prod Info Lexapro(TM), 2003; Dalton et al, 2003a; Prod Info CELEXA (R) oral tablet, solution, 2005).

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 increased bleeding.

7) Probable Mechanism: unknown

8) Literature Reports

a) SSRIs increase the risk of upper gastrointestinal bleeding and this effect is potentiated by concurrent use of NSAIDs or low-dose aspirin. Hospitalizations for upper gastrointestinal bleeding were searched among 26,005 users of antidepressant medications and compared with the number of hospitalizations in those patients who did not receive prescriptions for antidepressants. The amount of upper GI bleeding episodes was 3.6 times more than expected (95% confidence interval, 2.7 to 4.7). Combined use of an SSRI and NSAIDs or low-dose aspirin increased the risk to 12.2 (95% confidence interval, 7.1 to 19.5) and 5.2 (95% confidence interval, 3.2 to 8), respectively. The findings of this study demonstrate an increased risk of upper GI bleeding during the use of SSRIs. Combined use of SSRIs and NSAIDs or low-dose aspirin increased the risk even further (Dalton et al, 2003).

b) Coadministration of ketorolac with psychoactive drugs (such as fluoxetine) has been associated with hallucinations in some patients (Prod Info TORADOL(R) oral tablets, 2007).

3.5.1.BN 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 cohort studies have shown that the combined use of SSRIs and NSAIDs has been associated with an increased risk of bleeding. Bleeding events have included epistaxis, ecchymosis, hematoma, petechiae, and life-threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension, 2008) (Prod Info Lexapro(TM), 2003; Dalton et al, 2003a; Prod Info CELEXA (R) oral tablet, solution, 2005).

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 increased bleeding.

7) Probable Mechanism: unknown

8) Literature Reports

a) SSRIs increase the risk of upper gastrointestinal bleeding and this effect is potentiated by concurrent use of NSAIDs or low-dose aspirin. Hospitalizations for upper gastrointestinal bleeding were searched among 26,005 users of antidepressant medications and compared with the number of hospitalizations in those patients who did not receive prescriptions for antidepressants. The amount of upper GI bleeding episodes was 3.6 times more than expected (95% confidence interval, 2.7 to 4.7). Combined use of an SSRI and NSAIDs or low-dose aspirin increased the risk to 12.2 (95% confidence interval, 7.1 to 19.5) and 5.2 (95% confidence interval, 3.2 to 8), respectively. The findings of this study demonstrate an increased risk of upper GI bleeding during the use of SSRIs. Combined use of SSRIs and NSAIDs or low-dose aspirin increased the risk even further (Dalton et al, 2003).

b) Coadministration of ketorolac with psychoactive drugs (such as fluoxetine) has been associated with hallucinations in some patients (Prod Info TORADOL(R) oral tablets, 2007).

3.5.1.BO 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 cohort studies have shown that the combined use of SSRIs and NSAIDs has been associated with an increased risk of bleeding. Bleeding events have included epistaxis, ecchymosis, hematoma, petechiae, and life-threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension, 2008) (Prod Info Lexapro(TM), 2003; Dalton et al, 2003a; Prod Info CELEXA (R) oral tablet, solution, 2005).
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 increased bleeding.
7) Probable Mechanism: unknown
8) Literature Reports
a) SSRIs increase the risk of upper gastrointestinal bleeding and this effect is potentiated by concurrent use of NSAIDs or low-dose aspirin. Hospitalizations for upper gastrointestinal bleeding were searched among 26,005 users of antidepressant medications and compared with the number of hospitalizations in those patients who did not receive prescriptions for antidepressants. The amount of upper GI bleeding episodes was 3.6 times more than expected (95% confidence interval, 2.7 to 4.7). Combined use of an SSRI and NSAIDs or low-dose aspirin increased the risk to 12.2 (95% confidence interval, 7.1 to 19.5) and 5.2 (95% confidence interval, 3.2 to 8), respectively. The findings of this study demonstrate an increased risk of upper GI bleeding during the use of SSRIs. Combined use of SSRIs and NSAIDs or low-dose aspirin increased the risk even further (Dalton et al, 2003).
b) Coadministration of ketorolac with psychoactive drugs (such as fluoxetine) has been associated with hallucinations in some patients (Prod Info TORADOL(R) oral tablets, 2007).

3.5.1.BP 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 and inhibits serotonin reuptake. Combination therapy with fenfluramine and another selective serotonin reuptake inhibitor, such as paroxetine, has the potential to cause serotonin syndrome (Schneck & Mahowald, 1996). Serotonin syndrome is a hyperserotonergic state characterized by symptoms such as restlessness, myoclonus, changes in mental status, hyperreflexia, diaphoresis, shivering, and tremor. Serious, even fatal, reactions have been reported (Sternbach, 1991). Until more data are available, fenfluramine should not be used in combination with paroxetine.
3) Severity: major
4) Onset: rapid
5) Substantiation: theoretical
6) Clinical Management: Concurrent use of fenfluramine and paroxetine may result in an additive increase in serotonin levels in the central nervous system, and could result in serotonin syndrome (hypertension, hyperthermia, myoclonus, mental status changes). Fenfluramine should not be used in combination with paroxetine or other serotonin specific reuptake inhibitors.
7) Probable Mechanism: additive serotonergic effects

3.5.1.BQ 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 cohort studies have shown that the combined use of SSRIs and NSAIDs has been associated with an increased risk of bleeding. Bleeding events have included epistaxis, ecchymosis, hematoma, petechiae, and life-threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension, 2008) (Prod Info Lexapro(TM), 2003; Dalton et al, 2003a; Prod Info CELEXA (R) oral tablet, solution, 2005).
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 increased bleeding.
7) Probable Mechanism: unknown
8) Literature Reports
a) SSRIs increase the risk of upper gastrointestinal bleeding and this effect is potentiated by concurrent use of NSAIDs or low-dose aspirin. Hospitalizations for upper gastrointestinal bleeding were searched among 26,005 users of antidepressant medications and compared with the number of hospitalizations in those patients who did not receive prescriptions for antidepressants. The amount of upper GI bleeding episodes was 3.6 times more than expected (95% confidence interval, 2.7 to 4.7). Combined use of an SSRI and NSAIDs or low-dose aspirin increased the risk to 12.2 (95% confidence interval, 7.1 to 19.5) and 5.2 (95% confidence interval, 3.2 to 8), respectively. The findings of this study demonstrate an increased risk of upper GI bleeding during the use of SSRIs. Combined use of SSRIs and NSAIDs or low-dose aspirin increased the risk even further (Dalton et al, 2003).
b) Coadministration of ketorolac with psychoactive drugs (such as fluoxetine) has been associated with hallucinations in some patients (Prod Info TORADOL(R) oral tablets, 2007).

3.5.1.BR 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 cohort studies have shown that the combined use of SSRIs and NSAIDs has been associated with an increased risk of bleeding. Bleeding events have included epistaxis, ecchymosis, hematoma, petechiae, and life-threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension, 2008) (Prod Info Lexapro(TM), 2003; Dalton et al, 2003a; Prod Info CELEXA (R) oral tablet, solution, 2005).
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 increased bleeding.
7) Probable Mechanism: unknown
8) Literature Reports
a) SSRIs increase the risk of upper gastrointestinal bleeding and this effect is potentiated by concurrent use of NSAIDs or low-dose aspirin. Hospitalizations for upper gastrointestinal bleeding were searched among 26,005 users of antidepressant medications and compared with the number of hospitalizations in those patients who did not receive prescriptions for antidepressants. The amount of upper GI bleeding episodes was 3.6 times more than expected (95% confidence interval, 2.7 to 4.7). Combined use of an SSRI and NSAIDs or low-dose aspirin increased the risk to 12.2 (95% confidence interval, 7.1 to 19.5) and 5.2 (95% confidence interval, 3.2 to 8), respectively. The findings of this study demonstrate an increased risk of upper GI bleeding during the use of SSRIs. Combined use of SSRIs and NSAIDs or low-dose aspirin increased the risk even further (Dalton et al, 2003).
b) Coadministration of ketorolac with psychoactive drugs (such as fluoxetine) has been associated with hallucinations in some patients (Prod Info TORADOL(R) oral tablets, 2007).

3.5.1.BS Flecainide
1) Interaction Effect: an increased risk of flecainide toxicity (cardiac arrhythmia)
2) Summary: No data are currently available related to concomitant flecainide - paroxetine administration. Lower doses than usually prescribed for both paroxetine or flecainide may be required. Flecainide is metabolized in the liver by cytochrome P4502D6. Paroxetine is a potent inhibitor of this isoenzyme, in addition to being metabolized by cytochrome P4502D6 itself (Prod Info Paxil CR(TM), 2032; Caley & Weber, 1993).
3) Severity: moderate
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: Monitor heart rate and the EKG in patients receiving concurrent flecainide and paroxetine. Doses may need to be reduced. Coadministration of these agents should be approached with caution.
7) Probable Mechanism: inhibition of flecainide metabolism

3.5.1.BT 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 cohort studies have shown that the combined use of SSRIs and NSAIDs has been associated with an increased risk of bleeding. Bleeding events have included epistaxis, ecchymosis, hematoma, petechiae, and life-threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension, 2008) (Prod Info Lexapro(TM), 2003; Dalton et al, 2003a; Prod Info CELEXA (R) oral tablet, solution, 2005).
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 increased bleeding.
7) Probable Mechanism: unknown
8) Literature Reports
a) SSRIs increase the risk of upper gastrointestinal bleeding and this effect is potentiated by concurrent use of NSAIDs or low-dose aspirin. Hospitalizations for upper gastrointestinal bleeding were searched among 26,005 users of antidepressant medications and compared with the number of hospitalizations in those patients who did not receive prescriptions for antidepressants. The amount of upper GI bleeding episodes was 3.6 times more than expected (95% confidence interval, 2.7 to 4.7). Combined use of an SSRI and NSAIDs or low-dose aspirin increased the risk to 12.2 (95% confidence interval, 7.1 to 19.5) and 5.2 (95% confidence interval, 3.2 to 8), respectively. The findings of this study demonstrate an increased risk of upper GI bleeding during the use of SSRIs. Combined use of SSRIs and NSAIDs or low-dose aspirin increased the risk even further (Dalton et al, 2003).
b) Coadministration of ketorolac with psychoactive drugs (such as fluoxetine) has been associated with hallucinations in some patients (Prod Info TORADOL(R) oral tablets, 2007).

3.5.1.BU 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 cohort studies have shown that the combined use of SSRIs and NSAIDs has been associated with an increased risk of bleeding. Bleeding events have included epistaxis, ecchymosis, hematoma, petechiae, and life-threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension, 2008) (Prod Info Lexapro(TM), 2003; Dalton et al, 2003a; Prod Info CELEXA (R) oral tablet, solution, 2005).
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 increased bleeding.
7) Probable Mechanism: unknown
8) Literature Reports
a) SSRIs increase the risk of upper gastrointestinal bleeding and this effect is potentiated by concurrent use of NSAIDs or low-dose aspirin. Hospitalizations for upper gastrointestinal bleeding were searched among 26,005 users of antidepressant medications and compared with the number of hospitalizations in those patients who did not receive prescriptions for antidepressants. The amount of upper GI bleeding episodes was 3.6 times more than expected (95% confidence interval, 2.7 to 4.7). Combined use of an SSRI and NSAIDs or low-dose aspirin increased the risk to 12.2 (95% confidence interval, 7.1 to 19.5) and 5.2 (95% confidence interval, 3.2 to 8), respectively. The findings of this study demonstrate an increased risk of upper GI bleeding during the use of SSRIs. Combined use of SSRIs and NSAIDs or low-dose aspirin increased the risk even further (Dalton et al, 2003).
b) Coadministration of ketorolac with psychoactive drugs (such as fluoxetine) has been associated with hallucinations in some patients (Prod Info TORADOL(R) oral tablets, 2007).

3.5.1.BV Fluoxetine
1) Interaction Effect: fluoxetine toxicity (dry mouth, sedation, urinary retention)
2) Summary: Coadministration of paroxetine with drugs that are metabolized by cytochrome P450 2D6 (CYP2D6), such as fluoxetine, should be approached with caution (Prod Info Paxil CR(TM), 2002).
3) Severity: moderate
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: When paroxetine is coadministered with fluoxetine monitor patients for signs and symptoms of fluoxetine toxicity (dry mouth, sedation, urinary retention, blurred vision). Fluoxetine doses may need to be reduced.
7) Probable Mechanism: decreased cytochrome P450 2D6-mediated fluoxetine metabolism

3.5.1.BW 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 fluphenazine for Tourette's syndrome and paroxetine for depression. Upon discontinuation of paroxetine, the parkinsonism resolved. A similar interaction has been observed when fluphenazine was given in combination with fluoxetine or sertraline (Kurlan, 1998a).
3) Severity: moderate
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: Monitor patients receiving concurrent therapy with fluphenazine and paroxetine for the development of drug-induced parkinsonism. Therapy with paroxetine may need to be discontinued.
7) Probable Mechanism: inhibition of cytochrome P450-mediated fluphenazine metabolism by paroxetine
8) Literature Reports
a) A 48-year-old male with depression and chronic, multiple motor and vocal tics was controlled with fluphenazine 2.5 mg daily and nortriptyline 100 mg daily. Because of a worsening of the depression, nortriptyline therapy was discontinued and paroxetine 20 mg daily was initiated. After three weeks, the patient developed an acute, severe parkinsonian syndrome marked by resting tremor, rigidity, bradykinesia, stooped posture, and postural imbalance. These symptoms resolved within three weeks of discontinuing both the fluphenazine and paroxetine, and therapy with risperidone and imipramine was instituted with no recurrence of parkinsonism (Kurlan, 1998).

3.5.1.BX 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 cohort studies have shown that the combined use of SSRIs and NSAIDs has been associated with an increased risk of bleeding. Bleeding events have included epistaxis, ecchymosis, hematoma, petechiae, and life-threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension, 2008) (Prod Info Lexapro(TM), 2003; Dalton et al, 2003a; Prod Info CELEXA (R) oral tablet, solution, 2005).
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

increased bleeding.
7) Probable Mechanism: unknown
8) Literature Reports
a) SSRIs increase the risk of upper gastrointestinal bleeding and this effect is potentiated by concurrent use of NSAIDs or low-dose aspirin. Hospitalizations for upper gastrointestinal bleeding were searched among 26,005 users of antidepressant medications and compared with the number of hospitalizations in those patients who did not receive prescriptions for antidepressants. The amount of upper GI bleeding episodes was 3.6 times more than expected (95% confidence interval, 2.7 to 4.7). Combined use of an SSRI and NSAIDs or low-dose aspirin increased the risk to 12.2 (95% confidence interval, 7.1 to 19.5) and 5.2 (95% confidence interval, 3.2 to 8), respectively. The findings of this study demonstrate an increased risk of upper GI bleeding during the use of SSRIs. Combined use of SSRIs and NSAIDs or low-dose aspirin increased the risk even further (Dalton et al, 2003).
b) Coadministration of ketorolac with psychoactive drugs (such as fluoxetine) has been associated with hallucinations in some patients (Prod Info TORADOL(R) oral tablets, 2007).

3.5.1.BY 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 cohort studies have shown that the combined use of SSRIs and anticoagulants has been associated with an increased risk of bleeding (Wallerstedt et al, 2009; Schalekamp et al, 2008; Prod Info PAXIL(R) oral tablets, suspension, 2008). Bleeding events reported have included epistaxis, ecchymosis, hematoma, petechiae, and life-threatening hemorrhages. Altered anticoagulant effects (including increased bleeding) have been reported with the coadministration of SSRIs with warfarin (Schalekamp et al, 2008; Prod Info PAXIL(R) oral tablets, suspension, 2008).
3) Severity: major
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: When paroxetine and an anticoagulant are given concurrently, monitor patients for signs of increased bleeding. Patients who are taking warfarin should be monitored closely for altered anticoagulant effects, including increased bleeding, when paroxetine therapy is initiated or discontinued (Prod Info PAXIL(R) oral tablets, suspension, 2008).
7) Probable Mechanism: unknown
8) Literature Reports
a) According to a retrospective cohort study (n=234), there was an increased risk of clinically relevant bleeding (hospital admission due to bleeding) in patients receiving warfarin for atrial fibrillation during concomitant SSRI therapy or within 2 weeks following SSRI therapy termination. Patients with a mean age of 72 +/- 7 years receiving warfarin plus SSRI (n=117) were matched with randomly selected patients who received warfarin only (n=117). SSRI included fluoxetine, citalopram, paroxetine, sertraline, fluvoxamine, or escitalopram. Nine patients experienced 11 bleeding episodes during 213.9 treatment years in the warfarin plus SSRI group, and 10 patients experienced 14 bleedings during 586.4 treatment years in the warfarin-only group. The corresponding total incidences of bleedings were 51.4 and 23.9 per 1000 treatment years, respectively. The hazard ratio for first bleedings during treatment with warfarin plus SSRI was 3.49 (95% CI; 1.37 to 8.91, p=0.009) compared with warfarin only. The SSRI implicated in patients experiencing bleeding at the time of concomitant administration were sertraline or citalopram. The addition of an SSRI was not associated with a change in warfarin dose or INR (p=0.48 and p=0.31 respectively). The results of the study may be limited by earlier bleeding events, unknown patient adherence, and exclusion of clopidogrel, dipyridamol, corticosteroids and anticoagulants other than warfarin in the model (Wallerstedt et al, 2009).
b) A population-based, case-controlled study of new coumarin users (acenocoumarol and phenprocoumon) with concomitant selective serotonin reuptake inhibitors (SSRIs) resulted in an increased risk of hospitalization due to nongastrointestinal bleeding. Using national pharmacy and hospitalization records, Netherlands researchers identified 1848 cases that were admitted for abnormal bleeding and compared them with 5818 control subjects also taking coumarins. Median duration of treatment in patients was 220 days (range, 1 to 4690 days). Patients on SSRIs showed greater risk for hospitalization for nongastrointestinal bleeding (adjusted odds ratio (OR) 1.7, 95% confidence interval (CI), 1.1 to 2.5), however, the rate of gastrointestinal bleeding (adjusted OR 0.8, 95% CI, 0.4 to 1.5) was not significantly different (Schalekamp et al, 2008).
c) Preliminary data suggest that there may be a pharmacodynamic interaction (that causes an increased bleeding diathesis with unaltered prothrombin time) between paroxetine and warfarin. The concomitant use of paroxetine and warfarin should be undertaken with caution (Prod Info PAXIL(R) oral tablets, suspension, 2008).
d) In a multiple-dose study, several days of combined therapy with warfarin and paroxetine resulted in mild but clinically significant bleeding in 5 of 27 subjects. This effect occurred in the absence of a significant enhancement in warfarin-induced hypoprothrombinemia or changes in either paroxetine or warfarin disposition (Bannister et al, 1989b).

3.5.1.BZ Fosamprenavir
1) Interaction Effect: decreased paroxetine plasma levels

2) Summary: The concurrent administration of fosamprenavir/ritonavir and paroxetine has resulted in significantly decreased paroxetine plasma levels. Caution is advised if these agents are used concurrently. Dose adjustments should be guided by clinical efficacy and tolerability (Prod Info LEXIVA(R) oral solution, oral tablets, 2009; Prod Info PAXIL(R) oral tablets, oral suspension, 2006). Patients may need to be monitored for loss of paroxetine efficacy.
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: Coadministration of fosamprenavir/ritonavir and paroxetine has led to significantly decreased paroxetine plasma levels. Use caution if these agents are coadministered. Dose adjustments should be made based on clinical efficacy and tolerability (Prod Info LEXIVA(R) oral solution, oral tablets, 2009; Prod Info PAXIL(R) oral tablets, oral suspension, 2006). Monitor patients for loss of paroxetine efficacy.
7) Probable Mechanism: unknown

3.5.1.CA Fosaprepitant
1) Interaction Effect: decreased plasma concentrations of aprepitant and paroxetine
2) Summary: Once daily doses of aprepitant, as a tablet formulation comparable to 85 mg or 170 mg of the capsule formulation, coadministered with paroxetine 20 mg/day, resulted in a decrease in AUC by approximately 25% and Cmax by approximately 20% of both aprepitant and paroxetine (Prod Info EMEND (R) IV injection, 2008).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Concomitant administration of fosaprepitant and paroxetine should be approached with caution as this may lead to decreased plasma concentrations of both agents (Prod Info EMEND(R) IV injection, 2008).
7) Probable Mechanism: unknown

3.5.1.CB Fosphenytoin
1) Interaction Effect: reduced paroxetine efficacy
2) Summary: Fosphenytoin is a prodrug of phenytoin and the same interactions that occur with phenytoin are expected to occur with fosphenytoin (Prod Info Cerebyx(R), 1999). Limited reports related to the effects of combined phenytoin-paroxetine are currently available. Because of its enzyme-inducing effect, coadministered phenytoin apparently reduces serum concentrations of paroxetine, possibly leading to reduced efficacy of paroxetine (Prod Info Paxil(R), 1999a; Andersen et al, 1991a; Boyer & Blumhardt, 1992). There has been one case report of an elevated phenytoin level after four weeks of concurrent paroxetine and phenytoin coadministration (Prod Info Paxil(R), 1999a).
3) Severity: moderate
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: Monitor patients for paroxetine effectiveness. Doses of paroxetine might need to be increased when these two agents are coadministered.
7) Probable Mechanism: induction of paroxetine metabolism
8) Literature Reports
a) Concomitant administration of a single-dose of paroxetine and phenytoin (300 mg once a day for 14 days) resulted in a reduction in the area under the plasma concentration-time curve (AUC) of paroxetine by 27% to 50%, as well as a decrease of 35% in the half-life of paroxetine (Kaye et al, 1989; Prod Info Paxil(R), 1999). This interaction appears to be related to the enzyme-inducing properties of phenytoin. Alternatively, in a single-dose phenytoin study, paroxetine (30 mg once a day for 14 days) had no effect on the mean peak plasma levels or the elimination half-life of phenytoin 300 mg. However, a 12% reduction in the area under the plasma concentration-time curve (AUC) for phenytoin was observed.
b) Nineteen epilepsy patients who were well controlled on either phenytoin (n=5), carbamazepine (n=6), or valproate (n=8) took part in a single-blind, placebo-controlled, cross-over study to determine the effect of concurrent use of paroxetine and anticonvulsants. Subjects received placebo for seven days, then paroxetine 10 mg daily for three days, 20 mg daily for three days, and 30 mg daily for 10 days. There were no statistically significant changes in plasma levels and free fractions in any of the anticonvulsant drugs during any phase of the study. Mean paroxetine plasma levels were lowest with concurrent phenytoin therapy (p less than 0.005 when compared with valproate); however, there is no clear association between paroxetine plasma concentrations and efficacy. No severe adverse effects were seen with co-therapy, no seizures occurred, and no changes in protein binding were found (Andersen et al, 1991).
c) Paroxetine does not alter in vitro protein binding of phenytoin (Prod Info Paxil(R), 1999).

3.5.1.CC Frovatriptan
1) Interaction Effect: an increased risk of serotonin syndrome
2) Summary: There have been case reports of weakness, hyperreflexia, and incoordination following concomitant use of sumatriptan, a 5-hydroxytryptamine-1 (5HT-1) agonist, and a serotonin specific reuptake

inhibitor (SSRI) (Prod Info Imitrex(R) Nasal Spray, 2003). Because frovatriptan is a 5HT 1B/1D agonist, a similar interaction between SSRIs and frovatriptan may occur (Prod Info Frova(R), 2004). Concurrent use of frovatriptan and an SSRI may result in serotonin syndrome which may be life-threatening. Symptoms of serotonin syndrome may include restlessness, hallucinations, loss of coordination, fast heart beat, rapid changes in blood pressure, increased body temperature, overreactive reflexes, nausea, vomiting, and diarrhea. Clinicians should be aware that triptans may be commonly used intermittently and that either the triptan or the SSRI may be prescribed by a different physician. Discuss the risks of serotonin syndrome with patients who are prescribed this combination and monitor them closely for symptoms of serotonin syndrome (US Food and Drug Administration, 2006).
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-threatening condition called serotonin syndrome. Be aware that triptans may be commonly used intermittently and that either the triptan or the SSRI may be prescribed by a different physician. If these agents are used together, discuss the risks of serotonin syndrome with the patient and monitor closely for symptoms of serotonin syndrome (restlessness, hyperthermia, hyperreflexia, incoordination).
7) Probable Mechanism: additive pharmacologic effects resulting in excessive serotonergic stimulation

3.5.1.CD Furazolidone
1) Interaction Effect: weakness, hyperreflexia, and incoordination
2) Summary: Although not its primary mechanism of action, furazolidone has monoamine oxidase inhibitor activity. Cases of serious sometimes fatal reactions have been reported in patients receiving selective serotonin reuptake inhibitors (SSRI) in combination with monoamine oxidase inhibitors (MAOIs). Hyperthermia, rigidity, myoclonus, autonomic instability with possible rapid fluctuations of vital signs, and mental status changes that include extreme agitation progressing to delirium and coma have been reported. Furazolidone should not be used in combination with an 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 (SSRI) is deemed to be necessary, closely monitor the patient for signs of serotonergic excess (mental status changes, diaphoresis, fever, weakness, hyperreflexia, incoordination).
7) Probable Mechanism: additive pharmacologic effects resulting in excessive serotonergic stimulation

3.5.1.CE Galantamine
1) Interaction Effect: increased galantamine plasma concentrations
2) Summary: Based upon in vitro studies, the major enzymes involved in galantamine metabolism are CYP3A4 and CYP2D6. Paroxetine is a potent inhibitor of CYP2D6. When paroxetine 20 mg daily for 16 days was administered concurrently with galantamine, the galantamine oral bioavailability increased approximately 40%. Such an increase may warrant caution when coadministering these two medications. Monitor for galantamine toxicity including anorexia, nausea, vomiting, dizziness, arrhythmias or gastrointestinal bleeding (Prod Info RAZADYNE(R) ER extended release oral capsules, oral tablets, oral solution, 2007).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: Increased galantamine plasma concentrations may result from paroxetine inhibition of galantamine CYP2D6-mediated metabolism. Monitor for galantamine toxicity including anorexia, nausea, vomiting, dizziness, arrhythmias, or gastrointestinal bleeding (Prod Info RAZADYNE(R) ER extended release oral capsules, oral tablets, oral solution, 2007).
7) Probable Mechanism: inhibition of cytochrome CYP2D6-mediated galantamine metabolism

3.5.1.CF Ginkgo
1) Interaction Effect: increased risk of serotonin syndrome (hypertension, hyperthermia, myoclonus, mental status changes)
2) Summary: The addition of Ginkgo biloba and/or St. John's Wort to therapy with buspirone and fluoxetine may have precipitated a hypomanic episode in a case report (Spinella & Eaton, 2002a). It is unclear if Ginkgo or St. John's Wort, the combination of both, or other patient factors, contributed to the effect. Theoretically, Ginkgo may increase the risk of serotonin syndrome when taken with selective serotonin reuptake inhibitors (SSRIs). Caution is advised, especially when ginkgo is taken to counteract sexual dysfunction associated with SSRIs. Ginkgo may inhibit monoamine oxidase (Sloley et al, 2000; White et al, 1996), and has demonstrated serotonergic activity in animals (Ramassamy et al, 1992) which might increase the risk of serotonin syndrome when ginkgo is combined with SSRIs. The potential MAO inhibitory activity of ginkgo is questionable. A human study did not show MAO inhibition in the brain following oral consumption (Fowler et al, 2000). Ginkgo biloba extract inhibited MAO-A/MAO-B in the rat brain in vitro (Sloley et al, 2000; White et al, 1996) and MAO-B in human platelets in vitro (White et al, 1996). No

significant MAO inhibition was found in mice 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 with selective serotonin reuptake inhibitors (SSRIs).
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 concomitant use of fluoxetine, buspirone, Ginkgo biloba, and St. John's Wort. The symptoms resolved following discontinuation of Ginkgo and St. John's Wort. The patient was being treated for depression following a mild traumatic brain injury with fluoxetine 20 milligrams (mg) twice daily and buspirone 15 mg twice daily. Several weeks prior to presentation, buspirone was increased to 20 mg twice daily for persistent anxiety and the patient began taking Ginkgo biloba, melatonin, and St. John's Wort in unspecified doses. Melatonin was considered unlikely to have contributed to her symptoms. Ginkgo and St. John's Wort were considered possible contributors since they may potentiate antidepressants, and considering the temporal relationship between the use of the herbs and onset of symptoms and discontinuation of the herbs and resolution of symptoms. However, the brain injury was considered a possible contributor (Spinella & Eaton, 2002).

3.5.1.CG 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 cohort studies have shown that the combined use of SSRIs and anticoagulants has been associated with an increased risk of bleeding (Wallerstedt et al, 2009; Schalekamp et al, 2008; Prod Info PAXIL(R) oral tablets, suspension, 2008). Bleeding events reported have included epistaxis, ecchymosis, hematoma, petechiae, and life-threatening hemorrhages. Altered anticoagulant effects (including increased bleeding) have been reported with the coadministration of SSRIs with warfarin (Schalekamp et al, 2008; Prod Info PAXIL(R) oral tablets, suspension, 2008).
3) Severity: major
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: When paroxetine and an anticoagulant are given concurrently, monitor patients for signs of increased bleeding. Patients who are taking warfarin should be monitored closely for altered anticoagulant effects, including increased bleeding, when paroxetine therapy is initiated or discontinued (Prod Info PAXIL(R) oral tablets, suspension, 2008).
7) Probable Mechanism: unknown
8) Literature Reports
a) According to a retrospective cohort study (n=234), there was an increased risk of clinically relevant bleeding (hospital admission due to bleeding) in patients receiving warfarin for atrial fibrillation during concomitant SSRI therapy or within 2 weeks following SSRI therapy termination. Patients with a mean age of 72 +/- 7 years receiving warfarin plus SSRI (n=117) were matched with randomly selected patients who received warfarin only (n=117). SSRI included fluoxetine, citalopram, paroxetine, sertraline, fluvoxamine, or escitalopram. Nine patients experienced 11 bleeding episodes during 213.9 treatment years in the warfarin plus SSRI group, and 10 patients experienced 14 bleedings during 586.4 treatment years in the warfarin-only group. The corresponding total incidences of bleedings were 51.4 and 23.9 per 1000 treatment years, respectively. The hazard ratio for first bleedings during treatment with warfarin plus SSRI was 3.49 (95% CI; 1.37 to 8.91, p=0.009) compared with warfarin only. The SSRI implicated in patients experiencing bleeding at the time of concomitant administration were sertraline or citalopram. The addition of an SSRI was not associated with a change in warfarin dose or INR (p=0.48 and p=0.31 respectively). The results of the study may be limited by earlier bleeding events, unknown patient adherence, and exclusion of clopidogrel, dipyridamol, corticosteroids and anticoagulants other than warfarin in the model (Wallerstedt et al, 2009).
b) A population-based, case-controlled study of new coumarin users (acenocoumarol and phenprocoumon) with concomitant selective serotonin reuptake inhibitors (SSRIs) resulted in an increased risk of hospitalization due to nongastrointestinal bleeding. Using national pharmacy and hospitalization records, Netherlands researchers identified 1848 cases that were admitted for abnormal bleeding and compared them with 5818 control subjects also taking coumarins. Median duration of treatment in patients was 220 days (range, 1 to 4690 days). Patients on SSRIs showed greater risk for hospitalization for nongastrointestinal bleeding (adjusted odds ratio (OR) 1.7, 95% confidence interval (CI), 1.1 to 2.5), however, the rate of gastrointestinal bleeding (adjusted OR 0.8, 95% CI, 0.4 to 1.5) was not significantly different (Schalekamp et al, 2008).
c) Preliminary data suggest that there may be a pharmacodynamic interaction (that causes an increased bleeding diathesis with unaltered prothrombin time) between paroxetine and warfarin. The concomitant use of paroxetine and warfarin should be undertaken with caution (Prod Info PAXIL(R) oral tablets, suspension, 2008).
d) In a multiple-dose study, several days of combined therapy with warfarin and paroxetine resulted in mild but clinically significant bleeding in 5 of 27 subjects. This effect occurred in the absence of a

significant enhancement in warfarin-induced hypoprothrombinemia or changes in either paroxetine or warfarin disposition (Bannister et al, 1989b).

3.5.1.CH Hydroxytryptophan

1) Interaction Effect: an increased risk of serotonin syndrome (hypertension, hyperthermia, myoclonus, mental status changes)

2) Summary: Hydroxytryptophan (5-HTP) may potentiate the serotonergic effect of selective serotonin reuptake inhibitors (SSRIs) (Meltzer et al, 1997a). Since 5-HTP increases serotonin levels, when combined with an SSRI, the serotonin level may be increased sufficiently to produce serotonin syndrome. Caution is advised with concomitant use of 5-HTP and SSRIs.

3) Severity: moderate

4) Onset: rapid

5) Substantiation: theoretical

6) Clinical Management: No cases have been reported of serotonin syndrome resulting from this combination. Caution is advised if hydroxytryptophan (5-HTP) and a selective serotonin reuptake inhibitor (SSRI) are used concomitantly. Monitor the patient for early signs of serotonin syndrome such as anxiety, confusion, and disorientation.

7) Probable Mechanism: additive serotonergic effect

8) Literature Reports

a) Hydroxytryptophan (5-HTP) (200 milligrams (mg) orally) as a single dose increased plasma cortisol and prolactin levels in both medicated and unmedicated patients with major depression or obsessive compulsive disorder (OCD). These responses were greater if the patient was also taking fluoxetine (n = 16) (p less than 0.0001). Mean fluoxetine dose for depressed patients was 44 mg/day,and for OCD patients it was 60 mg/day. Cortisol or prolactin (PRL) levels in patients taking 5-HTP with tricyclic antidepressants (n = 14) or those receiving no medication (n = 83) were not significantly different from each other. A measurement of serotonergic effects of antidepressants can be evaluated by measuring hypothalamic-pituitary-adrenal (HPA) axis or PRL response. No clinical manifestations of serotonin syndrome were reported in patients taking 5-HTP concomitantly with fluoxetine (Meltzer et al, 1997).

3.5.1.CI 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 cohort studies have shown that the combined use of SSRIs and NSAIDs has been associated with an increased risk of bleeding. Bleeding events have included epistaxis, ecchymosis, hematoma, petechiae, and life-threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension, 2008) (Prod Info Lexapro(TM), 2003; Dalton et al, 2003a; Prod Info CELEXA (R) oral tablet, solution, 2005).

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 increased bleeding.

7) Probable Mechanism: unknown

8) Literature Reports

a) SSRIs increase the risk of upper gastrointestinal bleeding and this effect is potentiated by concurrent use of NSAIDs or low-dose aspirin. Hospitalizations for upper gastrointestinal bleeding were searched among 26,005 users of antidepressant medications and compared with the number of hospitalizations in those patients who did not receive prescriptions for antidepressants. The amount of upper GI bleeding episodes was 3.6 times more than expected (95% confidence interval, 2.7 to 4.7). Combined use of an SSRI and NSAIDs or low-dose aspirin increased the risk to 12.2 (95% confidence interval, 7.1 to 19.5) and 5.2 (95% confidence interval, 3.2 to 8), respectively. The findings of this study demonstrate an increased risk of upper GI bleeding during the use of SSRIs. Combined use of SSRIs and NSAIDs or low-dose aspirin increased the risk even further (Dalton et al, 2003).

b) Coadministration of ketorolac with psychoactive drugs (such as fluoxetine) has been associated with hallucinations in some patients (Prod Info TORADOL(R) oral tablets, 2007).

3.5.1.CJ Iloperidone

1) Interaction Effect: increased plasma concentrations of iloperidone

2) Summary: Coadministration of iloperidone and paroxetine results in increased plasma levels of iloperidone and therefore requires a dose reduction of iloperidone (Prod Info FANAPT(TM) oral tablets, 2009).

3) Severity: moderate

4) Onset: unspecified

5) Substantiation: probable

6) Clinical Management: If administered with paroxetine, reduce iloperidone doses by one-half. Upon withdrawal of paroxetine from the combination therapy, resume the previous iloperidone dose (Prod Info FANAPT(TM) oral tablets, 2009).

7) Probable Mechanism: inhibition of the CYP2D6-mediated metabolism of iloperidone

8) Literature Reports

a) Schizophrenic patients (ages 18 to 65 years) receiving paroxetine 20 mg/day for 5 to 8 days and multiple doses of iloperidone 8 or 12 mg twice daily experienced an increase in mean steady-state peak iloperidone concentrations by about 1.6-fold. Concentrations of the P88 metabolite were similarly increased, while the mean steady-state peak concentrations of the P95 metabolite were decreased by one-half(Prod Info FANAPT(TM) oral tablets, 2009).

3.5.1.CK 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 cohort studies have shown that the combined use of SSRIs and antiplatelet agents has been associated with an increased risk of bleeding. Bleeding events reported have included epistaxis, ecchymosis, hematoma, petechiae, and life-threatening hemorrhages (Prod Info PAXIL(R) oral 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 signs of increased bleeding (Prod Info PAXIL(R) oral tablets, suspension, 2008; Prod Info PROZAC(R) oral capsules, delayed-release capsules, solution, 2008)
7) Probable Mechanism: unknown

3.5.1.CL Imipramine

1) Interaction Effect: imipramine toxicity (dry mouth, sedation, urinary retention)
2) Summary: Paroxetine coadministered with desipramine or imipramine produced higher serum concentrations of the tricyclic antidepressant (TCA) in some patients (Prod Info Paxil CR(TM), 2003b; Hartter et al, 1994; Brosen et al, 1993a). Paroxetine's effect on TCAs may resemble that of fluoxetine (another selective serotonin reuptake inhibitor), which is known to inhibit TCA metabolism (Aranow et al, 1989; Vaughan, 1988; Goodnick, 1989). With coadministration, monitor patients for imipramine toxicity. Imipramine doses may need to be reduced.
3) Severity: moderate
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: Coadministration of paroxetine with other drugs that are metabolized by cytochrome P450 2D6 (CYP2D6) should be approached with caution. When paroxetine is coadministered with imipramine, monitor patients for signs and symptoms of imipramine toxicity (dry mouth, sedation, urinary retention, blurred vision). Imipramine doses may need to be reduced.
7) Probable Mechanism: decreased cytochrome P450 2D6-mediated imipramine metabolism
8) Literature Reports

a) The effect of paroxetine on desipramine metabolism was studied in nine extensive metabolizers (EM) and eight poor metabolizers (PM) of desipramine. Subjects took a single oral dose of desipramine before starting paroxetine and a second dose after 11 days of paroxetine use. After the addition of paroxetine, EMs experienced a 5-fold decrease in clearance of desipramine, indicating that paroxetine inhibits oxidation reactions catalyzed by CYP2D6. PMs had a slight increase in clearance of desipramine with paroxetine. With concurrent administration of desipramine and paroxetine, interaction of the two drugs may result in a need for dosage adjustments, especially in extensive metabolizers of desipramine (Brosen et al, 1993).

3.5.1.CM 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 cohort studies have shown that the combined use of SSRIs and NSAIDs has been associated with an increased risk of bleeding. Bleeding events have included epistaxis, ecchymosis, hematoma, petechiae, and life-threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension, 2008) (Prod Info Lexapro(TM), 2003; Dalton et al, 2003a; Prod Info CELEXA (R) oral tablet, solution, 2005).
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 increased bleeding.
7) Probable Mechanism: unknown
8) Literature Reports

a) SSRIs increase the risk of upper gastrointestinal bleeding and this effect is potentiated by concurrent use of NSAIDs or low-dose aspirin. Hospitalizations for upper gastrointestinal bleeding were searched among 26,005 users of antidepressant medications and compared with the number of hospitalizations in those patients who did not receive prescriptions for antidepressants. The amount of upper GI bleeding episodes was 3.6 times more than expected (95% confidence interval, 2.7 to 4.7). Combined use of an SSRI and NSAIDs or low-dose aspirin increased the risk to 12.2 (95% confidence interval, 7.1 to 19.5) and 5.2 (95% confidence interval, 3.2 to 8), respectively. The findings of this study demonstrate

an increased risk of upper GI bleeding during the use of SSRIs. Combined use of SSRIs and NSAIDs or low-dose aspirin increased the risk even further (Dalton et al, 2003).

b) Coadministration of ketorolac with psychoactive drugs (such as fluoxetine) has been associated with hallucinations in some patients (Prod Info TORADOL(R) oral tablets, 2007).

3.5.1.CN 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 cohort studies have shown that the combined use of SSRIs and NSAIDs has been associated with an increased risk of bleeding. Bleeding events have included epistaxis, ecchymosis, hematoma, petechiae, and life-threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension, 2008) (Prod Info Lexapro(TM), 2003; Dalton et al, 2003a; Prod Info CELEXA (R) oral tablet, solution, 2005).

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 increased bleeding.

7) Probable Mechanism: unknown

8) Literature Reports

a) SSRIs increase the risk of upper gastrointestinal bleeding and this effect is potentiated by concurrent use of NSAIDs or low-dose aspirin. Hospitalizations for upper gastrointestinal bleeding were searched among 26,005 users of antidepressant medications and compared with the number of hospitalizations in those patients who did not receive prescriptions for antidepressants. The amount of upper GI bleeding episodes was 3.6 times more than expected (95% confidence interval, 2.7 to 4.7). Combined use of an SSRI and NSAIDs or low-dose aspirin increased the risk to 12.2 (95% confidence interval, 7.1 to 19.5) and 5.2 (95% confidence interval, 3.2 to 8), respectively. The findings of this study demonstrate an increased risk of upper GI bleeding during the use of SSRIs. Combined use of SSRIs and NSAIDs or low-dose aspirin increased the risk even further (Dalton et al, 2003).

b) Coadministration of ketorolac with psychoactive drugs (such as fluoxetine) has been associated with hallucinations in some patients (Prod Info TORADOL(R) oral tablets, 2007).

3.5.1.CO Iproniazid

1) Interaction Effect: CNS toxicity or serotonin syndrome (hypertension, hyperthermia, myoclonus, mental status changes)

2) Summary: Concurrent administration or overlapping therapy with paroxetine and a monoamine oxidase (MAO) inhibitor may result in CNS toxicity or serotonin syndrome, a hyperserotonergic state characterized by symptoms such as restlessness, myoclonus, changes in mental status, hyperreflexia, diaphoresis, shivering, and tremor. Serious, even fatal, reactions have been reported with concomitant use of serotonin specific reuptake inhibitors and MAO inhibitors (Prod Info Paxil(R), 1999d; Lappin & Auchincloss, 1994k; Graber et al, 1994k; Suchowersky & de Vries, 1990k). Concomitant use is contraindicated.

3) Severity: contraindicated

4) Onset: rapid

5) Substantiation: probable

6) Clinical Management: Concurrent use of paroxetine and a MAO inhibitor is contraindicated. Wait at least two weeks after discontinuing a MAO inhibitor before initiating paroxetine, and at least two weeks after discontinuing paroxetine 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 serotonin syndrome (Sternbach, 1991j). Serotonin syndrome is a condition of serotonergic hyperstimulation and manifests as restlessness, myoclonus, changes in mental status, hyperreflexia, diaphoresis, shivering, and tremor. If the syndrome is not recognized and correctly treated, fatality can result.

b) A 26-year old woman who had been taking isocarboxazid for eight weeks stopped taking the drug for 11 days before beginning therapy with sertraline. After a single 100 mg sertraline dose, the patient became restless and developed leg twitches. The patients was later admitted to the emergency room with diaphoresis, tachycardia, hyperreflexia, and various neuromuscular disturbances. After treatment with diazepam and propranolol the patient did not improve. The patient was then given two 4 mg doses of cyproheptadine an hour apart, with notable improvement in 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 added to a regimen of lithium, phenelzine, thioridazine, and doxepin. Three hours after taking the first sertraline dose, the patient was found in a semicomatose state, with elevated body temperature, increased pulse, increased respiration rate, and a blood pressure of 140/110 mm Hg. After transportation to the hospital, the patient was misdiagnosed as having neuroleptic malignant syndrome (NMS) which was later changed to serotonin syndrome due to a reaction between sertraline and phenelzine. The authors suggest that monoamine oxidase inhibitor (MAOI) therapy should be discontinued for at least two weeks before initiation of therapy with a selective serotonin reuptake

inhibitor (SSRI) and that before starting a MAOI, SSRI therapy should be discontinued for at least five half-lives of the parent drug and any active metabolites (Graber et al, 1994j).

d) Two cases reports suggested a possible interaction between fluoxetine and selegiline (Suchowersky & de Vries, 1990j). One case involved a first episode of mania being observed approximately one month after adding selegiline to fluoxetine. The patient improved two months after both drugs were discontinued, and no further details were provided. The second case involved diaphoresis, vasoconstriction, and cyanosis of the hands which occurred in close temporal relationship to adding fluoxetine to selegiline. Both drugs were discontinued, with relatively quick resolution of symptoms. Rechallenge with fluoxetine alone occurred without incident.

3.5.1.CP Isocarboxazid

1) Interaction Effect: CNS toxicity or serotonin syndrome (hypertension, hyperthermia, myoclonus, mental status changes)

2) Summary: Concurrent administration or overlapping therapy with paroxetine and a monoamine oxidase (MAO) inhibitor may result in CNS toxicity or serotonin syndrome, a hyperserotonergic state characterized by symptoms such as restlessness, myoclonus, changes in mental status, hyperreflexia, diaphoresis, shivering, and tremor. Serious, even fatal, reactions have been reported with concomitant use of serotonin specific reuptake inhibitors and MAO inhibitors (Prod Info Paxil(R), 2003f; Lappin & Auchincloss, 1994m; Graber et al, 1994m; Suchowersky & de Vries, 1990m). Concomitant use is contraindicated (Prod Info Marplan(R), 1998).

3) Severity: contraindicated

4) Onset: rapid

5) Substantiation: theoretical

6) Clinical Management: Concurrent use of paroxetine and an MAO inhibitor is contraindicated. Wait at least two weeks after discontinuing an MAO inhibitor before initiating paroxetine, and at least two weeks after discontinuing paroxetine before initiating therapy with an MAOI.

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 serotonin syndrome (Sternbach, 1991k). Serotonin syndrome is a condition of serotonergic hyperstimulation and manifests as restlessness, myoclonus, changes in mental status, hyperreflexia, diaphoresis, shivering, and tremor. If the syndrome is not recognized and correctly treated, fatality can result.

b) A 26-year old woman who had been taking isocarboxazid for eight weeks stopped taking the drug for 11 days before beginning therapy with sertraline. After a single 100 mg sertraline dose, the patient became restless and developed leg twitches. The patients was later admitted to the emergency room with diaphoresis, tachycardia, hyperreflexia, and various neuromuscular disturbances. After treatment with diazepam and propranolol the patient did not improve. The patient was then given two 4 mg doses of cyproheptadine an hour apart, with notable improvement 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 added to a regimen of lithium, phenelzine, thioridazine, and doxepin. Three hours after taking the first sertraline dose, the patient was found in a semicomatose state, with elevated body temperature, increased pulse, increased respiration rate, and a blood pressure of 140/110 mm Hg. After transportation to the hospital, the patient was misdiagnosed as having neuroleptic malignant syndrome (NMS) which was later changed to serotonin syndrome due to a reaction between sertraline and phenelzine. The authors suggest that monoamine oxidase inhibitor (MAOI) therapy should be discontinued for at least two weeks before initiation of therapy with a selective serotonin reuptake inhibitor (SSRI) and that before starting a MAOI, SSRI therapy should be discontinued for at least five half-lives of the parent drug and any active metabolites (Graber et al, 1994l).

d) Two cases reports suggested a possible interaction between fluoxetine and selegiline (Suchowersky & de Vries, 1990l). One case involved a first episode of mania being observed approximately one month after adding selegiline to fluoxetine. The patient improved two months after both drugs were discontinued, and no further details were provided. The second case involved diaphoresis, vasoconstriction, and cyanosis of the hands which occurred in close temporal relationship to adding fluoxetine to selegiline. Both drugs were discontinued, with relatively quick resolution of symptoms. Rechallenge with fluoxetine alone occurred without incident.

3.5.1.CQ 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 cohort studies have shown that the combined use of SSRIs and NSAIDs has been associated with an increased risk of bleeding. Bleeding events have included epistaxis, ecchymosis, hematoma, petechiae, and life-threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension, 2008) (Prod Info Lexapro(TM), 2003; Dalton et al, 2003a; Prod Info CELEXA (R) oral tablet, solution, 2005).

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 increased bleeding.
7) Probable Mechanism: unknown
8) Literature Reports
a) SSRIs increase the risk of upper gastrointestinal bleeding and this effect is potentiated by concurrent use of NSAIDs or low-dose aspirin. Hospitalizations for upper gastrointestinal bleeding were searched among 26,005 users of antidepressant medications and compared with the number of hospitalizations in those patients who did not receive prescriptions for antidepressants. The amount of upper GI bleeding episodes was 3.6 times more than expected (95% confidence interval, 2.7 to 4.7). Combined use of an SSRI and NSAIDs or low-dose aspirin increased the risk to 12.2 (95% confidence interval, 7.1 to 19.5) and 5.2 (95% confidence interval, 3.2 to 8), respectively. The findings of this study demonstrate an increased risk of upper GI bleeding during the use of SSRIs. Combined use of SSRIs and NSAIDs or low-dose aspirin increased the risk even further (Dalton et al, 2003).
b) Coadministration of ketorolac with psychoactive drugs (such as fluoxetine) has been associated with hallucinations in some patients (Prod Info TORADOL(R) oral tablets, 2007).

3.5.1.CR 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 cohort studies have shown that the combined use of SSRIs and NSAIDs has been associated with an increased risk of bleeding. Bleeding events have included epistaxis, ecchymosis, hematoma, petechiae, and life-threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension, 2008) (Prod Info Lexapro(TM), 2003; Dalton et al, 2003a; Prod Info CELEXA (R) oral tablet, solution, 2005).
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 increased bleeding.
7) Probable Mechanism: unknown
8) Literature Reports
a) SSRIs increase the risk of upper gastrointestinal bleeding and this effect is potentiated by concurrent use of NSAIDs or low-dose aspirin. Hospitalizations for upper gastrointestinal bleeding were searched among 26,005 users of antidepressant medications and compared with the number of hospitalizations in those patients who did not receive prescriptions for antidepressants. The amount of upper GI bleeding episodes was 3.6 times more than expected (95% confidence interval, 2.7 to 4.7). Combined use of an SSRI and NSAIDs or low-dose aspirin increased the risk to 12.2 (95% confidence interval, 7.1 to 19.5) and 5.2 (95% confidence interval, 3.2 to 8), respectively. The findings of this study demonstrate an increased risk of upper GI bleeding during the use of SSRIs. Combined use of SSRIs and NSAIDs or low-dose aspirin increased the risk even further (Dalton et al, 2003).
b) Coadministration of ketorolac with psychoactive drugs (such as fluoxetine) has been associated with hallucinations in some patients (Prod Info TORADOL(R) oral tablets, 2007).

3.5.1.CS 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 cohort studies have shown that the combined use of SSRIs and NSAIDs has been associated with an increased risk of bleeding. Bleeding events have included epistaxis, ecchymosis, hematoma, petechiae, and life-threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension, 2008) (Prod Info Lexapro(TM), 2003; Dalton et al, 2003a; Prod Info CELEXA (R) oral tablet, solution, 2005).
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 increased bleeding.
7) Probable Mechanism: unknown
8) Literature Reports
a) SSRIs increase the risk of upper gastrointestinal bleeding and this effect is potentiated by concurrent use of NSAIDs or low-dose aspirin. Hospitalizations for upper gastrointestinal bleeding were searched among 26,005 users of antidepressant medications and compared with the number of hospitalizations in those patients who did not receive prescriptions for antidepressants. The amount of upper GI bleeding episodes was 3.6 times more than expected (95% confidence interval, 2.7 to 4.7). Combined use of an SSRI and NSAIDs or low-dose aspirin increased the risk to 12.2 (95% confidence interval, 7.1 to 19.5) and 5.2 (95% confidence interval, 3.2 to 8), respectively. The findings of this study demonstrate an increased risk of upper GI bleeding during the use of SSRIs. Combined use of SSRIs and NSAIDs or low-dose aspirin increased the risk even further (Dalton et al, 2003).
b) Coadministration of ketorolac with psychoactive drugs (such as fluoxetine) has been associated with hallucinations in some patients (Prod Info TORADOL(R) oral tablets, 2007).

3.5.1.CT 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 cohort studies have shown that the combined use of SSRIs and antiplatelet agents has been associated with an increased risk of bleeding. Bleeding events reported have included epistaxis, ecchymosis, hematoma, petechiae, and life-threatening hemorrhages (Prod Info PAXIL(R) oral 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 signs of increased bleeding (Prod Info PAXIL(R) oral tablets, suspension, 2008; Prod Info PROZAC(R) oral capsules, delayed-release capsules, solution, 2008)

7) Probable Mechanism: unknown

3.5.1.CU 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 cohort studies have shown that the combined use of SSRIs and antiplatelet agents has been associated with an increased risk of bleeding. Bleeding events reported have included epistaxis, ecchymosis, hematoma, petechiae, and life-threatening hemorrhages (Prod Info PAXIL(R) oral 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 signs of increased bleeding (Prod Info PAXIL(R) oral tablets, suspension, 2008; Prod Info PROZAC(R) oral capsules, delayed-release capsules, solution, 2008)

7) Probable Mechanism: unknown

3.5.1.CV Linezolid

1) Interaction Effect: CNS toxicity or serotonin syndrome (hypertension, hyperthermia, myoclonus, mental status changes)

2) Summary: Concurrent use of linezolid and paroxetine is contraindicated. A 2-week washout period should be used between the administration of linezolid and paroxetine (Prod Info PAXIL CR(R) controlled-release oral tablets, 2008; Prod Info PAXIL(R) oral tablets, suspension, 2008). Linezolid is a reversible, nonselective inhibitor of monoamine oxidase. Concurrent administration or overlapping therapy with paroxetine and a monoamine oxidase (MAO) inhibitor may result in CNS toxicity or serotonin syndrome such as neuromuscular abnormalities (including hyper-reflexia, tremor, muscle rigidity, clonus, peripheral hypertonicity, and shivering), autonomic hyperactivity (including tachycardia, mydriasis, diaphoresis, and diarrhea), and mental status changes (including agitation and delirium). Serious, even fatal, reactions have been reported (Boyer & Shannon, 2005). There have been spontaneous reports of serotonin syndrome associated with concomitant use of linezolid and serotonergic agents (Wigen & Goetz, 2002; Prod Info ZYVOX(R) IV injection, oral tablets, oral suspension, 2008).

3) Severity: contraindicated

4) Onset: rapid

5) Substantiation: probable

6) Clinical Management: Concurrent use of linezolid and paroxetine is contraindicated. Allow a minimum 2-week washout period between the administration of these drugs (Prod Info PAXIL CR(R) controlled-release oral tablets, 2008; Prod Info PAXIL(R) oral tablets, suspension, 2008).

7) Probable Mechanism: inhibition of serotonin metabolism by monoamine oxidase

8) Literature Reports

a) Linezolid may cause serotonin syndrome in patients receiving selective serotonin reuptake inhibitors. A 56-year-old female with a history of depression, chronic hepatitis C infection, hypertension, diabetes, and cervical stenosis was admitted for elective laminectomy. There was evidence of hepatic cirrhosis with an abdominal CT scan. Her medications preoperatively included paroxetine, IFN-alpha, felodipine, terazosin, lisinopril, insulin, methocarbamol, morphine sulfate, and ibuprofen. The last dose of paroxetine was administered on postoperative day 14. At that point it was discovered that the patient an infected surgical site and empiric therapy with vancomycin was initiated. The patient remained febrile, however, and linezolid was substituted for vancomycin. Within 24 hours the patient developed delirium, hypertension, hostility, anger, and tremors. Serotonin syndrome was diagnosed and linezolid therapy was discontinued. Vancomycin was reinstated and within 48 hours the patient returned to her baseline mental status. The serum half-life of paroxetine is 21 hours. It is likely that the inhibitory effect of linezolid combined with residual paroxetine activity produced serotonin syndrome in this patient. This particular patient may have been at increased risk for this syndrome because of her other medications as well as a decreased hepatic clearance. The author suggests that in high-risk patients, a 2-week washout period is advised between the discontinuation of selective serotonin reuptake inhibitors and initiation of linezolid (Wigen & Goetz, 2002).

3.5.1.CW Lithium

1) Interaction Effect: possible increased lithium concentrations and/or an increased risk of SSRI-related serotonin syndrome (hypertension, hyperthermia, myoclonus, mental status changes)

2) Summary: Concomitant use of lithium and various SSRIs has been associated with enhanced side effects of either or both drugs, and with or without elevated lithium levels. The combination has resulted in neurotoxicity and increased lithium levels in one case report (Salama & Shafey, 1989a). Signs and symptoms of lithium toxicity and serotonin syndrome have also been reported in patients who demonstrated therapeutic serum lithium levels while on concurrent fluoxetine and lithium (Muly et al, 1993a; Noveske et al, 1989a). Two studies have failed to identify a pharmacokinetic interaction between lithium and citalopram (Gram et al, 1993a; Baumann et al, 1996a). Combined administration of citalopram (40 mg daily for 10 days) and lithium (30 mmol/day for 5 days) had no significant effect on the pharmacokinetics of citalopram or lithium. However, plasma lithium levels should be monitored with appropriate adjustment to the lithium dose in accordance with standard clinical practice. Lithium may enhance the serotonergic effects of citalopram, therefore caution should be exercised when citalopram and lithium are coadministered (Prod Info Celexa(R), 2004). Concurrent use of fluvoxamine and lithium has led to case reports of increased lithium levels and neurotoxicity, serotonin syndrome, somnolence, and mania (Salama & Shafey, 1989a; Ohman & Spigset, 1993a; Evans & Marwick, 1990; Burrai et al, 1991a). No pharmacokinetic interference was apparent during a multiple-dose study of coadministered lithium and paroxetine (Prod Info Paxil CR(TM), 2003i). If these two agents are to be given concomitantly, the manufacturer suggests that caution be used until more clinical experience is available. Drug interactions leading to lithium toxicity have been reported when lithium was coadministered with fluoxetine and fluvoxamine (both in the same pharmacological class as paroxetine, eg, selective serotonin reuptake inhibitors) (Ohman & 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 therapy for increased plasma concentrations of lithium. In addition, monitor patients for signs and symptoms associated with serotonin syndrome (hypertension, hyperthermia, myoclonus, mental status changes).

7) Probable Mechanism: unknown

8) Literature Reports

a) Concomitant administration of oral lithium carbonate and oral fluoxetine resulted in increased lithium serum levels with lithium toxicity in a 44-year-old woman with a bipolar affective disorder (Salama & Shafey, 1989). Fluoxetine 20 mg daily was added to a regimen of lithium 1200 mg daily following patient complaints of weakness, tiredness, decreased concentration, and early morning awakening. Lithium serum levels increased to 1.7 mEq/L from a range of 0.75 to 1.15 mEq/L prior to fluoxetine. Fluoxetine was discontinued and the dose of lithium decreased; this resulted in a decrease in the lithium serum level within 48 hours to 1.2 mEq/L. The neurologic symptoms subsided within seven days as the lithium serum level decreased to 0.9 mEq/L. The contribution of fluoxetine to lithium toxicity in this patient was obscured by the fact that the lithium was reduced at the time of fluoxetine withdrawal.

b) A 53-year old woman who had been taking fluoxetine 20 mg daily and lorazepam 0.5 mg four times daily for a major depressive disorder had lithium 900 mg per day added to her regimen in order to augment her response to fluoxetine. Within 48 hours, the patient became confused, ataxic, and developed a coarse tremor in her right arm. Vital signs showed a rectal temperature of 101 degrees F, and laboratory values were normal except for an elevated leukocyte count and slightly elevated bilirubin level. After discontinuation of lithium and fluoxetine, the patient's symptoms resolved over the next four days. At no point did the lithium levels reach a toxic level, suggesting that the patient's symptoms were due to a toxic reaction between fluoxetine and lithium (Noveske et al, 1989).

c) Serotonin syndrome was precipitated when lithium 300 mg twice daily was added to a three-month regimen of fluoxetine 40 mg per day. Five days later, the patient's lithium level was measured at 0.65 mEq/L and the dose was increased to 300 mg three times daily. Two days after this dosage change, the patient experienced akathisia, myoclonus, hyperreflexia, shivering, tremor, diarrhea, and incoordination. After discontinuation of lithium and initiation of cyproheptadine therapy, the patient's symptoms began to improve. The patient was discharged on a regimen 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 of coadministered lithium and citalopram. All subjects were extensive metabolizers of sparteine, indicating normal cytochrome P450 2D6 enzyme activity. Although lithium is not influenced by drug oxidation, citalopram metabolites are excreted by the kidney, as is lithium. Each subject received citalopram 40 mg alone as a single daily dose for 10 days, lithium 30 mmol (1980 mg) alone daily for five days, and lithium coadministered with citalopram on days 3-7. At least two weeks separated each treatment phase. Results showed that the concurrent administration of citalopram and lithium did not significantly alter the pharmacokinetics of lithium (Gram et al, 1993).

e) Twenty-four patients experiencing depression (DSM III criteria) were randomized under double-blind conditions to receive citalopram (40 mg to 60 mg daily) and lithium carbonate (800 mg daily) or placebo. All of the subjects had failed to respond to four weeks of citalopram monotherapy. Lithium was coadministered on days 29 to 42. No evidence of a pharmacokinetic interaction 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 daily (serum level 0.71 mmol/L) and was given fluvoxamine 50 mg daily. Over a 10-day period the fluvoxamine dose was increased to 200 mg daily; tremor and difficulty with fine hand movements developed. After two weeks, tremor, impaired motor function coordination, marked bilateral hyperreflexia of biceps and knee jerks, and clonus in both ankles were seen. After 12 weeks of continued therapy, during which time no further deterioration occurred, nortriptyline 100 mg daily replaced fluvoxamine, and the neuromuscular symptoms abated over a 2-week period. After four weeks the patient's neurological exam was normal (Ohman & Spigset, 1993).
g) Three cases of mania were reported in patients who were treated with lithium and fluvoxamine. The mania appeared 10 days, four weeks, and five weeks, respectively, after cotherapy was begun. Fluvoxamine was discontinued and, in two of the three patients, the mania resolved, and successful treatment of depression occurred with lithium alone. The third patient improved, but 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 twice daily on days one through eight and once in the morning on day nine. In addition, oral sertraline 100 mg or placebo was given twice, ten hours and two hours prior to lithium dosing on day nine. The steady-state lithium level was only decreased by 1.4% (0.01 mEq/L) and the lithium renal clearance increased by 6.9% (0.11 L/hour) when sertraline was coadministered. Seven subjects experienced side effects, mainly tremors, after receiving lithium and sertraline, whereas no subjects who ingested placebo and lithium experienced side effects (Wilner et al, 1991).

3.5.1.CX Lofepramine

1) Interaction Effect: lofepramine toxicity (dry mouth, sedation, urinary retention)
2) Summary: Paroxetine coadministered with desipramine or imipramine produced higher serum concentrations of the tricyclic antidepressant (TCA) in some patients (Hartter et al, 1994a; Brosen et al, 1993c). Although not reported specifically with lofepramine, a similar interaction could be expected. Paroxetine's effect on TCAs may resemble that of fluoxetine (another selective serotonin reuptake inhibitor), which is known to inhibit TCA metabolism (Aranow et al, 1989a; Vaughan, 1988a; Goodnick, 1989a). With coadministration, monitor patients for lofepramine toxicity. Lofepramine doses may need to be reduced (Prod Info Paxil CR(TM), 2003c).
3) Severity: moderate
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: When lofepramine is coadministered with paroxetine, monitor patients for signs and symptoms of lofepramine toxicity (dry mouth, sedation, urinary retention, blurred vision). Lofepramine doses may need to be reduced.
7) Probable Mechanism: decreased lofepramine metabolism
8) Literature Reports
a) The effect of paroxetine on desipramine metabolism was studied in 9 extensive metabolizers (EM) and 8 poor metabolizers (PM) of desipramine. Subjects took a single oral dose of desipramine before starting paroxetine and a second dose after 11 days of paroxetine use. After the addition of paroxetine, EMs experienced a 5-fold decrease in clearance of desipramine, indicating that paroxetine inhibits oxidation reactions catalyzed by CYP2D6. PMs had a slight increase in clearance of desipramine with paroxetine. With concurrent administration of desipramine and paroxetine, interaction of the two drugs may result in a need for dosage adjustments, especially in extensive metabolizers of desipramine (Brosen et al, 1993b).

3.5.1.CY 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 cohort studies have shown that the combined use of SSRIs and NSAIDs has been associated with an increased risk of bleeding. Bleeding events have included epistaxis, ecchymosis, hematoma, petechiae, and life-threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension, 2008) (Prod Info Lexapro(TM), 2003; Dalton et al, 2003a; Prod Info CELEXA (R) oral tablet, solution, 2005).
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 increased bleeding.
7) Probable Mechanism: unknown
8) Literature Reports
a) SSRIs increase the risk of upper gastrointestinal bleeding and this effect is potentiated by concurrent use of NSAIDs or low-dose aspirin. Hospitalizations for upper gastrointestinal bleeding were searched among 26,005 users of antidepressant medications and compared with the number of hospitalizations in those patients who did not receive prescriptions for antidepressants. The amount of upper GI bleeding episodes was 3.6 times more than expected (95% confidence interval, 2.7 to 4.7). Combined use of an SSRI and NSAIDs or low-dose aspirin increased the risk to 12.2 (95% confidence interval, 7.1 to 19.5) and 5.2 (95% confidence interval, 3.2 to 8), respectively. The findings of this study demonstrate

an increased risk of upper GI bleeding during the use of SSRIs. Combined use of SSRIs and NSAIDs or low-dose aspirin increased the risk even further (Dalton et al, 2003).
b) Coadministration of ketorolac with psychoactive drugs (such as fluoxetine) has been associated with hallucinations in some patients (Prod Info TORADOL(R) oral tablets, 2007).

3.5.1.CZ 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 cohort studies have shown that the combined use of SSRIs and NSAIDs has been associated with an increased risk of bleeding. Bleeding events have included epistaxis, ecchymosis, hematoma, petechiae, and life-threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension, 2008) (Prod Info Lexapro(TM), 2003; Dalton et al, 2003a; Prod Info CELEXA (R) oral tablet, solution, 2005).
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 increased bleeding.
7) Probable Mechanism: unknown
8) Literature Reports
a) SSRIs increase the risk of upper gastrointestinal bleeding and this effect is potentiated by concurrent use of NSAIDs or low-dose aspirin. Hospitalizations for upper gastrointestinal bleeding were searched among 26,005 users of antidepressant medications and compared with the number of hospitalizations in those patients who did not receive prescriptions for antidepressants. The amount of upper GI bleeding episodes was 3.6 times more than expected (95% confidence interval, 2.7 to 4.7). Combined use of an SSRI and NSAIDs or low-dose aspirin increased the risk to 12.2 (95% confidence interval, 7.1 to 19.5) and 5.2 (95% confidence interval, 3.2 to 8), respectively. The findings of this study demonstrate an increased risk of upper GI bleeding during the use of SSRIs. Combined use of SSRIs and NSAIDs or low-dose aspirin increased the risk even further (Dalton et al, 2003).
b) Coadministration of ketorolac with psychoactive drugs (such as fluoxetine) has been associated with hallucinations in some patients (Prod Info TORADOL(R) oral tablets, 2007).

3.5.1.DA 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 cohort studies have shown that the combined use of SSRIs and NSAIDs has been associated with an increased risk of bleeding. Bleeding events have included epistaxis, ecchymosis, hematoma, petechiae, and life-threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension, 2008) (Prod Info Lexapro(TM), 2003; Dalton et al, 2003a; Prod Info CELEXA (R) oral tablet, solution, 2005).
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 increased bleeding.
7) Probable Mechanism: unknown
8) Literature Reports
a) SSRIs increase the risk of upper gastrointestinal bleeding and this effect is potentiated by concurrent use of NSAIDs or low-dose aspirin. Hospitalizations for upper gastrointestinal bleeding were searched among 26,005 users of antidepressant medications and compared with the number of hospitalizations in those patients who did not receive prescriptions for antidepressants. The amount of upper GI bleeding episodes was 3.6 times more than expected (95% confidence interval, 2.7 to 4.7). Combined use of an SSRI and NSAIDs or low-dose aspirin increased the risk to 12.2 (95% confidence interval, 7.1 to 19.5) and 5.2 (95% confidence interval, 3.2 to 8), respectively. The findings of this study demonstrate an increased risk of upper GI bleeding during the use of SSRIs. Combined use of SSRIs and NSAIDs or low-dose aspirin increased the risk even further (Dalton et al, 2003).
b) Coadministration of ketorolac with psychoactive drugs (such as fluoxetine) has been associated with hallucinations in some patients (Prod Info TORADOL(R) oral tablets, 2007).

3.5.1.DB 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 cohort studies have shown that the combined use of SSRIs and NSAIDs has been associated with an increased risk of bleeding. Bleeding events have included epistaxis, ecchymosis, hematoma, petechiae, and life-threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension, 2008) (Prod Info Lexapro(TM), 2003; Dalton et al, 2003a; Prod Info CELEXA (R) oral tablet, solution, 2005).
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

increased bleeding.
7) Probable Mechanism: unknown
8) Literature Reports
a) SSRIs increase the risk of upper gastrointestinal bleeding and this effect is potentiated by concurrent use of NSAIDs or low-dose aspirin. Hospitalizations for upper gastrointestinal bleeding were searched among 26,005 users of antidepressant medications and compared with the number of hospitalizations in those patients who did not receive prescriptions for antidepressants. The amount of upper GI bleeding episodes was 3.6 times more than expected (95% confidence interval, 2.7 to 4.7). Combined use of an SSRI and NSAIDs or low-dose aspirin increased the risk to 12.2 (95% confidence interval, 7.1 to 19.5) and 5.2 (95% confidence interval, 3.2 to 8), respectively. The findings of this study demonstrate an increased risk of upper GI bleeding during the use of SSRIs. Combined use of SSRIs and NSAIDs or low-dose aspirin increased the risk even further (Dalton et al, 2003).
b) Coadministration of ketorolac with psychoactive drugs (such as fluoxetine) has been associated with hallucinations in some patients (Prod Info TORADOL(R) oral tablets, 2007).

3.5.1.DC Methylphenidate
1) Interaction Effect: increased selective serotonin reuptake inhibitor plasma concentrations
2) Summary: Human pharmacologic studies have demonstrated that methylphenidate may inhibit the metabolism of selective serotonin reuptake inhibitors (SSRIs). Downward dose adjustments of the SSRI may be necessary when it is used concurrently with methylphenidate. Additionally, when initiating or discontinuing methylphenidate, the SSRI dose may need to be adjusted as needed (Prod 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 serotonin reuptake inhibitor (SSRI). Concomitant use of methylphenidate and an SSRI may cause elevated SSRI plasma concentrations. Consider a decrease in the dose of SSRI when these agents are coadministered. Additionally, consider adjusting the SSRI dose if necessary when initiating or discontinuing methylphenidate therapy (Prod Info METADATE CD(R) extended-release oral capsules, 2007).
7) Probable Mechanism: inhibition of selective serotonin reuptake inhibitor metabolism by methylphenidate

3.5.1.DD Metoprolol
1) Interaction Effect: an increased risk of metoprolol adverse effects (shortness of breath, bradycardia, hypotension, acute heart failure)
2) Summary: Paroxetine was shown to alter the pharmacokinetics and enhance the pharmacodynamics of metoprolol, most likely through inhibition of cytochrome P450 2D6 enzymes necessary for metoprolol metabolism. Multiple-dose intake of both paroxetine and metoprolol may require a reduction in the dose of metoprolol to prevent metoprolol adverse effects, such as bradycardia, hypotension, and bronchoconstriction due to loss of cardioselectivity (Hemeryck et al, 2000a). Consider other therapies, such as atenolol or bisoprolol, which are not metabolized through CYP2D6 mechanisms, or alternative antidepressant therapy (Onalan et al, 2008).
3) Severity: moderate
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: Patients receiving concurrent therapy with metoprolol and paroxetine should be monitored for bradycardia and loss of cardioselectivity. Dose reductions of metoprolol, a change from metoprolol to atenolol or bisoprolol, or substitution of paroxetine with an alternative antidepressant may be necessary.
7) Probable Mechanism: inhibition of cytochrome P450 2D6-mediated metoprolol metabolism
8) Literature Reports
a) Eight healthy male volunteers participated in an open-label trial to determine whether administration of multiple-dose paroxetine altered the stereoselective pharmacokinetics and pharmacodynamics of metoprolol. All participants received metoprolol 100 mg on day 1, followed on day 2 through 7 by paroxetine 10 mg twice daily. Another dose of metoprolol 100 mg was given on day 8. Paroxetine caused an 8-fold (from 169 ng/h/mL to 1340 ng/h/mL) and a 5-fold (from 279 ng/h/mL to 1418 ng/h/mL) increase in the area under the concentration-time curve (AUC) of (R)- and (S)- metoprolol, respectively. For both enantiomers of metoprolol, the maximum concentration (Cmax) and half-life were approximately doubled during therapy with paroxetine. The stereoselectivity of metoprolol was virtually eliminated following paroxetine, with the (S)/(R) AUC ratio decreasing from 1.72 to 1.07. Pharmacodynamically, the increase in (S)- metoprolol plasma concentrations was associated with a more sustained beta-blockade as demonstrated by a reduction in exercise heart rate and exercise systolic blood pressure (Hemeryck et al, 2000).
b) Fifteen days after initiating metoprolol (50 mg/day) therapy, a 63-year-old woman maintained on paroxetine 20 mg/day and alprazolam 0.5 mg/day for the previous year experienced complete atrioventricular (AV) block and syncope. Metoprolol was discontinued, and 3 days later the patient was asymptomatic with normal blood pressure and heart rate. A 12-lead electrocardiography (ECG) showed complete AV block with a narrow QRS escape rhythm of 40 beats/minute. Coronary angiogram was

unremarkable and the results of all other diagnostic tests were normal. Paroxetine was discontinued, and by day 5 the AV block had completely resolved. Subsequent similar doses of either paroxetine or metoprolol monotherapy did not induce bradyarrhythmia in this patient (Onalan et al, 2008).

3.5.1.DE Milnacipran

1) Interaction Effect: increased risk of serotonin syndrome (hypertension, hyperthermia, myoclonus, mental status changes)

2) Summary: Concurrent use of milnacipran and an SSRI may result in hypertension, coronary artery vasoconstriction or serotonin syndrome, which may be life-threatening. Symptoms of serotonin syndrome may include restlessness, hallucinations, loss of coordination, fast heart beat, rapid changes in blood pressure, increased body temperature, overreactive reflexes, nausea, vomiting, and 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 coronary artery vasoconstriction, through the additive serotonergic effects. If these agents are used together, discuss the risks of serotonin syndrome with the patient and monitor closely for symptoms of serotonin syndrome (restlessness, hyperthermia, hyperreflexia, incoordination), especially during treatment initiation and dose increases (Prod Info SAVELLA(R) oral tablets, 2009).

7) Probable Mechanism: additive serotonergic effect

3.5.1.DF Moclobemide

1) Interaction Effect: CNS toxicity or serotonin syndrome (hypertension, hyperthermia, myoclonus, mental status changes)

2) Summary: Concurrent administration or overlapping therapy with paroxetine and a monoamine oxidase (MAO) inhibitor may result in CNS toxicity or serotonin syndrome, a hyperserotonergic state characterized by symptoms such as restlessness, myoclonus, changes in mental status, hyperreflexia, diaphoresis, shivering, and tremor. Serious, even fatal, reactions have been reported with concomitant use of serotonin specific reuptake inhibitors and MAO inhibitors (Prod Info Paxil(R), 2003h; Lappin & Auchincloss, 1994s; Graber et al, 1994s; Suchowersky & de Vries, 1990s). Concomitant use is contraindicated.

3) Severity: contraindicated

4) Onset: rapid

5) Substantiation: probable

6) Clinical Management: Concurrent use of paroxetine and an MAO inhibitor is contraindicated. Wait at least two weeks after discontinuing an MAO inhibitor before initiating paroxetine, and at least two weeks after discontinuing paroxetine before initiating therapy with an MAOI.

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 serotonin syndrome (Sternbach, 1991n). Serotonin syndrome is a condition of serotonergic hyperstimulation and manifests as restlessness, myoclonus, changes in mental status, hyperreflexia, diaphoresis, shivering, and tremor. If the syndrome is not recognized and correctly treated, fatality can result.

b) A 26-year old woman who had been taking isocarboxazid for eight weeks stopped taking the drug for 11 days before beginning therapy with sertraline. After a single 100 mg sertraline dose, the patient became restless and developed leg twitches. The patients was later admitted to the emergency room with diaphoresis, tachycardia, hyperreflexia, and various neuromuscular disturbances. After treatment with diazepam and propranolol the patient did not improve. The patient was then given two 4 mg doses of cyproheptadine an hour apart, with notable improvement in 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 added to a regimen of lithium, phenelzine, thioridazine, and doxepin. Three hours after taking the first sertraline dose, the patient was found in a semicomatose state, with elevated body temperature, increased pulse, increased respiration rate, and a blood pressure of 140/110 mm Hg. After transportation to the hospital, the patient was misdiagnosed as having neuroleptic malignant syndrome (NMS) which was later changed to serotonin syndrome due to a reaction between sertraline and phenelzine. The authors suggest that monoamine oxidase inhibitor (MAOI) therapy should be discontinued for at least two weeks before initiation of therapy with a selective serotonin reuptake inhibitor (SSRI) and that before starting a MAOI, SSRI therapy should be discontinued for at least five half-lives of the parent drug and any active metabolites (Graber et al, 1994r).

d) Two cases reports suggested a possible interaction between fluoxetine and selegiline (Suchowersky & de Vries, 1990r). One case involved a first episode of mania being observed approximately one month after adding selegiline to fluoxetine. The patient improved two months after both drugs were discontinued, and no further details were provided. The second case involved diaphoresis, vasoconstriction, and cyanosis of the hands which occurred in close temporal relationship to adding fluoxetine to selegiline. Both drugs were discontinued, with relatively quick resolution of symptoms. Rechallenge with fluoxetine alone occurred without incident.

e) Five fatal overdose cases were reported due to serotonin syndrome. In three of the five cases, the drug combination that induced the fatal syndrome was moclobemide, a selective monoamine oxidase inhibitor, and citalopram. Of the three patients, blood concentrations of moclobemide ranged from five times the therapeutic level to 50 times the therapeutic level, and citalopram concentrations ranged from normal therapeutic levels to five times the therapeutic level (Neuvonen et al, 1993).

3.5.1.DG 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 cohort studies have shown that the combined use of SSRIs and NSAIDs has been associated with an increased risk of bleeding. Bleeding events have included epistaxis, ecchymosis, hematoma, petechiae, and life-threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension, 2008) (Prod Info Lexapro(TM), 2003; Dalton et al, 2003a; Prod Info CELEXA (R) oral tablet, solution, 2005).

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 increased bleeding.

7) Probable Mechanism: unknown

8) Literature Reports

a) SSRIs increase the risk of upper gastrointestinal bleeding and this effect is potentiated by concurrent use of NSAIDs or low-dose aspirin. Hospitalizations for upper gastrointestinal bleeding were searched among 26,005 users of antidepressant medications and compared with the number of hospitalizations in those patients who did not receive prescriptions for antidepressants. The amount of upper GI bleeding episodes was 3.6 times more than expected (95% confidence interval, 2.7 to 4.7). Combined use of an SSRI and NSAIDs or low-dose aspirin increased the risk to 12.2 (95% confidence interval, 7.1 to 19.5) and 5.2 (95% confidence interval, 3.2 to 8), respectively. The findings of this study demonstrate an increased risk of upper GI bleeding during the use of SSRIs. Combined use of SSRIs and NSAIDs or low-dose aspirin increased the risk even further (Dalton et al, 2003).

b) Coadministration of ketorolac with psychoactive drugs (such as fluoxetine) has been associated with hallucinations in some patients (Prod Info TORADOL(R) oral tablets, 2007).

3.5.1.DH 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 cohort studies have shown that the combined use of SSRIs and NSAIDs has been associated with an increased risk of bleeding. Bleeding events have included epistaxis, ecchymosis, hematoma, petechiae, and life-threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension, 2008) (Prod Info Lexapro(TM), 2003; Dalton et al, 2003a; Prod Info CELEXA (R) oral tablet, solution, 2005).

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 increased bleeding.

7) Probable Mechanism: unknown

8) Literature Reports

a) SSRIs increase the risk of upper gastrointestinal bleeding and this effect is potentiated by concurrent use of NSAIDs or low-dose aspirin. Hospitalizations for upper gastrointestinal bleeding were searched among 26,005 users of antidepressant medications and compared with the number of hospitalizations in those patients who did not receive prescriptions for antidepressants. The amount of upper GI bleeding episodes was 3.6 times more than expected (95% confidence interval, 2.7 to 4.7). Combined use of an SSRI and NSAIDs or low-dose aspirin increased the risk to 12.2 (95% confidence interval, 7.1 to 19.5) and 5.2 (95% confidence interval, 3.2 to 8), respectively. The findings of this study demonstrate an increased risk of upper GI bleeding during the use of SSRIs. Combined use of SSRIs and NSAIDs or low-dose aspirin increased the risk even further (Dalton et al, 2003).

b) Coadministration of ketorolac with psychoactive drugs (such as fluoxetine) has been associated with hallucinations in some patients (Prod Info TORADOL(R) oral tablets, 2007).

3.5.1.DI 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 cohort studies have shown that the combined use of SSRIs and anticoagulants has been associated with an increased risk of bleeding (Wallerstedt et al, 2009; Schalekamp et al, 2008; Prod Info PAXIL(R) oral tablets, suspension, 2008). Bleeding events reported have included epistaxis, ecchymosis, hematoma, petechiae, and life-threatening hemorrhages. Altered anticoagulant effects (including increased bleeding) have been reported with the coadministration of SSRIs with warfarin (Schalekamp et al, 2008; Prod Info PAXIL(R) oral tablets, suspension, 2008).

3) Severity: major

4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: When paroxetine and an anticoagulant are given concurrently, monitor patients for signs of increased bleeding. Patients who are taking warfarin should be monitored closely for altered anticoagulant effects, including increased bleeding, when paroxetine therapy is initiated or discontinued (Prod Info PAXIL(R) oral tablets, suspension, 2008).
7) Probable Mechanism: unknown
8) Literature Reports

a) According to a retrospective cohort study (n=234), there was an increased risk of clinically relevant bleeding (hospital admission due to bleeding) in patients receiving warfarin for atrial fibrillation during concomitant SSRI therapy or within 2 weeks following SSRI therapy termination. Patients with a mean age of 72 +/- 7 years receiving warfarin plus SSRI (n=117) were matched with randomly selected patients who received warfarin only (n=117). SSRI included fluoxetine, citalopram, paroxetine, sertraline, fluvoxamine, or escitalopram. Nine patients experienced 11 bleeding episodes during 213.9 treatment years in the warfarin plus SSRI group, and 10 patients experienced 14 bleedings during 586.4 treatment years in the warfarin-only group. The corresponding total incidences of bleedings were 51.4 and 23.9 per 1000 treatment years, respectively. The hazard ratio for first bleedings during treatment with warfarin plus SSRI was 3.49 (95% CI; 1.37 to 8.91, p=0.009) compared with warfarin only. The SSRI implicated in patients experiencing bleeding at the time of concomitant administration were sertraline or citalopram. The addition of an SSRI was not associated with a change in warfarin dose or INR (p=0.48 and p=0.31 respectively). The results of the study may be limited by earlier bleeding events, unknown patient adherence, and exclusion of clopidogrel, dipyridamol, corticosteroids and anticoagulants other than warfarin in the model (Wallerstedt et al, 2009).

b) A population-based, case-controlled study of new coumarin users (acenocoumarol and phenprocoumon) with concomitant selective serotonin reuptake inhibitors (SSRIs) resulted in an increased risk of hospitalization due to nongastrointestinal bleeding. Using national pharmacy and hospitalization records, Netherlands researchers identified 1848 cases that were admitted for abnormal bleeding and compared them with 5818 control subjects also taking coumarins. Median duration of treatment in patients was 220 days (range, 1 to 4690 days). Patients on SSRIs showed greater risk for hospitalization for nongastrointestinal bleeding (adjusted odds ratio (OR) 1.7, 95% confidence interval (CI), 1.1 to 2.5), however, the rate of gastrointestinal bleeding (adjusted OR 0.8, 95% CI, 0.4 to 1.5) was not significantly different (Schalekamp et al, 2008).

c) Preliminary data suggest that there may be a pharmacodynamic interaction (that causes an increased bleeding diathesis with unaltered prothrombin time) between paroxetine and warfarin. The concomitant use of paroxetine and warfarin should be undertaken with caution (Prod Info PAXIL(R) oral tablets, suspension, 2008).

d) In a multiple-dose study, several days of combined therapy with warfarin and paroxetine resulted in mild but clinically significant bleeding in 5 of 27 subjects. This effect occurred in the absence of a significant enhancement in warfarin-induced hypoprothrombinemia or changes in either paroxetine or warfarin disposition (Bannister et al, 1989b).

3.5.1.DJ 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 cohort studies have shown that the combined use of SSRIs and NSAIDs has been associated with an increased risk of bleeding. Bleeding events have included epistaxis, ecchymosis, hematoma, petechiae, and life-threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension, 2008) (Prod Info Lexapro(TM), 2003; Dalton et al, 2003a; Prod Info CELEXA (R) oral tablet, solution, 2005).
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 increased bleeding.
7) Probable Mechanism: unknown
8) Literature Reports

a) SSRIs increase the risk of upper gastrointestinal bleeding and this effect is potentiated by concurrent use of NSAIDs or low-dose aspirin. Hospitalizations for upper gastrointestinal bleeding were searched among 26,005 users of antidepressant medications and compared with the number of hospitalizations in those patients who did not receive prescriptions for antidepressants. The amount of upper GI bleeding episodes was 3.6 times more than expected (95% confidence interval, 2.7 to 4.7). Combined use of an SSRI and NSAIDs or low-dose aspirin increased the risk to 12.2 (95% confidence interval, 7.1 to 19.5) and 5.2 (95% confidence interval, 3.2 to 8), respectively. The findings of this study demonstrate an increased risk of upper GI bleeding during the use of SSRIs. Combined use of SSRIs and NSAIDs or low-dose aspirin increased the risk even further (Dalton et al, 2003).

b) Coadministration of ketorolac with psychoactive drugs (such as fluoxetine) has been associated with hallucinations in some patients (Prod Info TORADOL(R) oral tablets, 2007).

3.5.1.DK Naratriptan

1) Interaction Effect: an increased risk of serotonin syndrome
2) Summary: Rare incidences of weakness, hyperreflexia, and incoordination have been reported with the concurrent use of a selective serotonin reuptake inhibitor (SSRI) and a 5-hydroxytryptamine-1 (5HT-1) agonist (Prod Info Amerge(TM), 2002). Concurrent use of a triptan and an SSRI may result in serotonin syndrome which may be life-threatening. Symptoms of serotonin syndrome may include restlessness, hallucinations, loss of coordination, fast heart beat, rapid changes in blood pressure, increased body temperature, overreactive reflexes, nausea, vomiting, and diarrhea. Clinicians should be aware that triptans may be commonly used intermittently and that either the triptan or the SSRI may be prescribed by a different physician. Discuss the risks of serotonin syndrome with patients who are prescribed this combination and monitor them closely for symptoms of serotonin syndrome (US Food and Drug Administration, 2006).
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-threatening condition called serotonin syndrome. Be aware that triptans may be commonly used intermittently and that either the triptan or the SSRI may be prescribed by a different physician. If these agents are used together, discuss the risks of serotonin syndrome with the patient and monitor closely for symptoms of serotonin syndrome (restlessness, hyperthermia, hyperreflexia, incoordination).
7) Probable Mechanism: additive pharmacologic effects resulting in excessive serotonergic stimulation

3.5.1.DL Nebivolol

1) Interaction Effect: increased nebivolol exposure and plasma levels
2) Summary: Nebivolol is partially metabolized by the CYP2D6 isozyme. Coadministration of a single 10 mg dose of dose of nebivolol in healthy adults (n=10) receiving fluoxetine, a CYP2D6 inhibitor, at a dose of 20 mg/day for 21 days led to 8- and 3-fold increases in the AUC and Cmax, respectively, of d-nebivolol (pharmacologically active isomer). Although not studied with paroxetine, also a CYP2D6 inhibitor, a similar interaction can be expected. Closely monitor blood pressure in patients receiving nebivolol and paroxetine concomitantly. Downward dose adjustments of nebivolol may be necessary (Prod Info BYSTOLIC(TM) oral tablets, 2007).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Coadministration of nebivolol with a CYP2D6 inhibitor, such as paroxetine, may result in increased exposure and plasma concentrations of nebivolol. In patients receiving these agents concomitantly, closely monitor blood pressure. Reduced doses of nebivolol may be necessary (Prod Info BYSTOLIC(TM) oral tablets, 2007).
7) Probable Mechanism: inhibition of CYP2D6-mediated nebivolol metabolism

3.5.1.DM Nefazodone

1) Interaction Effect: CNS toxicity or serotonin syndrome (hypertension, hyperthermia, myoclonus, mental status changes)
2) Summary: One case report describes the development of serotonin syndrome in a female who had stopped nefazodone after a two-week tapering period and started paroxetine therapy one day after the complete discontinuation of nefazodone. A repeat challenge with paroxetine seven days later did not result in the recurrence of symptoms (John et al, 1997a).
3) Severity: major
4) Onset: rapid
5) Substantiation: probable
6) Clinical Management: Because of the long half-lives of some nefazodone active metabolites, a seven-day washout period should be observed between the discontinuation of nefazodone and the initiation of paroxetine therapy.
7) Probable Mechanism: unknown
8) Literature Reports
a) A 51-year old female with bipolar affective disorder had received nefazodone for six months and had tapered the dose to 75 mg every twelve hours over two weeks. One day after stopping nefazodone therapy, she started paroxetine 20 mg daily and valproic acid 250 mg three times daily. She was agitated and incoherent and then became unresponsive, with shaking movements in her arms and legs. Upon admission to the emergency department, she was diaphoretic, with uncoordinated body tremors, flailing arms, twitching legs, and dilated pupils. Her body temperature rose to 102.2 F, and her creatine kinase (CK) values reached 25,520 U/L by day 3. She became afebrile, and muscle rigidity dissipated by day 4. A repeat challenge with paroxetine seven days later did not result in the recurrence of symptoms. Nefazodone has a half-life of 1.9 to 2.9 hours, but several active metabolites exist, with half-lives of 18 to 33 hours. The authors postulated that in this patient, nefazodone metabolites caused serotonin syndrome when the patient ingested paroxetine. A seven day washout period is recommended after the discontinuation of nefazodone before the administration of any selective serotonin reuptake inhibitor is started (John et al, 1997).
b) Serotonin syndrome is a condition of serotonergic hyperstimulation and manifests as restlessness, myoclonus, changes in mental status, hyperreflexia, diaphoresis, shivering, and tremor. If the syndrome

is not recognized and correctly treated, fatality can result (Sternbach, 1991e).

3.5.1.DN Nialamide

1) Interaction Effect: CNS toxicity or serotonin syndrome (hypertension, hyperthermia, myoclonus, mental status changes)

2) Summary: Concurrent administration or overlapping therapy with paroxetine and a monoamine oxidase (MAO) inhibitor may result in CNS toxicity or serotonin syndrome, a hyperserotonergic state characterized by symptoms such as restlessness, myoclonus, changes in mental status, hyperreflexia, diaphoresis, shivering, and tremor. Serious, even fatal, reactions have been reported with concomitant use of serotonin specific reuptake inhibitors and MAO inhibitors (Prod Info Paxil(R), 1999g; Lappin & Auchincloss, 1994u; Graber et al, 1994u; Suchowersky & de Vries, 1990u). Concomitant use is contraindicated.

3) Severity: contraindicated

4) Onset: rapid

5) Substantiation: probable

6) Clinical Management: Concurrent use of paroxetine and a MAO inhibitor is contraindicated. Wait at least two weeks after discontinuing a MAO inhibitor before initiating paroxetine, and at least two weeks after discontinuing paroxetine 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 serotonin syndrome (Sternbach, 1991p). Serotonin syndrome is a condition of serotonergic hyperstimulation and manifests as restlessness, myoclonus, changes in mental status, hyperreflexia, diaphoresis, shivering, and tremor. If the syndrome is not recognized and correctly treated, fatality can result.

b) A 26-year old woman who had been taking isocarboxazid for eight weeks stopped taking the drug for 11 days before beginning therapy with sertraline. After a single 100 mg sertraline dose, the patient became restless and developed leg twitches. The patients was later admitted to the emergency room with diaphoresis, tachycardia, hyperreflexia, and various neuromuscular disturbances. After treatment with diazepam and propranolol the patient did not improve. The patient was then given two 4 mg doses of cyproheptadine an hour apart, with notable improvement 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 added to a regimen of lithium, phenelzine, thioridazine, and doxepin. Three hours after taking the first sertraline dose, the patient was found in a semicomatose state, with elevated body temperature, increased pulse, increased respiration rate, and a blood pressure of 140/110 mm Hg. After transportation to the hospital, the patient was misdiagnosed as having neuroleptic malignant syndrome (NMS) which was later changed to serotonin syndrome due to a reaction between sertraline and phenelzine. The authors suggest that monoamine oxidase inhibitor (MAOI) therapy should be discontinued for at least two weeks before initiation of therapy with a selective serotonin reuptake inhibitor (SSRI) and that before starting a MAOI, SSRI therapy should be discontinued for at least five half-lives of the parent drug and any active metabolites (Graber et al, 1994t).

d) Two cases reports suggested a possible interaction between fluoxetine and selegiline (Suchowersky & de Vries, 1990t). One case involved a first episode of mania being observed approximately one month after adding selegiline to fluoxetine. The patient improved two months after both drugs were discontinued, and no further details were provided. The second case involved diaphoresis, vasoconstriction, and cyanosis of the hands which occurred in close temporal relationship to adding fluoxetine to selegiline. Both drugs were discontinued, with relatively quick resolution of symptoms. Rechallenge with fluoxetine alone occurred without incident.

3.5.1.DO 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 and cohort studies have shown that the combined use of SSRIs and NSAIDs has been associated with an increased risk of bleeding. Bleeding events have included epistaxis, ecchymosis, hematoma, petechiae, and life-threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension, 2008) (Prod Info Lexapro(TM), 2003; Dalton et al, 2003a; Prod Info CELEXA (R) oral tablet, solution, 2005).

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 increased bleeding.

7) Probable Mechanism: unknown

8) Literature Reports

a) SSRIs increase the risk of upper gastrointestinal bleeding and this effect is potentiated by concurrent use of NSAIDs or low-dose aspirin. Hospitalizations for upper gastrointestinal bleeding were searched among 26,005 users of antidepressant medications and compared with the number of hospitalizations in those patients who did not receive prescriptions for antidepressants. The amount of upper GI bleeding episodes was 3.6 times more than expected (95% confidence interval, 2.7 to 4.7). Combined

use of an SSRI and NSAIDs or low-dose aspirin increased the risk to 12.2 (95% confidence interval, 7.1 to 19.5) and 5.2 (95% confidence interval, 3.2 to 8), respectively. The findings of this study demonstrate an increased risk of upper GI bleeding during the use of SSRIs. Combined use of SSRIs and NSAIDs or low-dose aspirin increased the risk even further (Dalton et al, 2003).

b) Coadministration of ketorolac with psychoactive drugs (such as fluoxetine) has been associated with hallucinations in some patients (Prod Info TORADOL(R) oral tablets, 2007).

3.5.1.DP Nimesulide

1) Interaction Effect: an increased risk of bleeding

2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs and NSAIDs has been associated with an increased risk of bleeding. Bleeding events have included epistaxis, ecchymosis, hematoma, petechiae, and life-threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension, 2008) (Prod Info Lexapro(TM), 2003; Dalton et al, 2003a; Prod Info CELEXA (R) oral tablet, solution, 2005).

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 increased bleeding.

7) Probable Mechanism: unknown

8) Literature Reports

a) SSRIs increase the risk of upper gastrointestinal bleeding and this effect is potentiated by concurrent use of NSAIDs or low-dose aspirin. Hospitalizations for upper gastrointestinal bleeding were searched among 26,005 users of antidepressant medications and compared with the number of hospitalizations in those patients who did not receive prescriptions for antidepressants. The amount of upper GI bleeding episodes was 3.6 times more than expected (95% confidence interval, 2.7 to 4.7). Combined use of an SSRI and NSAIDs or low-dose aspirin increased the risk to 12.2 (95% confidence interval, 7.1 to 19.5) and 5.2 (95% confidence interval, 3.2 to 8), respectively. The findings of this study demonstrate an increased risk of upper GI bleeding during the use of SSRIs. Combined use of SSRIs and NSAIDs or low-dose aspirin increased the risk even further (Dalton et al, 2003).

b) Coadministration of ketorolac with psychoactive drugs (such as fluoxetine) has been associated with hallucinations in some patients (Prod Info TORADOL(R) oral tablets, 2007).

3.5.1.DQ Nortriptyline

1) Interaction Effect: nortriptyline toxicity (dry mouth, sedation, urinary retention)

2) Summary: Concurrent use of paroxetine with tricyclic antidepressants (TCAs) produces increased TCA serum concentrations and may result in TCA toxicity (Prod Info Paxil CR(TM), 2003d; DeVane, 1994; Riesenman, 1995; Murray, 1992; Brosen et al, 1993e). The mechanism of this interaction involves potent inhibition by paroxetine of the cytochrome P450IID6 (CYP2D6) isoenzyme, the principal enzyme in TCA metabolism. Paroxetine may also weakly inhibit other P450 isoenzymes involved in TCA clearance. Other selective serotonin reuptake inhibitors (fluoxetine, fluvoxamine) have demonstrated similar effects on TCA metabolism.

3) Severity: moderate

4) Onset: delayed

5) Substantiation: probable

6) Clinical Management: When paroxetine is coadministered with nortriptyline, monitor patients for signs and symptoms of nortriptyline toxicity (dry mouth, sedation, urinary retention, blurred vision). Nortriptyline doses may need to be reduced.

7) Probable Mechanism: decreased cytochrome P450 2D6-mediated nortriptyline metabolism

8) Literature Reports

a) The effect of paroxetine on desipramine metabolism was studied in 9 extensive metabolizers (EM) and 8 poor metabolizers (PM) of desipramine (Brosen et al, 1993d). Subjects took a single oral dose of desipramine before starting paroxetine and a second dose after 11 days of paroxetine use. After the addition of paroxetine, EMs experienced a 5-fold decrease in clearance of desipramine, indicating that paroxetine inhibits oxidation reactions catalyzed by CYP2D6. PMs had a slight increase in clearance of desipramine during paroxetine coadministration. With concurrent administration of desipramine and paroxetine, an interaction of the two drugs may result in a need for dosage adjustments, especially in extensive metabolizers of desipramine.

b) A 35-year-old male began treatment with nortriptyline for his first depressive episode and obtained a steady-state serum level of 122 ng/mL (therapeutic level 50 to 150 ng/mL) at a daily dose of 150 mg. Because no improvement of his depression occurred, paroxetine 30 mg daily and thioridazine 50 mg at bedtime were added. A week later, the patient was irritable and complained of dry mouth and constipation. His nortriptyline level at this time was 337 ng/mL and his dose of nortriptyline was decreased to 75 mg daily. The most likely explanation for the increase in this patient's nortriptyline concentration was the addition of paroxetine, although thioridazine may have also played a role. Paroxetine may have inhibited the 10-hydroxylation of nortriptyline via the cytochrome P450 2D6 pathway. However, other studies have shown that thioridazine has the potential to also inhibit this metabolic pathway (Ghaemi & Kirkwood, 1998).

3.5.1.DR 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 cohort studies have shown that the combined use of SSRIs and NSAIDs has been associated with an increased risk of bleeding. Bleeding events have included epistaxis, ecchymosis, hematoma, petechiae, and life-threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension, 2008) (Prod Info Lexapro(TM), 2003; Dalton et al, 2003a; Prod Info CELEXA (R) oral tablet, solution, 2005).

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 increased bleeding.

7) Probable Mechanism: unknown

8) Literature Reports

a) SSRIs increase the risk of upper gastrointestinal bleeding and this effect is potentiated by concurrent use of NSAIDs or low-dose aspirin. Hospitalizations for upper gastrointestinal bleeding were searched among 26,005 users of antidepressant medications and compared with the number of hospitalizations in those patients who did not receive prescriptions for antidepressants. The amount of upper GI bleeding episodes was 3.6 times more than expected (95% confidence interval, 2.7 to 4.7). Combined use of an SSRI and NSAIDs or low-dose aspirin increased the risk to 12.2 (95% confidence interval, 7.1 to 19.5) and 5.2 (95% confidence interval, 3.2 to 8), respectively. The findings of this study demonstrate an increased risk of upper GI bleeding during the use of SSRIs. Combined use of SSRIs and NSAIDs or low-dose aspirin increased the risk even further (Dalton et al, 2003).

b) Coadministration of ketorolac with psychoactive drugs (such as fluoxetine) has been associated with hallucinations in some patients (Prod Info TORADOL(R) oral tablets, 2007).

3.5.1.DS Paliperidone

1) Interaction Effect: increased plasma concentrations of paliperidone

2) Summary: Concurrent use of paliperidone and paroxetine may result in increased paliperidone plasma concentrations. Paliperidone (9-hydroxyrisperidone) is the major active metabolite of risperidone (Prod Info INVEGA(TM) extended-release oral tablets, 2007). Concomitant use of paroxetine and risperidone has resulted in increased plasma concentrations of both risperidone and 9-hydroxyrisperidone, particularly at higher (40 mg) paroxetine doses (Saito et al, 2005; Spina et al, 2001). Use caution when paliperidone and paroxetine are used concomitantly. Consider monitoring for increased paliperidone side effects, including neuroleptic malignant syndrome, QTc prolongation, or tardive dyskinesia.

3) Severity: moderate

4) Onset: unspecified

5) Substantiation: probable

6) Clinical Management: Use caution when paliperidone and paroxetine are used concomitantly as this may result in increased paliperidone plasma concentrations (Prod Info INVEGA(TM) extended-release oral tablets, 2007). Consider monitoring for increased paliperidone side effects, including neuroleptic malignant syndrome, QTc prolongation, or tardive dyskinesia.

7) Probable Mechanism: inhibition of the CYP2D6-mediated metabolism of paliperidone

8) Literature Reports

a) In a drug interaction study, paliperidone exposures were a significant 16% (90% confidence interval, 4% to 30%) higher on average in CYP2D6 extensive metabolizers who were treated concomitantly with a single dose of paliperidone 3 mg and paroxetine 20 mg/day. Studies with higher paroxetine doses have not been conducted. The clinical relevance is not known (Prod Info INVEGA(TM) extended-release oral tablets, 2007).

b) Paroxetine, a potent inhibitor of cytochrome CYP2D6, may impair the elimination of risperidone, primarily by inhibiting CYP2D6-mediated alpha-hydroxylation and, to a lesser extent, by simultaneously affecting the further metabolism of 9-hydroxyrisperidone (9-OH-risperidone) or other pathways of risperidone biotransformation. In a study including 10 patients diagnosed with schizophrenia (n=7) or schizoaffective disorder depressive type (n=3), risperidone plasma concentrations increased when paroxetine was coadministered with risperidone. Patients were stabilized on risperidone therapy 4 to 8 mg/day and received adjunctive paroxetine 20 mg/day to treat negative symptoms, concomitant depression, or both. Risperidone dosage remained constant throughout the duration of the study. A significant elevation in risperidone plasma concentrations (p less than 0.01) and a slight, nonsignificant decrease in 9-OH-risperidone occurred. After 4 weeks of paroxetine treatment, the total concentration of risperidone and 9-OH-risperidone was increased by 45% (p less than 0.05). The mean plasma risperidone to 9-OH-risperidone ratio also changed significantly (p less than 0.001) with concomitant paroxetine treatment. Extrapyramidal side effects occurred in one patient during the second week of paroxetine coadministration. Total plasma levels of risperidone in this patient increased 62% over baseline values during paroxetine coadministration. The occurrence of extrapyramidal symptoms in patients after addition of SSRIs to antipsychotics might also be caused by an additive pharmacodynamic effect of paroxetine (Spina et al, 2001).

c) Risperidone plasma concentrations increased when risperidone-treated inpatients (n=12) with

schizophrenia and negative symptoms were coadministered incremental doses of paroxetine. Prior to initiating paroxetine, patients were receiving risperidone 2 mg twice daily for at least 6 weeks and steady-state plasma concentrations of risperidone and 9-hydroxyrisperidone (9-OH-risperidone) had been achieved. Paroxetine doses were administered in 3 consecutive 4-week increments of 10 mg/day, 20 mg/day, and 40 mg/day. Mean risperidone plasma concentrations during 10-, 20-, and 40-mg paroxetine treatment were 3.8- (95% confidence interval (CI), 3.2 to 5.8; p less than 0.01) , 7.1- (95% CI, 5.3 to 16.5; p less than 0.01), and 9.7-fold (95% CI, 7.8 to 22.5; p less than 0.01) higher compared with baseline. Increases in 9-OH-risperidone concentrations were not significant with paroxetine use. Mean active moiety (risperidone plus 9-OH-risperidone) plasma concentrations increased by 1.8-fold (95% CI, 1.4 to 2.7; p less than 0.05) during the 40-mg paroxetine dose; increases were not significant with 10- or 20-mg doses. Metabolic ratio was significantly increased (p less than 0.01) by 4.2-fold (95% CI, 3.4 to 6.2) with 10 mg of paroxetine, by 8.2-fold (95% CI, 6 to 16) with 20 mg, and by 12.6-fold (95% CI, 9.6 to 26.8) with 40 mg. Negative symptom scores were significantly improved during all paroxetine doses; however, extrapyramidal symptoms scores were significantly higher during 20- and 40-mg doses. The authors suggest that low-dose coadministration of paroxetine with risperidone may be safe and effective for treating schizophrenia with negative symptoms (Saito et al, 2005).

3.5.1.DT Parecoxib

1) Interaction Effect: an increased risk of bleeding

2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs and NSAIDs has been associated with an increased risk of bleeding. Bleeding events have included epistaxis, ecchymosis, hematoma, petechiae, and life-threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension, 2008) (Prod Info Lexapro(TM), 2003; Dalton et al, 2003a; Prod Info CELEXA (R) oral tablet, solution, 2005).

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 increased bleeding.

7) Probable Mechanism: unknown

8) Literature Reports

a) SSRIs increase the risk of upper gastrointestinal bleeding and this effect is potentiated by concurrent use of NSAIDs or low-dose aspirin. Hospitalizations for upper gastrointestinal bleeding were searched among 26,005 users of antidepressant medications and compared with the number of hospitalizations in those patients who did not receive prescriptions for antidepressants. The amount of upper GI bleeding episodes was 3.6 times more than expected (95% confidence interval, 2.7 to 4.7). Combined use of an SSRI and NSAIDs or low-dose aspirin increased the risk to 12.2 (95% confidence interval, 7.1 to 19.5) and 5.2 (95% confidence interval, 3.2 to 8), respectively. The findings of this study demonstrate an increased risk of upper GI bleeding during the use of SSRIs. Combined use of SSRIs and NSAIDs or low-dose aspirin increased the risk even further (Dalton et al, 2003).

b) Coadministration of ketorolac with psychoactive drugs (such as fluoxetine) has been associated with hallucinations in some patients (Prod Info TORADOL(R) oral tablets, 2007).

3.5.1.DU Pargyline

1) Interaction Effect: CNS toxicity or serotonin syndrome (hypertension, hyperthermia, myoclonus, mental status changes)

2) Summary: Concurrent administration or overlapping therapy with paroxetine and a monoamine oxidase (MAO) inhibitor may result in CNS toxicity or serotonin syndrome, a hyperserotonergic state characterized by symptoms such as restlessness, myoclonus, changes in mental status, hyperreflexia, diaphoresis, shivering, and tremor. Serious, even fatal, reactions have been reported with concomitant use of serotonin specific reuptake inhibitors and MAO inhibitors (Prod Info Paxil(R), 1999c; Lappin & Auchincloss, 1994i; Graber et al, 1994i; Suchowersky & de Vries, 1990i). Concomitant use is contraindicated.

3) Severity: contraindicated

4) Onset: rapid

5) Substantiation: probable

6) Clinical Management: Concurrent use of paroxetine and a MAO inhibitor is contraindicated. Wait at least two weeks after discontinuing a MAO inhibitor before initiating paroxetine, and at least two weeks after discontinuing paroxetine 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 serotonin syndrome (Sternbach, 1991i). Serotonin syndrome is a condition of serotonergic hyperstimulation and manifests as restlessness, myoclonus, changes in mental status, hyperreflexia, diaphoresis, shivering, and tremor. If the syndrome is not recognized and correctly treated, fatality can result.

b) A 26-year old woman who had been taking isocarboxazid for eight weeks stopped taking the drug for 11 days before beginning therapy with sertraline. After a single 100 mg sertraline dose, the patient became restless and developed leg twitches. The patients was later admitted to the emergency room

with diaphoresis, tachycardia, hyperreflexia, and various neuromuscular disturbances. After treatment with diazepam and propranolol the patient did not improve. The patient was then given two 4 mg doses of cyproheptadine an hour apart, with notable improvement 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 added to a regimen of lithium, phenelzine, thioridazine, and doxepin. Three hours after taking the first sertraline dose, the patient was found in a semicomatose state, with elevated body temperature, increased pulse, increased respiration rate, and a blood pressure of 140/110 mm Hg. After transportation to the hospital, the patient was misdiagnosed as having neuroleptic malignant syndrome (NMS) which was later changed to serotonin syndrome due to a reaction between sertraline and phenelzine. The authors suggest that monoamine oxidase inhibitor (MAOI) therapy should be discontinued for at least two weeks before initiation of therapy with a selective serotonin reuptake inhibitor (SSRI) and that before starting a MAOI, SSRI therapy should be discontinued for at least five half-lives of the parent drug and any active metabolites (Graber et al, 1994h).

d) Two cases reports suggested a possible interaction between fluoxetine and selegiline (Suchowersky & de Vries, 1990h). One case involved a first episode of mania being observed approximately one month after adding selegiline to fluoxetine. The patient improved two months after both drugs were discontinued, and no further details were provided. The second case involved diaphoresis, vasoconstriction, and cyanosis of the hands which occurred in close temporal relationship to adding fluoxetine to selegiline. Both drugs were discontinued, with relatively quick resolution of symptoms. Rechallenge with fluoxetine alone occurred without incident.

3.5.1.DV Parnaparin

1) Interaction Effect: an increased risk of bleeding

2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs and anticoagulants has been associated with an increased risk of bleeding (Wallerstedt et al, 2009; Schalekamp et al, 2008; Prod Info PAXIL(R) oral tablets, suspension, 2008). Bleeding events reported have included epistaxis, ecchymosis, hematoma, petechiae, and life-threatening hemorrhages. Altered anticoagulant effects (including increased bleeding) have been reported with the coadministration of SSRIs with warfarin (Schalekamp et al, 2008; Prod Info PAXIL(R) oral tablets, suspension, 2008).

3) Severity: major

4) Onset: delayed

5) Substantiation: probable

6) Clinical Management: When paroxetine and an anticoagulant are given concurrently, monitor patients for signs of increased bleeding. Patients who are taking warfarin should be monitored closely for altered anticoagulant effects, including increased bleeding, when paroxetine therapy is initiated or discontinued (Prod Info PAXIL(R) oral tablets, suspension, 2008).

7) Probable Mechanism: unknown

8) Literature Reports

a) According to a retrospective cohort study (n=234), there was an increased risk of clinically relevant bleeding (hospital admission due to bleeding) in patients receiving warfarin for atrial fibrillation during concomitant SSRI therapy or within 2 weeks following SSRI therapy termination. Patients with a mean age of 72 +/- 7 years receiving warfarin plus SSRI (n=117) were matched with randomly selected patients who received warfarin only (n=117). SSRI included fluoxetine, citalopram, paroxetine, sertraline, fluvoxamine, or escitalopram. Nine patients experienced 11 bleeding episodes during 213.9 treatment years in the warfarin plus SSRI group, and 10 patients experienced 14 bleedings during 586.4 treatment years in the warfarin-only group. The corresponding total incidences of bleedings were 51.4 and 23.9 per 1000 treatment years, respectively. The hazard ratio for first bleedings during treatment with warfarin plus SSRI was 3.49 (95% CI; 1.37 to 8.91, p=0.009) compared with warfarin only. The SSRI implicated in patients experiencing bleeding at the time of concomitant administration were sertraline or citalopram. The addition of an SSRI was not associated with a change in warfarin dose or INR (p=0.48 and p=0.31 respectively). The results of the study may be limited by earlier bleeding events, unknown patient adherence, and exclusion of clopidogrel, dipyridamol, corticosteroids and anticoagulants other than warfarin in the model (Wallerstedt et al, 2009).

b) A population-based, case-controlled study of new coumarin users (acenocoumarol and phenprocoumon) with concomitant selective serotonin reuptake inhibitors (SSRIs) resulted in an increased risk of hospitalization due to nongastrointestinal bleeding. Using national pharmacy and hospitalization records, Netherlands researchers identified 1848 cases that were admitted for abnormal bleeding and compared them with 5818 control subjects also taking coumarins. Median duration of treatment in patients was 220 days (range, 1 to 4690 days). Patients on SSRIs showed greater risk for hospitalization for nongastrointestinal bleeding (adjusted odds ratio (OR) 1.7, 95% confidence interval (CI), 1.1 to 2.5), however, the rate of gastrointestinal bleeding (adjusted OR 0.8, 95% CI, 0.4 to 1.5) was not significantly different (Schalekamp et al, 2008).

c) Preliminary data suggest that there may be a pharmacodynamic interaction (that causes an increased bleeding diathesis with unaltered prothrombin time) between paroxetine and warfarin. The concomitant use of paroxetine and warfarin should be undertaken with caution (Prod Info PAXIL(R) oral tablets, suspension, 2008).

d) In a multiple-dose study, several days of combined therapy with warfarin and paroxetine resulted in mild but clinically significant bleeding in 5 of 27 subjects. This effect occurred in the absence of a significant enhancement in warfarin-induced hypoprothrombinemia or changes in either paroxetine or warfarin disposition (Bannister et al, 1989b).

3.5.1.DW 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 cohort studies have shown that the combined use of SSRIs and anticoagulants has been associated with an increased risk of bleeding (Wallerstedt et al, 2009; Schalekamp et al, 2008; Prod Info PAXIL(R) oral tablets, suspension, 2008). Bleeding events reported have included epistaxis, ecchymosis, hematoma, petechiae, and life-threatening hemorrhages. Altered anticoagulant effects (including increased bleeding) have been reported with the coadministration of SSRIs with warfarin (Schalekamp et al, 2008; Prod Info PAXIL(R) oral tablets, suspension, 2008).

3) Severity: major

4) Onset: delayed

5) Substantiation: probable

6) Clinical Management: When paroxetine and an anticoagulant are given concurrently, monitor patients for signs of increased bleeding. Patients who are taking warfarin should be monitored closely for altered anticoagulant effects, including increased bleeding, when paroxetine therapy is initiated or discontinued (Prod Info PAXIL(R) oral tablets, suspension, 2008).

7) Probable Mechanism: unknown

8) Literature Reports

a) According to a retrospective cohort study (n=234), there was an increased risk of clinically relevant bleeding (hospital admission due to bleeding) in patients receiving warfarin for atrial fibrillation during concomitant SSRI therapy or within 2 weeks following SSRI therapy termination. Patients with a mean age of 72 +/- 7 years receiving warfarin plus SSRI (n=117) were matched with randomly selected patients who received warfarin only (n=117). SSRI included fluoxetine, citalopram, paroxetine, sertraline, fluvoxamine, or escitalopram. Nine patients experienced 11 bleeding episodes during 213.9 treatment years in the warfarin plus SSRI group, and 10 patients experienced 14 bleedings during 586.4 treatment years in the warfarin-only group. The corresponding total incidences of bleedings were 51.4 and 23.9 per 1000 treatment years, respectively. The hazard ratio for first bleedings during treatment with warfarin plus SSRI was 3.49 (95% CI; 1.37 to 8.91, p=0.009) compared with warfarin only. The SSRI implicated in patients experiencing bleeding at the time of concomitant administration were sertraline or citalopram. The addition of an SSRI was not associated with a change in warfarin dose or INR (p=0.48 and p=0.31 respectively). The results of the study may be limited by earlier bleeding events, unknown patient adherence, and exclusion of clopidogrel, dipyridamol, corticosteroids and anticoagulants other than warfarin in the model (Wallerstedt et al, 2009).

b) A population-based, case-controlled study of new coumarin users (acenocoumarol and phenprocoumon) with concomitant selective serotonin reuptake inhibitors (SSRIs) resulted in an increased risk of hospitalization due to nongastrointestinal bleeding. Using national pharmacy and hospitalization records, Netherlands researchers identified 1848 cases that were admitted for abnormal bleeding and compared them with 5818 control subjects also taking coumarins. Median duration of treatment in patients was 220 days (range, 1 to 4690 days). Patients on SSRIs showed greater risk for hospitalization for nongastrointestinal bleeding (adjusted odds ratio (OR) 1.7, 95% confidence interval (CI), 1.1 to 2.5), however, the rate of gastrointestinal bleeding (adjusted OR 0.8, 95% CI, 0.4 to 1.5) was not significantly different (Schalekamp et al, 2008).

c) Preliminary data suggest that there may be a pharmacodynamic interaction (that causes an increased bleeding diathesis with unaltered prothrombin time) between paroxetine and warfarin. The concomitant use of paroxetine and warfarin should be undertaken with caution (Prod Info PAXIL(R) oral tablets, suspension, 2008).

d) In a multiple-dose study, several days of combined therapy with warfarin and paroxetine resulted in mild but clinically significant bleeding in 5 of 27 subjects. This effect occurred in the absence of a significant enhancement in warfarin-induced hypoprothrombinemia or changes in either paroxetine or warfarin disposition (Bannister et al, 1989b).

3.5.1.DX Perhexiline

1) Interaction Effect: an increased risk of perhexiline toxicity (ataxia, lethargy, nausea)

2) Summary: Paroxetine therapy resulted in perhexiline toxicity in an 86-year-old female patient following five weeks of concurrent therapy. Perhexiline is metabolized by the cytochrome P450 2D6 enzyme system, and paroxetine is widely known to inhibit these same enzymes (Alderman, 1998a).

3) Severity: moderate

4) Onset: delayed

5) Substantiation: probable

6) Clinical Management: Closely monitor patients receiving concurrent therapy with perhexiline and paroxetine for signs and symptoms of perhexiline toxicity, including ataxia, lethargy, and nausea. Trough serum perhexiline levels (normal range 0.15 to 0.60 mg/L) may also be helpful in diagnosing perhexiline toxicity.

7) Probable Mechanism: inhibition by paroxetine of cytochrome P450 2D6-mediated perhexiline metabolism
8) Literature Reports
a) An elderly female patient receiving perhexiline 100 mg twice daily experienced recurrent falls, dizziness, and nausea five weeks after paroxetine 20 mg once daily was prescribed for depression. A perhexiline serum concentration one week after paroxetine was initiated was 0.67 mg/L. Four weeks later, upon admission to the hospital, her perhexiline concentration was 2.02 mg/L. Both paroxetine and perhexiline were discontinued, and a repeat perhexiline concentration 10 days later was 1.42 mg/L. Paroxetine, a cytochrome P450 2D6 inhibitor, was thought to be substantially inhibiting the metabolism of perhexiline (Alderman, 1998).

3.5.1.DY Perphenazine
1) Interaction Effect: increased plasma concentrations and side effects of perphenazine
2) Summary: Paroxetine significantly inhibited the metabolism of perphenazine in 8 healthy volunteers, resulting in increased plasma concentrations and side effects of perphenazine (Ozdemir et al, 1997a). Coadministration of paroxetine with other drugs that are metabolized by cytochrome P450 2D6, such as perphenazine, should be approached with caution (Prod Info Paxil CR(TM), 2003h).
3) Severity: moderate
4) Onset: rapid
5) Substantiation: probable
6) Clinical Management: In patients receiving paroxetine, the dose of perphenazine should be reduced and patients should be monitored closely for perphenazine side effects. The concomitant administration of paroxetine and perphenazine should be approached with caution.
7) Probable Mechanism: inhibition of cytochrome P450 2D6-mediated metabolism of perphenazine by paroxetine
8) Literature Reports
a) Paroxetine significantly inhibited the metabolism of perphenazine in 8 healthy volunteers, resulting in increased plasma concentrations and side effects of perphenazine. All subjects were extensive metabolizers in CYP2D6 isoenzyme activity as determined by a dextromethorphan metabolism study. Subjects were randomized to receive a single dose of perphenazine 0.11 mg/kg or placebo alone in a crossover design. Then subjects received paroxetine 20 mg/day for 10 days and then another dose of perphenazine or placebo on the tenth day. The average peak plasma concentration of perphenazine was significantly increased from 2.2 nmol/L when given alone, compared to 13.5 nmol/L when given with paroxetine. The average area under the plasma concentration-time curve (0 to 8 hours) was significantly increased from 9.4 mg (h)/L, with perphenazine alone, to 65.4 mg (h)/L when perphenazine was given with paroxetine. Side effects of perphenazine were significantly increased as demonstrated by oversedation, extrapyramidal side effects, and impaired performance on psychomotor tests. In patients receiving paroxetine the dose of perphenazine should be reduced and patients should be monitored for perphenazine side effects (Ozdemir et al, 1997).

3.5.1.DZ Phenelzine
1) Interaction Effect: CNS toxicity or serotonin syndrome (hypertension, hyperthermia, myoclonus, mental status changes)
2) Summary: Concurrent administration or overlapping therapy with paroxetine and a monoamine oxidase (MAO) inhibitor may result in CNS toxicity or serotonin syndrome, a hyperserotonergic state characterized by symptoms such as restlessness, myoclonus, changes in mental status, hyperreflexia, diaphoresis, shivering, and tremor. Serious, even fatal, reactions have been reported with concomitant use of serotonin specific reuptake inhibitors and MAO inhibitors (Prod Info Paxil(R), 2003g; Lappin & Auchincloss, 1994q; Graber et al, 1994q; Suchowersky & de Vries, 1990q). Concomitant use is contraindicated.
3) Severity: contraindicated
4) Onset: rapid
5) Substantiation: theoretical
6) Clinical Management: Concurrent use of paroxetine and an MAO inhibitor is contraindicated. Wait at least two weeks after discontinuing an MAO inhibitor before initiating paroxetine, and at least two weeks after discontinuing paroxetine before initiating therapy with an MAOI.
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 serotonin syndrome (Sternbach, 1991m). Serotonin syndrome is a condition of serotonergic hyperstimulation and manifests as restlessness, myoclonus, changes in mental status, hyperreflexia, diaphoresis, shivering, and tremor. If the syndrome is not recognized and correctly treated, fatality can result.
b) A 26-year old woman who had been taking isocarboxazid for eight weeks stopped taking the drug for 11 days before beginning therapy with sertraline. After a single 100 mg sertraline dose, the patient became restless and developed leg twitches. The patients was later admitted to the emergency room with diaphoresis, tachycardia, hyperreflexia, and various neuromuscular disturbances. After treatment with diazepam and propranolol the patient did not improve. The patient was then given two 4 mg doses of cyproheptadine an hour apart, with notable improvement 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 added to a regimen of lithium, phenelzine, thioridazine, and doxepin. Three hours after taking the first sertraline dose, the patient was found in a semicomatose state, with elevated body temperature, increased pulse, increased respiration rate, and a blood pressure of 140/110 mm Hg. After transportation to the hospital, the patient was misdiagnosed as having neuroleptic malignant syndrome (NMS) which was later changed to serotonin syndrome due to a reaction between sertraline and phenelzine. The authors suggest that monoamine oxidase inhibitor (MAOI) therapy should be discontinued for at least two weeks before initiation of therapy with a selective serotonin reuptake inhibitor (SSRI) and that before starting a MAOI, SSRI therapy should be discontinued for at least five half-lives of the parent drug and any active metabolites (Graber et al, 1994p).
d) Two cases reports suggested a possible interaction between fluoxetine and selegiline (Suchowersky & de Vries, 1990p). One case involved a first episode of mania being observed approximately one month after adding selegiline to fluoxetine. The patient improved two months after both drugs were discontinued, and no further details were provided. The second case involved diaphoresis, vasoconstriction, and cyanosis of the hands which occurred in close temporal relationship to adding fluoxetine to selegiline. Both drugs were discontinued, with relatively quick resolution of symptoms. Rechallenge with fluoxetine alone occurred without incident.

3.5.1.EA 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 cohort studies have shown that the combined use of SSRIs and anticoagulants has been associated with an increased risk of bleeding (Wallerstedt et al, 2009; Schalekamp et al, 2008; Prod Info PAXIL(R) oral tablets, suspension, 2008). Bleeding events reported have included epistaxis, ecchymosis, hematoma, petechiae, and life-threatening hemorrhages. Altered anticoagulant effects (including increased bleeding) have been reported with the coadministration of SSRIs with warfarin (Schalekamp et al, 2008; Prod Info PAXIL(R) oral tablets, suspension, 2008).
3) Severity: major
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: When paroxetine and an anticoagulant are given concurrently, monitor patients for signs of increased bleeding. Patients who are taking warfarin should be monitored closely for altered anticoagulant effects, including increased bleeding, when paroxetine therapy is initiated or discontinued (Prod Info PAXIL(R) oral tablets, suspension, 2008).
7) Probable Mechanism: unknown
8) Literature Reports

a) According to a retrospective cohort study (n=234), there was an increased risk of clinically relevant bleeding (hospital admission due to bleeding) in patients receiving warfarin for atrial fibrillation during concomitant SSRI therapy or within 2 weeks following SSRI therapy termination. Patients with a mean age of 72 +/- 7 years receiving warfarin plus SSRI (n=117) were matched with randomly selected patients who received warfarin only (n=117). SSRI included fluoxetine, citalopram, paroxetine, sertraline, fluvoxamine, or escitalopram. Nine patients experienced 11 bleeding episodes during 213.9 treatment years in the warfarin plus SSRI group, and 10 patients experienced 14 bleedings during 586.4 treatment years in the warfarin-only group. The corresponding total incidences of bleedings were 51.4 and 23.9 per 1000 treatment years, respectively. The hazard ratio for first bleedings during treatment with warfarin plus SSRI was 3.49 (95% CI; 1.37 to 8.91, p=0.009) compared with warfarin only. The SSRI implicated in patients experiencing bleeding at the time of concomitant administration were sertraline or citalopram. The addition of an SSRI was not associated with a change in warfarin dose or INR (p=0.48 and p=0.31 respectively). The results of the study may be limited by earlier bleeding events, unknown patient adherence, and exclusion of clopidogrel, dipyridamol, corticosteroids and anticoagulants other than warfarin in the model (Wallerstedt et al, 2009).
b) A population-based, case-controlled study of new coumarin users (acenocoumarol and phenprocoumon) with concomitant selective serotonin reuptake inhibitors (SSRIs) resulted in an increased risk of hospitalization due to nongastrointestinal bleeding. Using national pharmacy and hospitalization records, Netherlands researchers identified 1848 cases that were admitted for abnormal bleeding and compared them with 5818 control subjects also taking coumarins. Median duration of treatment in patients was 220 days (range, 1 to 4690 days). Patients on SSRIs showed greater risk for hospitalization for nongastrointestinal bleeding (adjusted odds ratio (OR) 1.7, 95% confidence interval (CI), 1.1 to 2.5), however, the rate of gastrointestinal bleeding (adjusted OR 0.8, 95% CI, 0.4 to 1.5) was not significantly different (Schalekamp et al, 2008).
c) Preliminary data suggest that there may be a pharmacodynamic interaction (that causes an increased bleeding diathesis with unaltered prothrombin time) between paroxetine and warfarin. The concomitant use of paroxetine and warfarin should be undertaken with caution (Prod Info PAXIL(R) oral tablets, suspension, 2008).
d) In a multiple-dose study, several days of combined therapy with warfarin and paroxetine resulted in mild but clinically significant bleeding in 5 of 27 subjects. This effect occurred in the absence of a significant enhancement in warfarin-induced hypoprothrombinemia or changes in either paroxetine or warfarin disposition (Bannister et al, 1989b).

3.5.1.EB Phenobarbital

1) Interaction Effect: reduced paroxetine effectiveness

2) Summary: Coadministration of paroxetine and phenobarbital may result in decreased serum concentrations of paroxetine (Prod Info Paxil(R), 2002a); however, considerable interindividual variation should be expected (Greb et al, 1989c). The clinical significance of individual pharmacokinetic alterations is uncertain at this time.

3) Severity: minor

4) Onset: rapid

5) Substantiation: probable

6) Clinical Management: Monitor patients for a reduced therapeutic response to paroxetine. Any adjustment of paroxetine should be guided by clinical effect.

7) Probable Mechanism: enhanced paroxetine clearance

8) Literature Reports

a) A study reported that the degree of psychomotor impairment healthy subjects experienced when receiving the barbiturate amylobarbitone with paroxetine was not greater compared with the degree of impairment associated with either drug alone (Cooper et al, 1989).

b) Concomitant administration of paroxetine and phenobarbital resulted in no significant effect on the mean pharmacokinetic parameters of paroxetine in a study involving 10 healthy subjects (Greb et al, 1989b). However, individual decreases in half-life and area under the plasma concentration-time curve (AUC) for paroxetine were observed. This effect appears to be related to the induction of hepatic isoenzymes by phenobarbital. As this study employed a single dose of paroxetine, further studies are needed to evaluate this combination during multiple-dose therapy.

c) When a single oral 30 mg dose was administered at phenobarbital steady state (100 mg daily for 14 days) paroxetine AUC and half-life were reduced by an average of 25% and 38%, respectively, when compared to paroxetine administered alone. The effect of paroxetine on phenobarbital pharmacokinetics was not studied (Prod Info Paxil(R), 2002).

3.5.1.EC 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 cohort studies have shown that the combined use of SSRIs and anticoagulants has been associated with an increased risk of bleeding (Wallerstedt et al, 2009; Schalekamp et al, 2008; Prod Info PAXIL(R) oral tablets, suspension, 2008). Bleeding events reported have included epistaxis, ecchymosis, hematoma, petechiae, and life-threatening hemorrhages. Altered anticoagulant effects (including increased bleeding) have been reported with the coadministration of SSRIs with warfarin (Schalekamp et al, 2008; Prod Info PAXIL(R) oral tablets, suspension, 2008).

3) Severity: major

4) Onset: delayed

5) Substantiation: probable

6) Clinical Management: When paroxetine and an anticoagulant are given concurrently, monitor patients for signs of increased bleeding. Patients who are taking warfarin should be monitored closely for altered anticoagulant effects, including increased bleeding, when paroxetine therapy is initiated or discontinued (Prod Info PAXIL(R) oral tablets, suspension, 2008).

7) Probable Mechanism: unknown

8) Literature Reports

a) According to a retrospective cohort study (n=234), there was an increased risk of clinically relevant bleeding (hospital admission due to bleeding) in patients receiving warfarin for atrial fibrillation during concomitant SSRI therapy or within 2 weeks following SSRI therapy termination. Patients with a mean age of 72 +/- 7 years receiving warfarin plus SSRI (n=117) were matched with randomly selected patients who received warfarin only (n=117). SSRI included fluoxetine, citalopram, paroxetine, sertraline, fluvoxamine, or escitalopram. Nine patients experienced 11 bleeding episodes during 213.9 treatment years in the warfarin plus SSRI group, and 10 patients experienced 14 bleedings during 586.4 treatment years in the warfarin-only group. The corresponding total incidences of bleedings were 51.4 and 23.9 per 1000 treatment years, respectively. The hazard ratio for first bleedings during treatment with warfarin plus SSRI was 3.49 (95% CI; 1.37 to 8.91, p=0.009) compared with warfarin only. The SSRI implicated in patients experiencing bleeding at the time of concomitant administration were sertraline or citalopram. The addition of an SSRI was not associated with a change in warfarin dose or INR (p=0.48 and p=0.31 respectively). The results of the study may be limited by earlier bleeding events, unknown patient adherence, and exclusion of clopidogrel, dipyridamol, corticosteroids and anticoagulants other than warfarin in the model (Wallerstedt et al, 2009).

b) A population-based, case-controlled study of new coumarin users (acenocoumarol and phenprocoumon) with concomitant selective serotonin reuptake inhibitors (SSRIs) resulted in an increased risk of hospitalization due to nongastrointestinal bleeding. Using national pharmacy and hospitalization records, Netherlands researchers identified 1848 cases that were admitted for abnormal bleeding and compared them with 5818 control subjects also taking coumarins. Median duration of treatment in patients was 220 days (range, 1 to 4690 days). Patients on SSRIs showed greater risk for hospitalization for nongastrointestinal bleeding (adjusted odds ratio (OR) 1.7, 95% confidence interval

(CI), 1.1 to 2.5), however, the rate of gastrointestinal bleeding (adjusted OR 0.8, 95% CI, 0.4 to 1.5) was not significantly different (Schalekamp et al, 2008).

c) Preliminary data suggest that there may be a pharmacodynamic interaction (that causes an increased bleeding diathesis with unaltered prothrombin time) between paroxetine and warfarin. The concomitant use of paroxetine and warfarin should be undertaken with caution (Prod Info PAXIL(R) oral tablets, suspension, 2008).

d) In a multiple-dose study, several days of combined therapy with warfarin and paroxetine resulted in mild but clinically significant bleeding in 5 of 27 subjects. This effect occurred in the absence of a significant enhancement in warfarin-induced hypoprothrombinemia or changes in either paroxetine or warfarin disposition (Bannister et al, 1989b).

3.5.1.ED 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 cohort studies have shown that the combined use of SSRIs and NSAIDs has been associated with an increased risk of bleeding. Bleeding events have included epistaxis, ecchymosis, hematoma, petechiae, and life-threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension, 2008) (Prod Info Lexapro(TM), 2003; Dalton et al, 2003a; Prod Info CELEXA (R) oral tablet, solution, 2005).

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 increased bleeding.

7) Probable Mechanism: unknown

8) Literature Reports

a) SSRIs increase the risk of upper gastrointestinal bleeding and this effect is potentiated by concurrent use of NSAIDs or low-dose aspirin. Hospitalizations for upper gastrointestinal bleeding were searched among 26,005 users of antidepressant medications and compared with the number of hospitalizations in those patients who did not receive prescriptions for antidepressants. The amount of upper GI bleeding episodes was 3.6 times more than expected (95% confidence interval, 2.7 to 4.7). Combined use of an SSRI and NSAIDs or low-dose aspirin increased the risk to 12.2 (95% confidence interval, 7.1 to 19.5) and 5.2 (95% confidence interval, 3.2 to 8), respectively. The findings of this study demonstrate an increased risk of upper GI bleeding during the use of SSRIs. Combined use of SSRIs and NSAIDs or low-dose aspirin increased the risk even further (Dalton et al, 2003).

b) Coadministration of ketorolac with psychoactive drugs (such as fluoxetine) has been associated with hallucinations in some patients (Prod Info TORADOL(R) oral tablets, 2007).

3.5.1.EE Phenytoin

1) Interaction Effect: reduced phenytoin efficacy; reduced paroxetine efficacy

2) Summary: Limited reports related to the effects of combined phenytoin-paroxetine are currently available. Because of its enzyme-inducing effect, coadministered phenytoin apparently reduces serum concentrations of phenytoin and paroxetine, possibly leading to reduced efficacy of phenytoin and paroxetine (Prod Info Paxil(R), 2003e; Andersen et al, 1991c; Boyer & Blumhardt, 1992a). There has been one case report of an elevated phenytoin level after four weeks of concurrent paroxetine and phenytoin coadministration (Prod Info Paxil(R), 2003e).

3) Severity: moderate

4) Onset: delayed

5) Substantiation: probable

6) Clinical Management: Monitor patients for phenytoin and paroxetine effectiveness. No initial dosage adjustments are necessary when these drugs are coadministered, however, subsequent adjustments should be guided by clinical effect.

7) Probable Mechanism: induction of phenytoin and paroxetine metabolism

8) Literature Reports

a) Concomitant administration of a single-dose of paroxetine 30 mg and phenytoin (300 mg once a day for 14 days) resulted in a reduction in the area under the plasma concentration-time curve (AUC) of paroxetine by 27% to 50%, as well as a decrease of 35% in the half-life of paroxetine (Kaye et al, 1989a). This interaction appears to be related to the enzyme-inducing properties of phenytoin. Alternatively, in a single-dose phenytoin study, paroxetine (30 mg once a day for 14 days) had no effect on the mean peak plasma levels or the elimination half-life of phenytoin 300 mg. However, a 12% reduction in the area under the plasma concentration-time curve (AUC) for phenytoin was observed. No initial dose adjustments are necessary upon coadministration of these agents. Subsequent adjustments should be guided by clinical effect (Prod Info Paxil(R), 2003d).

b) Nineteen epilepsy patients who were well controlled on either phenytoin (n=5), carbamazepine (n=6), or valproate (n=8) took part in a single-blind, placebo-controlled, cross-over study to determine the effect of concurrent use of paroxetine and anticonvulsants (Andersen et al, 1991b). Subjects received placebo for seven days, then paroxetine 10 mg daily for three days, 20 mg daily for three days, and 30 mg daily for 10 days. There were no statistically significant changes in plasma levels and free fractions in any of the anticonvulsant drugs during any phase of the study. Mean paroxetine plasma

levels were lowest with concurrent phenytoin therapy (p less than 0.005 when compared with valproate); however, there is no clear association between paroxetine plasma concentrations and efficacy. No severe adverse effects were seen with cotherapy, no seizures occurred, and no changes in protein binding were found.

3.5.1.EF Pimozide

1) Interaction Effect: an increased risk of pimozide toxicity including cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Coadministration of paroxetine and pimozide is contraindicated. A controlled study involving concurrent administration of pimozide and paroxetine to healthy volunteers resulted in a mean increase in AUC and Cmax of 151% and 62%, respectively. The consequence of such an extreme increase of pimozide plasma concentrations may be pimozide toxicity, including risk of QT prolongation leading to torsades de pointes (Prod Info PAXIL CR(R) CONTROLLED-RELEASE TABLETS, 2005).
3) Severity: contraindicated
4) Onset: rapid
5) Substantiation: probable
6) Clinical Management: The concurrent administration of paroxetine and pimozide is contraindicated due to the possibility of significantly increased pimozide plasma concentrations resulting in a dangerous risk of pimozide toxicity.
7) Probable Mechanism: unknown
8) Literature Reports
a) A group of healthy volunteers in a controlled study received a single dose of 2 mg pimozide after being titrated up to a daily dose of 60 mg of immediate-release paroxetine hydrochloride. The study resulted in a mean increase of pimozide area under the concentration time-curve (AUC) and maximum concentration (Cmax) of 151% and 62%, respectively (Prod Info PAXIL CR(R) CONTROLLED-RELEASE TABLETS, 2005).

3.5.1.EG 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 cohort studies have shown that the combined use of SSRIs and NSAIDs has been associated with an increased risk of bleeding. Bleeding events have included epistaxis, ecchymosis, hematoma, petechiae, and life-threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension, 2008) (Prod Info Lexapro(TM), 2003; Dalton et al, 2003a; Prod Info CELEXA (R) oral tablet, solution, 2005).
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 increased bleeding.
7) Probable Mechanism: unknown
8) Literature Reports
a) SSRIs increase the risk of upper gastrointestinal bleeding and this effect is potentiated by concurrent use of NSAIDs or low-dose aspirin. Hospitalizations for upper gastrointestinal bleeding were searched among 26,005 users of antidepressant medications and compared with the number of hospitalizations in those patients who did not receive prescriptions for antidepressants. The amount of upper GI bleeding episodes was 3.6 times more than expected (95% confidence interval, 2.7 to 4.7). Combined use of an SSRI and NSAIDs or low-dose aspirin increased the risk to 12.2 (95% confidence interval, 7.1 to 19.5) and 5.2 (95% confidence interval, 3.2 to 8), respectively. The findings of this study demonstrate an increased risk of upper GI bleeding during the use of SSRIs. Combined use of SSRIs and NSAIDs or low-dose aspirin increased the risk even further (Dalton et al, 2003).
b) Coadministration of ketorolac with psychoactive drugs (such as fluoxetine) has been associated with hallucinations in some patients (Prod Info TORADOL(R) oral tablets, 2007).

3.5.1.EH 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 cohort studies have shown that the combined use of SSRIs and NSAIDs has been associated with an increased risk of bleeding. Bleeding events have included epistaxis, ecchymosis, hematoma, petechiae, and life-threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension, 2008) (Prod Info Lexapro(TM), 2003; Dalton et al, 2003a; Prod Info CELEXA (R) oral tablet, solution, 2005).
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 increased bleeding.
7) Probable Mechanism: unknown
8) Literature Reports
a) SSRIs increase the risk of upper gastrointestinal bleeding and this effect is potentiated by concurrent

use of NSAIDs or low-dose aspirin. Hospitalizations for upper gastrointestinal bleeding were searched among 26,005 users of antidepressant medications and compared with the number of hospitalizations in those patients who did not receive prescriptions for antidepressants. The amount of upper GI bleeding episodes was 3.6 times more than expected (95% confidence interval, 2.7 to 4.7). Combined use of an SSRI and NSAIDs or low-dose aspirin increased the risk to 12.2 (95% confidence interval, 7.1 to 19.5) and 5.2 (95% confidence interval, 3.2 to 8), respectively. The findings of this study demonstrate an increased risk of upper GI bleeding during the use of SSRIs. Combined use of SSRIs and NSAIDs or low-dose aspirin increased the risk even further (Dalton et al, 2003).

b) Coadministration of ketorolac with psychoactive drugs (such as fluoxetine) has been associated with hallucinations in some patients (Prod Info TORADOL(R) oral tablets, 2007).

3.5.1.EI 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 cohort studies have shown that the combined use of SSRIs and NSAIDs has been associated with an increased risk of bleeding. Bleeding events have included epistaxis, ecchymosis, hematoma, petechiae, and life-threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension, 2008) (Prod Info Lexapro(TM), 2003; Dalton et al, 2003a; Prod Info CELEXA (R) oral tablet, solution, 2005).

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 increased bleeding.

7) Probable Mechanism: unknown

8) Literature Reports

a) SSRIs increase the risk of upper gastrointestinal bleeding and this effect is potentiated by concurrent use of NSAIDs or low-dose aspirin. Hospitalizations for upper gastrointestinal bleeding were searched among 26,005 users of antidepressant medications and compared with the number of hospitalizations in those patients who did not receive prescriptions for antidepressants. The amount of upper GI bleeding episodes was 3.6 times more than expected (95% confidence interval, 2.7 to 4.7). Combined use of an SSRI and NSAIDs or low-dose aspirin increased the risk to 12.2 (95% confidence interval, 7.1 to 19.5) and 5.2 (95% confidence interval, 3.2 to 8), respectively. The findings of this study demonstrate an increased risk of upper GI bleeding during the use of SSRIs. Combined use of SSRIs and NSAIDs or low-dose aspirin increased the risk even further (Dalton et al, 2003).

b) Coadministration of ketorolac with psychoactive drugs (such as fluoxetine) has been associated with hallucinations in some patients (Prod Info TORADOL(R) oral tablets, 2007).

3.5.1.EJ Procarbazine

1) Interaction Effect: CNS toxicity or serotonin syndrome (hypertension, hyperthermia, myoclonus, mental status changes)

2) Summary: Concurrent administration or overlapping therapy with paroxetine and a monoamine oxidase (MAO) inhibitor may result in CNS toxicity or serotonin syndrome, a hyperserotonergic state characterized by symptoms such as restlessness, myoclonus, changes in mental status, hyperreflexia, diaphoresis, shivering, and tremor. Serious, even fatal, reactions have been reported with concomitant use of serotonin specific reuptake inhibitors and MAO inhibitors (Prod Info Paxil(R), 1999f; Lappin & Auchincloss, 1994o; Graber et al, 1994o; Suchowersky & de Vries, 1990o). Concomitant use is contraindicated.

3) Severity: contraindicated

4) Onset: rapid

5) Substantiation: probable

6) Clinical Management: Concurrent use of paroxetine and a MAO inhibitor is contraindicated. Wait at least two weeks after discontinuing a MAO inhibitor before initiating paroxetine, and at least two weeks after discontinuing paroxetine before initiating therapy with a MAOI.

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 serotonin syndrome (Sternbach, 1991l). Serotonin syndrome is a condition of serotonergic hyperstimulation and manifests as restlessness, myoclonus, changes in mental status, hyperreflexia, diaphoresis, shivering, and tremor. If the syndrome is not recognized and correctly treated, fatality can result.

b) A 26-year old woman who had been taking isocarboxazid for eight weeks stopped taking the drug for 11 days before beginning therapy with sertraline. After a single 100 mg sertraline dose, the patient became restless and developed leg twitches. The patients was later admitted to the emergency room with diaphoresis, tachycardia, hyperreflexia, and various neuromuscular disturbances. After treatment with diazepam and propranolol the patient did not improve. The patient was then given two 4 mg doses of cyproheptadine an hour apart, with notable improvement in 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 added to a regimen of lithium, phenelzine, thioridazine, and doxepin. Three hours after taking the first

sertraline dose, the patient was found in a semicomatose state, with elevated body temperature, increased pulse, increased respiration rate, and a blood pressure of 140/110 mm Hg. After transportation to the hospital, the patient was misdiagnosed as having neuroleptic malignant syndrome (NMS) which was later changed to serotonin syndrome due to a reaction between sertraline and phenelzine. The authors suggest that monoamine oxidase inhibitor (MAOI) therapy should be discontinued for at least two weeks before initiation of therapy with a selective serotonin reuptake inhibitor (SSRI) and that before starting a MAOI, SSRI therapy should be discontinued for at least five half-lives of the parent drug and any active metabolites (Graber et al, 1994n).

d) Two cases reports suggested a possible interaction between fluoxetine and selegiline (Suchowersky & de Vries, 1990n). One case involved a first episode of mania being observed approximately one month after adding selegiline to fluoxetine. The patient improved two months after both drugs were discontinued, and no further details were provided. The second case involved diaphoresis, vasoconstriction, and cyanosis of the hands which occurred in close temporal relationship to adding fluoxetine to selegiline. Both drugs were discontinued, with relatively quick resolution of symptoms. Rechallenge with fluoxetine alone occurred without incident.

3.5.1.EK Procyclidine

1) Interaction Effect: an increased risk of anticholinergic effects (dry mouth, sedation, mydriasis)

2) Summary: Coadministered procyclidine and paroxetine may produce increased serum concentrations of procyclidine, accompanied by increased anticholinergic effects (Prod Info Paxil CR(TM), 2003a). If anticholinergic effects are seen, the dose of procyclidine should be reduced.

3) Severity: moderate

4) Onset: rapid

5) Substantiation: probable

6) Clinical Management: Monitor patients for anticholinergic effects. Depending on patient response, doses of procyclidine may need to be reduced.

7) Probable Mechanism: unknown

8) Literature Reports

a) In a multiple dose study of procyclidine and paroxetine, study subjects received paroxetine 30 mg once a day and procyclidine 5 mg once a day. Elevated procyclidine concentrations were seen at steady-state. Procyclidine area under the concentration-time curve (AUC), maximum concentration (Cmax), and minimum concentration (Cmin) were increased by 35%, 37%, and 67%, respectively, potentially leading to adverse anticholinergic effects (Prod Info Paxil CR(TM), 2003).

3.5.1.EL Propafenone

1) Interaction Effect: an increased risk of propafenone toxicity (cardiac arrhythmia)

2) Summary: Coadministration of paroxetine with other drugs that are metabolized by the cytochrome P450 2D6 enzyme, such as propafenone, should be approached with caution (Prod Info Paxil CR(TM), 2003e).

3) Severity: moderate

4) Onset: rapid

5) Substantiation: probable

6) Clinical Management: Monitor heart rate and the EKG in patients receiving concurrent paroxetine and propafenone. Doses may need to be reduced. Coadministration of these agents should be approached with caution.

7) Probable Mechanism: inhibition of propafenone metabolism

3.5.1.EM 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 cohort studies have shown that the combined use of SSRIs and NSAIDs has been associated with an increased risk of bleeding. Bleeding events have included epistaxis, ecchymosis, hematoma, petechiae, and life-threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension, 2008) (Prod Info Lexapro(TM), 2003; Dalton et al, 2003a; Prod Info CELEXA (R) oral tablet, solution, 2005).

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 increased bleeding.

7) Probable Mechanism: unknown

8) Literature Reports

a) SSRIs increase the risk of upper gastrointestinal bleeding and this effect is potentiated by concurrent use of NSAIDs or low-dose aspirin. Hospitalizations for upper gastrointestinal bleeding were searched among 26,005 users of antidepressant medications and compared with the number of hospitalizations in those patients who did not receive prescriptions for antidepressants. The amount of upper GI bleeding episodes was 3.6 times more than expected (95% confidence interval, 2.7 to 4.7). Combined use of an SSRI and NSAIDs or low-dose aspirin increased the risk to 12.2 (95% confidence interval, 7.1 to 19.5) and 5.2 (95% confidence interval, 3.2 to 8), respectively. The findings of this study demonstrate an increased risk of upper GI bleeding during the use of SSRIs. Combined use of SSRIs and NSAIDs or

low-dose aspirin increased the risk even further (Dalton et al, 2003).
b) Coadministration of ketorolac with psychoactive drugs (such as fluoxetine) has been associated with hallucinations in some patients (Prod Info TORADOL(R) oral tablets, 2007).

3.5.1.EN 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 cohort studies have shown that the combined use of SSRIs and NSAIDs has been associated with an increased risk of bleeding. Bleeding events have included epistaxis, ecchymosis, hematoma, petechiae, and life-threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension, 2008) (Prod Info Lexapro(TM), 2003; Dalton et al, 2003a; Prod Info CELEXA (R) oral tablet, solution, 2005).
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 increased bleeding.
7) Probable Mechanism: unknown
8) Literature Reports
a) SSRIs increase the risk of upper gastrointestinal bleeding and this effect is potentiated by concurrent use of NSAIDs or low-dose aspirin. Hospitalizations for upper gastrointestinal bleeding were searched among 26,005 users of antidepressant medications and compared with the number of hospitalizations in those patients who did not receive prescriptions for antidepressants. The amount of upper GI bleeding episodes was 3.6 times more than expected (95% confidence interval, 2.7 to 4.7). Combined use of an SSRI and NSAIDs or low-dose aspirin increased the risk to 12.2 (95% confidence interval, 7.1 to 19.5) and 5.2 (95% confidence interval, 3.2 to 8), respectively. The findings of this study demonstrate an increased risk of upper GI bleeding during the use of SSRIs. Combined use of SSRIs and NSAIDs or low-dose aspirin increased the risk even further (Dalton et al, 2003).
b) Coadministration of ketorolac with psychoactive drugs (such as fluoxetine) has been associated with hallucinations in some patients (Prod Info TORADOL(R) oral tablets, 2007).

3.5.1.EO Protriptyline

1) Interaction Effect: protriptyline toxicity (dry mouth, sedation, urinary retention)
2) Summary: Paroxetine coadministered with desipramine or imipramine produced higher serum concentrations of the tricyclic antidepressant (TCA) in some patients (Hartter et al, 1994d; Brosen et al, 1993k). Although not reported for protriptyline, a similar interaction could occur. Paroxetine's effect on TCAs may resemble that of fluoxetine (another selective serotonin reuptake inhibitor), which is known to inhibit TCA metabolism (Aranow et al, 1989d; Vaughan, 1988d; Goodnick, 1989d). With coadministration, monitor patients for protriptyline toxicity. Protriptyline doses may need to be reduced (Prod Info Paxil CR(TM), 2003j).
3) Severity: moderate
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: When paroxetine is coadministered with protriptyline, monitor patients for signs and symptoms of protriptyline toxicity (dry mouth, sedation, urinary retention, blurred vision). Protriptyline doses may need to be reduced.
7) Probable Mechanism: decreased protriptyline metabolism
8) Literature Reports
a) The effect of paroxetine on desipramine metabolism was studied in 9 extensive metabolizers (EM) and 8 poor metabolizers (PM) of desipramine. Subjects took a single oral dose of desipramine before starting paroxetine and a second dose after 11 days of paroxetine use. After the addition of paroxetine, EMs experienced a 5-fold decrease in clearance of desipramine, indicating that paroxetine inhibits oxidation reactions catalyzed by CYP2D6. PMs had a slight increase in clearance of desipramine with paroxetine. With concurrent administration of desipramine and paroxetine, interaction of the two drugs may result in a need for dosage adjustments, especially in extensive metabolizers of desipramine (Brosen et al, 1993j).

3.5.1.EP Quinidine

1) Interaction Effect: elevated paroxetine plasma concentrations and possible paroxetine toxicity (nausea, dry mouth, somnolence, headache)
2) Summary: Paroxetine is metabolized in part by cytochrome P450IID6 (CYP2D6) (Prod Info Paxil CR (TM), 2003l). Quinidine is known to inhibit the CYP2D6 isoenzyme. Quinidine and paroxetine coadministration could result in reduced paroxetine metabolism, increased paroxetine plasma concentrations, and possibly paroxetine toxicity. Controlled studies are needed to document the clinical impact of quinidine - paroxetine administration.
3) Severity: moderate
4) Onset: rapid
5) Substantiation: probable
6) Clinical Management: Monitor patients for signs of paroxetine toxicity. Doses of paroxetine may need to

be reduced.
7) Probable Mechanism: reduced paroxetine metabolism

3.5.1.EQ Ranolazine
1) Interaction Effect: an increase in ranolazine steady state plasma concentrations
2) Summary: Paroxetine is a potent inhibitor of cytochrome P450-2D6 enzyme. This inhibition increases the average steady state plasma concentrations of ranolazine by 1.2-fold. No adjustment in ranolazine dose is necessary when using ranolazine with paroxetine or other CYP2D6 inhibitors concomitantly (Prod Info RANEXA(TM) extended-release tablets, 2006).
3) Severity: minor
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: No dosage adjustment of ranolazine is required in patients treated with paroxetine.
7) Probable Mechanism: paroxetine inhibition of cytochrome P450-2D6 mediated ranolazine metabolism

3.5.1.ER Rasagiline
1) Interaction Effect: CNS toxicity or serotonin syndrome (hypertension, hyperthermia, myoclonus, mental status changes)
2) Summary: Concurrent administration or overlapping therapy with selective serotonin reuptake inhibitors, including paroxetine, and non-selective MAOIs or the selective MAO-B inhibitor selegiline, has been reported to cause serious, sometimes fatal reactions. Signs and symptoms included hyperthermia, rigidity, myoclonus, autonomic instability with rapid vital sign fluctuations, and mental status changes progressing to extreme agitation, delirium, and coma. Similar reactions have been reported with serotonin-norepinephrine reuptake inhibitors (SNRIs) and non-selective MAOIs or selegiline. Rasagiline clinical trials did allow concomitant use of paroxetine in doses less than or equal to 30 mg/day. However, the small number of patients exposed to SSRIs (n of 141) was not adequate to rule out the possibility of adverse events from the combination of rasagiline and paroxetine, and such use should be avoided. Wait at least 14 days after discontinuing rasagiline before initiating paroxetine treatment (Prod Info AZILECT(R) oral tablets, 2006).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Concurrent use of paroxetine and rasagiline should be avoided. Wait at least 14 days after discontinuing rasagiline before initiating therapy with paroxetine.
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 produce a toxic reaction known as serotonin syndrome (Sternbach, 1991f). Serotonin syndrome is a condition of serotonergic hyperstimulation and manifests as restlessness, myoclonus, changes in mental status, hyperreflexia, diaphoresis, shivering, and tremor. If the syndrome is not recognized and correctly treated, death can result.

3.5.1.ES 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 cohort studies have shown that the combined use of SSRIs and anticoagulants has been associated with an increased risk of bleeding (Wallerstedt et al, 2009; Schalekamp et al, 2008; Prod Info PAXIL(R) oral tablets, suspension, 2008). Bleeding events reported have included epistaxis, ecchymosis, hematoma, petechiae, and life-threatening hemorrhages. Altered anticoagulant effects (including increased bleeding) have been reported with the coadministration of SSRIs with warfarin (Schalekamp et al, 2008; Prod Info PAXIL(R) oral tablets, suspension, 2008).
3) Severity: major
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: When paroxetine and an anticoagulant are given concurrently, monitor patients for signs of increased bleeding. Patients who are taking warfarin should be monitored closely for altered anticoagulant effects, including increased bleeding, when paroxetine therapy is initiated or discontinued (Prod Info PAXIL(R) oral tablets, suspension, 2008).
7) Probable Mechanism: unknown
8) Literature Reports
a) According to a retrospective cohort study (n=234), there was an increased risk of clinically relevant bleeding (hospital admission due to bleeding) in patients receiving warfarin for atrial fibrillation during concomitant SSRI therapy or within 2 weeks following SSRI therapy termination. Patients with a mean age of 72 +/- 7 years receiving warfarin plus SSRI (n=117) were matched with randomly selected patients who received warfarin only (n=117). SSRI included fluoxetine, citalopram, paroxetine, sertraline, fluvoxamine, or escitalopram. Nine patients experienced 11 bleeding episodes during 213.9 treatment years in the warfarin plus SSRI group, and 10 patients experienced 14 bleedings during 586.4 treatment years in the warfarin-only group. The corresponding total incidences of bleedings were 51.4 and 23.9 per 1000 treatment years, respectively. The hazard ratio for first bleedings during treatment

with warfarin plus SSRI was 3.49 (95% CI; 1.37 to 8.91, p=0.009) compared with warfarin only. The SSRI implicated in patients experiencing bleeding at the time of concomitant administration were sertraline or citalopram. The addition of an SSRI was not associated with a change in warfarin dose or INR (p=0.48 and p=0.31 respectively). The results of the study may be limited by earlier bleeding events, unknown patient adherence, and exclusion of clopidogrel, dipyridamol, corticosteroids and anticoagulants other than warfarin in the model (Wallerstedt et al, 2009).

b) A population-based, case-controlled study of new coumarin users (acenocoumarol and phenprocoumon) with concomitant selective serotonin reuptake inhibitors (SSRIs) resulted in an increased risk of hospitalization due to nongastrointestinal bleeding. Using national pharmacy and hospitalization records, Netherlands researchers identified 1848 cases that were admitted for abnormal bleeding and compared them with 5818 control subjects also taking coumarins. Median duration of treatment in patients was 220 days (range, 1 to 4690 days). Patients on SSRIs showed greater risk for hospitalization for nongastrointestinal bleeding (adjusted odds ratio (OR) 1.7, 95% confidence interval (CI), 1.1 to 2.5), however, the rate of gastrointestinal bleeding (adjusted OR 0.8, 95% CI, 0.4 to 1.5) was not significantly different (Schalekamp et al, 2008).

c) Preliminary data suggest that there may be a pharmacodynamic interaction (that causes an increased bleeding diathesis with unaltered prothrombin time) between paroxetine and warfarin. The concomitant use of paroxetine and warfarin should be undertaken with caution (Prod Info PAXIL(R) oral tablets, suspension, 2008).

d) In a multiple-dose study, several days of combined therapy with warfarin and paroxetine resulted in mild but clinically significant bleeding in 5 of 27 subjects. This effect occurred in the absence of a significant enhancement in warfarin-induced hypoprothrombinemia or changes in either paroxetine or warfarin disposition (Bannister et al, 1989b).

3.5.1.ET Risperidone

1) Interaction Effect: increased plasma concentrations of risperidone

2) Summary: Concomitant use of paroxetine (potent CYP2D6 inhibitor) and risperidone (CYP2D6 substrate) has resulted in increased risperidone plasma concentrations and an increased risk of risperidone adverse effects such as serotonin syndrome, QT prolongation, and extrapyramidal effects. The postulated mechanism of action is inhibition of CYP2D6-mediated metabolism of risperidone by paroxetine. Two studies demonstrated increased risperidone levels resulting in a greater frequency of extrapyramidal symptoms in patients treated concurrently with paroxetine and risperidone (Saito et al, 2005; Spina et al, 2001). One of these studies showed an association between paroxetine dose increases and greater risperidone plasma concentrations (Spina et al, 2001). In a case report, serotonin syndrome was observed in a patient who had already been receiving risperidone and was initiated on paroxetine (Hamilton & Malone, 2000). Monitoring the patient for increased risperidone plasma levels side effects may be necessary. The risperidone dose should be reevaluated if paroxetine is initiated or discontinued. Concomitant use of a low dose of paroxetine with risperidone may be safe and effective in treating schizophrenia with negative symptoms (Prod Info RISPERDAL(R) oral tablets, oral solution, orally disintegrating tablets, 2008; Spina et al, 2001).

3) Severity: moderate

4) Onset: delayed

5) Substantiation: probable

6) Clinical Management: Concomitant use of paroxetine and risperidone has resulted in increased risperidone plasma concentrations and an increased risk of risperidone side effects (Prod Info RISPERDAL (R) oral tablets, oral solution, orally disintegrating tablets, 2008; Saito et al, 2005; Spina et al, 2001; Hamilton & Malone, 2000). Carefully monitor patients for increased plasma risperidone levels and side effects (serotonin syndrome, extrapyramidal symptoms, and cardiotoxicity) when paroxetine is coadministered with risperidone. Reevaluate the dose of risperidone when concomitant paroxetine is initiated or discontinued (Prod Info RISPERDAL(R) oral tablets, oral solution, orally disintegrating tablets, 2008). Coadministering a low dose of paroxetine with risperidone may be safe and effective in treating schizophrenia with negative symptoms (Saito et al, 2005).

7) Probable Mechanism: inhibition of CYP2D6-mediated metabolism of risperidone

8) Literature Reports

a) Paroxetine (a potent CYP2D6 inhibitor) 20 mg/day has been shown to increase the plasma concentration of risperidone (a CYP2D6 substrate) by 3- to 9- fold. Paroxetine also lowered the concentration of 9-hydroxyrisperidone by about 10%. In postmarketing surveillance of risperidone, torsade de pointes has been reported with combined overdose of risperidone and paroxetine. The dosage of risperidone should be reevaluated when paroxetine is initiated or discontinued (Prod Info RISPERDAL(R) oral tablets, oral solution, orally disintegrating tablets, 2008).

b) Risperidone plasma concentrations increased when risperidone-treated inpatients (n=12) with schizophrenia and negative symptoms were coadministered incremental doses of paroxetine. Prior to initiating paroxetine, patients were receiving risperidone 2 mg twice daily for at least 6 weeks and steady-state plasma concentrations of risperidone and 9-hydroxyrisperidone (9-OH-risperidone) had been achieved. Paroxetine doses were administered in 3 consecutive 4-week increments of 10 mg/day, 20 mg/day, and 40 mg/day. Mean risperidone plasma concentrations during 10-, 20-, and 40-mg paroxetine treatment were 3.8- (95% confidence interval (CI), 3.2 to 5.8; p less than 0.01) , 7.1- (95% CI, 5.3 to 16.5; p less than 0.01), and 9.7-fold (95% CI, 7.8 to 22.5; p less than 0.01) higher compared

with baseline. Increases in 9-OH-risperidone concentrations were not significant with paroxetine use. Mean active moiety (risperidone plus 9-OH-risperidone) plasma concentrations increased by 1.8-fold (95% CI, 1.4 to 2.7; p less than 0.05) during the 40-mg paroxetine dose; increases were not significant with 10- or 20-mg doses. Metabolic ratio was significantly increased (p less than 0.01) by 4.2-fold (95% CI, 3.4 to 6.2) with 10 mg of paroxetine, by 8.2-fold (95% CI, 6 to 16) with 20 mg, and by 12.6-fold (95% CI, 9.6 to 26.8) with 40 mg. Negative symptom scores were significantly improved during all paroxetine doses; however, extrapyramidal symptoms scores were significantly higher during 20- and 40-mg doses. The authors suggest that low-dose coadministration of paroxetine with risperidone may be safe and effective for treating schizophrenia with negative symptoms (Saito et al, 2005).

c) Paroxetine, a potent inhibitor of cytochrome CYP2D6, may impair the elimination of risperidone, primarily by inhibiting CYP2D6-mediated alpha-hydroxylation and, to a lesser extent, by simultaneously affecting the further metabolism of 9-hydroxyrisperidone (9-OH-risperidone) or other pathways of risperidone biotransformation. In a study including 10 patients diagnosed with schizophrenia (n=7) or schizoaffective disorder depressive type (n=3), risperidone plasma concentrations increased when paroxetine was coadministered with risperidone. Patients were stabilized on risperidone therapy 4 to 8 mg/day and received adjunctive paroxetine 20 mg/day to treat negative symptoms, concomitant depression, or both. Risperidone dosage remained constant throughout the duration of the study. A significant elevation in risperidone plasma concentrations (p less than 0.01) and a slight, nonsignificant decrease in 9-OH-risperidone occurred. After 4 weeks of paroxetine treatment, the total concentration of risperidone and 9-OH-risperidone was increased by 45% (p less than 0.05). The mean plasma risperidone to 9-OH-risperidone ratio also changed significantly (p less than 0.001) with concomitant paroxetine treatment. Extrapyramidal side effects occurred in one patient during the second week of paroxetine coadministration. Total plasma levels of risperidone in this patient increased 62% over baseline values during paroxetine coadministration. The occurrence of extrapyramidal symptoms in patients after addition of SSRIs to antipsychotics might also be caused by an additive pharmacodynamic effect of paroxetine (Spina et al, 2001).

d) Serotonin syndrome occurred in a patient using concomitant paroxetine and risperidone, an antipsychotic agent with potent serotonin antagonism and dopamine blocking activity . A 53-year-old male with a 7-month history of psychotic depression was being treated with risperidone 3 mg/day and paroxetine 20 mg/day for 10 weeks before presentation. Nine weeks into therapy, the patient showed decreased motivation and bilateral jerking movements of the mouth and legs. The patient discontinued his medication during the week before his admission. Upon presentation he was apathetic, confused, disorganized, and talked to himself. The doses of paroxetine and risperidone were doubled to 40 mg/day and 6 mg/day, respectively. Within 2 hours of taking his medication, he experienced bilateral jerking movements, ataxia, tremor, and shivering. He presented to the emergency room with involuntary jerking movements and lethargy. His mental status exam was notable for depression with psychomotor agitation, difficulty being aroused, and auditory hallucinations. Differential diagnosis included recurrent psychotic depression, neuroleptic malignant syndrome (NMS), drug overdose, and serotonin syndrome. Nortriptyline 100 mg at bedtime, haloperidol 10 mg twice daily and diphenhydramine 50 mg at night were initiated at discharge. The patient returned to baseline 9 months after discharge and is without symptoms of depression or psychosis (Hamilton & Malone, 2000).

3.5.1.EU Ritonavir

1) Interaction Effect: decreased paroxetine plasma levels

2) Summary: The concurrent administration of fosamprenavir/ritonavir and paroxetine has resulted in significantly decreased paroxetine plasma levels. Caution is advised if these agents are used concurrently. Dose adjustments should be guided by clinical efficacy and tolerability (Prod Info PAXIL(R) oral tablets, oral suspension, 2006). Patients may need to be monitored for loss of paroxetine efficacy.

3) Severity: moderate

4) Onset: unspecified

5) Substantiation: probable

6) Clinical Management: Coadministration of fosamprenavir/ritonavir and paroxetine has led to significantly decreased paroxetine plasma levels. Use caution if these agents are coadministered. Dose adjustments should be made based on clinical efficacy and tolerability (Prod Info PAXIL(R) oral tablets, oral suspension, 2006). Monitor patients for loss of paroxetine efficacy.

7) Probable Mechanism: unknown

3.5.1.EV Rizatriptan

1) Interaction Effect: an increased risk of serotonin syndrome

2) Summary: There have been case reports of weakness, hyperreflexia, and incoordination following concomitant use of sumatriptan, a 5-hydroxytryptamine-1 (5HT-1) agonist, and a serotonin specific reuptake inhibitor (SSRI) (Prod Info Imitrex(R), 1998). Because rizatriptan is a 5HT 1B/1D receptor agonist, a similar interaction between SSRIs and rizatriptan may occur (Prod Info Maxalt(R), 1998a). Concurrent use of a triptan and an SSRI may result in serotonin syndrome which may be life-threatening. Symptoms of serotonin syndrome may include restlessness, hallucinations, loss of coordination, fast heart beat, rapid changes in blood pressure, increased body temperature, overreactive reflexes, nausea, vomiting, and diarrhea. Clinicians should be aware that triptans may be commonly used intermittently and that either the triptan or the SSRI may be prescribed by a different physician. Discuss the risks of serotonin syndrome with patients

who are prescribed this combination and monitor them closely for symptoms of serotonin syndrome (US Food and Drug Administration, 2006).
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-threatening condition called serotonin syndrome. Be aware that triptans may be commonly used intermittently and that either the triptan or the SSRI may be prescribed by a different physician. If these agents are used together, discuss the risks of serotonin syndrome with the patient and monitor closely for symptoms of serotonin syndrome (restlessness, hyperthermia, hyperreflexia, incoordination).
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 rizatriptan 10 mg. Plasma concentrations of rizatriptan were not altered by the administration of paroxetine (Prod Info Maxalt(R), 1998).

3.5.1.EW 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 cohort studies have shown that the combined use of SSRIs and NSAIDs has been associated with an increased risk of bleeding. Bleeding events have included epistaxis, ecchymosis, hematoma, petechiae, and life-threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension, 2008) (Prod Info Lexapro(TM), 2003; Dalton et al, 2003a; Prod Info CELEXA (R) oral tablet, solution, 2005).
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 increased bleeding.
7) Probable Mechanism: unknown
8) Literature Reports
a) SSRIs increase the risk of upper gastrointestinal bleeding and this effect is potentiated by concurrent use of NSAIDs or low-dose aspirin. Hospitalizations for upper gastrointestinal bleeding were searched among 26,005 users of antidepressant medications and compared with the number of hospitalizations in those patients who did not receive prescriptions for antidepressants. The amount of upper GI bleeding episodes was 3.6 times more than expected (95% confidence interval, 2.7 to 4.7). Combined use of an SSRI and NSAIDs or low-dose aspirin increased the risk to 12.2 (95% confidence interval, 7.1 to 19.5) and 5.2 (95% confidence interval, 3.2 to 8), respectively. The findings of this study demonstrate an increased risk of upper GI bleeding during the use of SSRIs. Combined use of SSRIs and NSAIDs or low-dose aspirin increased the risk even further (Dalton et al, 2003).
b) Coadministration of ketorolac with psychoactive drugs (such as fluoxetine) has been associated with hallucinations in some patients (Prod Info TORADOL(R) oral tablets, 2007).

3.5.1.EX Selegiline
1) Interaction Effect: CNS toxicity or serotonin syndrome (hypertension, hyperthermia, myoclonus, mental status changes)
2) Summary: Concomitant administration of selegiline and paroxetine is contraindicated, and a minimum of 14 days should elapse after discontinuing selegiline before initiating therapy with paroxetine or a minimum of 7 days should elapse after discontinuing paroxetine before initiating therapy with selegiline (Prod Info EMSAM(R) transdermal patch, 2006). Concurrent administration or overlapping therapy may result in CNS toxicity or serotonin syndrome, a hyperserotonergic state characterized by symptoms such as restlessness, myoclonus, changes in mental status, hyperreflexia, diaphoresis, shivering, and tremor. Serious, even fatal, reactions have been reported with concomitant use of serotonin specific reuptake inhibitors and MAO inhibitors (Prod Info Paxil(R), 2003a; Lappin & Auchincloss, 1994c; Graber et al, 1994c; Suchowersky & de Vries, 1990c).
3) Severity: contraindicated
4) Onset: rapid
5) Substantiation: theoretical
6) Clinical Management: Concurrent use of paroxetine and selegiline is contraindicated. Wait at least two weeks after discontinuing selegiline before initiating paroxetine, or at least 7 days after discontinuing paroxetine before initiating therapy with an selegiline.
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 serotonin syndrome (Sternbach, 1991c). Serotonin syndrome is a condition of serotonergic hyperstimulation and manifests as restlessness, myoclonus, changes in mental status, hyperreflexia, diaphoresis, shivering, and tremor. If the syndrome is not recognized and correctly treated, fatality can result.
b) A 26-year old woman who had been taking isocarboxazid for eight weeks stopped taking the drug

for 11 days before beginning therapy with sertraline. After a single 100 mg sertraline dose, the patient became restless and developed leg twitches. The patients was later admitted to the emergency room with diaphoresis, tachycardia, hyperreflexia, and various neuromuscular disturbances. After treatment with diazepam and propranolol the patient did not improve. The patient was then given two 4 mg doses of cyproheptadine an hour apart, with notable improvement 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 added to a regimen of lithium, phenelzine, thioridazine, and doxepin. Three hours after taking the first sertraline dose, the patient was found in a semicomatose state, with elevated body temperature, increased pulse, increased respiration rate, and a blood pressure of 140/110 mm Hg. After transportation to the hospital, the patient was misdiagnosed as having neuroleptic malignant syndrome (NMS) which was later changed to serotonin syndrome due to a reaction between sertraline and phenelzine. The authors suggest that monoamine oxidase inhibitor (MAOI) therapy should be discontinued for at least two weeks before initiation of therapy with a selective serotonin reuptake inhibitor (SSRI) and that before starting a MAOI, SSRI therapy should be discontinued for at least five half-lives of the parent drug and any active metabolites (Graber et al, 1994b).

d) Two cases reports suggested a possible interaction between fluoxetine and selegiline (Suchowersky & de Vries, 1990b). One case involved a first episode of mania being observed approximately one month after adding selegiline to fluoxetine. The patient improved two months after both drugs were discontinued, and no further details were provided. The second case involved diaphoresis, vasoconstriction, and cyanosis of the hands which occurred in close temporal relationship to adding fluoxetine to selegiline. Both drugs were discontinued, with relatively quick resolution of symptoms. Rechallenge with fluoxetine alone occurred without incident.

3.5.1.EY 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 cohort studies have shown that the combined use of SSRIs and antiplatelet agents has been associated with an increased risk of bleeding. Bleeding events reported have included epistaxis, ecchymosis, hematoma, petechiae, and life-threatening hemorrhages (Prod Info PAXIL(R) oral 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 signs of increased bleeding (Prod Info PAXIL(R) oral tablets, suspension, 2008; Prod Info PROZAC(R) oral capsules, delayed-release capsules, solution, 2008)

7) Probable Mechanism: unknown

3.5.1.EZ Sibutramine

1) Interaction Effect: an increased risk of serotonin syndrome (hypertension, hyperthermia, myoclonus, mental status changes)

2) Summary: Sibutramine inhibits the reuptake of norepinephrine, dopamine, and serotonin. In addition, the two major metabolites of sibutramine, M1 and M2, also inhibit the reuptake of these neurotransmitters. A hyperserotonergic state, termed serotonin syndrome, may result if sibutramine is given concurrently with a selective serotonin reuptake inhibitor. Coadministration of sibutramine 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 selective serotonin reuptake inhibitors, because of the increased risk of serotonin syndrome.

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, myoclonus, changes in mental status, hyperreflexia, diaphoresis, shivering, and tremor. If the syndrome is not recognized and correctly treated, death can result (Sternbach, 1991b).

3.5.1.FA St John's Wort

1) Interaction Effect: an increased risk of serotonin syndrome (hypertension, hyperthermia, myoclonus, mental status changes)

2) Summary: Case reports describe the onset of serotonin syndrome-like symptoms, mania, and hypomania following the addition of St. John's Wort to sertraline, fluoxetine, and paroxetine therapy (Spinella & Eaton, 2002c; Barbanel et al, 2000a; Waksman et al, 2000a; Lantz et al, 1999a). A patient exhibited a syndrome resembling sedative/hypnotic intoxication after adding St. John's Wort to paroxetine therapy (Gordon, 1998a). St. John's Wort is thought to inhibit serotonin reuptake and may have mild monoamine oxidase inhibitory activity (Singer et al, 1999; Thiede & Walper, 1994), 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 restarting selective serotonin reuptake inhibitor therapy. If a patient plans to replace selective serotonin reuptake inhibitor (SSRI) therapy with St. John's Wort, the half-life of the specific SSRI should be taken into consideration, waiting at least 5 half-lives for the SSRI to be 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 antidepressants and St. John's Wort. Case 1 developed dizziness, nausea, vomiting and a headache 4 days after starting St. John's Wort 300 milligrams (mg) three times daily combined with sertraline 50 mg daily. Her symptoms resolved 2 to 3 days after stopping all medications. Case 2 developed nausea, epigastric pain and anxiety 3 days after starting St. John's Wort 300 mg twice daily combined with sertraline 75 mg daily. His symptoms resolved in one week after discontinuing both medications, and he resumed sertraline use without complications. The third case developed nausea, vomiting, anxiety, and confusion 2 days after starting St. John's Wort 300 mg twice daily combined with sertraline 50 mg daily. His symptoms improved in 4 to 5 days after stopping both medications and taking cyproheptadine 4 mg three times daily. Case 4 developed nausea, anxiety, restless, and irritability 2 days after starting St. John's Wort 300 mg three times daily combined with sertraline 50 mg daily. Cyproheptadine 4 mg twice daily was administered for seven days, and his symptoms improved in 1 week after stopping the medication. Cases 1 through 4 resumed their prescriptive sertraline after symptoms subsided and had no further problems. Case 5 developed nausea, vomiting and restlessness 3 days after starting St. John's Wort 300 mg three times daily combined with nefazodone 100 mg twice daily. She continued to take St. John's Wort but discontinued the nefazodone and over 1 week her symptoms Improved. She refused to resume therapy with nefazodone, but continued therapy with St. John's Wort and mild 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 intoxication when she ingested a single dose of paroxetine 20 mg. She was incoherent, groggy, slow-moving, and complained of nausea and weakness. Prior to starting St. John's Wort, she had been receiving paroxetine 40 mg daily for eight months without adverse effects. After a night of 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 beginning paroxetine 20 milligrams (mg) two days after discontinuing St. John's Wort 600 mg daily. The patient reported agitation and akathisia 8 hours after taking the first dose of paroxetine. She presented with diaphoresis and involuntary movement of all extremities with hyperreflexia and rigidity. Blood pressure, heart rate, and temperature were normal. After admission, blood pressure increased to 200/116 mmHg and heart rate increased to 145 beats per minute. Creatine kinase increased from 212 units/liter (U/L) initially to 1024 U/L. The patient was managed with supportive care and lorazepam and discharged after two days (Waksman et al, 2000).

d) A 28-year-old male developed a manic syndrome following comedication with St. John's Wort and sertraline. The patient was also on testosterone replacement therapy following bilateral orchidectomy 2 years earlier, but testosterone levels were subtherapeutic. The patient was prescribed sertraline 50 milligrams daily for depression following a 2 week trial of St. John's Wort per patient preference (dose not specified). Before sertraline was started, the patient was instructed to discontinue St. John'sWort, but continued it despite this advice. The patient experienced improved mood so did not see his physician, believing that he did not need further treatment. Over 2 months, the patient had elated mood, was irritable, and overspent, buying a car he could not afford, and was ultimately arrested for stealing fuel for the car. On arrest, he was referred to psychiatric services due to irritability and disinhibition. He was observed to be over-aroused, distractible, have flight of ideas, and grandiose delusions, leading to a diagnosis of a manic episode. The authors state the possibility of the manic state resulting from sertraline therapy alone, and that St. John's Wort may have increased the risk as a result of monoamine oxidase inhibition. Since the patient's testosterone level was subnormal, the possibility of its contribution to the manic state was considered low. However, the patient had elevated gonadotropin levels (luteinizing hormone and follicle-stimulating hormone) which may have predisposed the patient to mania (Barbanel et al, 2000).

e) A 42-year-old female experienced symptoms consistent with a mixed hypomanic episode following concomitant use of fluoxetine, buspirone, Ginkgo biloba, and St. John's Wort. The symptoms resolved following discontinuation of Ginkgo and St. John's Wort. The patient was being treated for depression following a mild traumatic brain injury with fluoxetine 20 milligrams (mg) twice daily and buspirone 15 mg twice daily. Several weeks prior to presentation, buspirone was increased to 20 mg twice daily for persistent anxiety and the patient began taking Ginkgo biloba, melatonin, and St. John's Wort in unspecified doses. Melatonin was considered unlikely to have contributed to her symptoms. Ginkgo and St. John's Wort were considered possible contributors since they may potentiate antidepressants, and considering the temporal relationship between the use of the herbs and onset of symptoms and discontinuation of the herbs and resolution of symptoms. However, the brain injury was considered a possible contributor (Spinella & Eaton, 2002b).

3.5.1.FB 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 cohort studies have shown that the combined use of SSRIs and antiplatelet agents has been associated with an increased risk of bleeding. Bleeding events reported have included epistaxis, ecchymosis, hematoma, petechiae, and life-threatening hemorrhages (Prod Info PAXIL(R) oral 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 signs of increased bleeding (Prod Info PAXIL(R) oral tablets, suspension, 2008; Prod Info PROZAC(R) oral capsules, delayed-release capsules, solution, 2008)

7) Probable Mechanism: unknown

3.5.1.FC 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 cohort studies have shown that the combined use of SSRIs and NSAIDs has been associated with an increased risk of bleeding. Bleeding events have included epistaxis, ecchymosis, hematoma, petechiae, and life-threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension, 2008) (Prod Info Lexapro(TM), 2003; Dalton et al, 2003a; Prod Info CELEXA (R) oral tablet, solution, 2005).

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 increased bleeding.

7) Probable Mechanism: unknown

8) Literature Reports

a) SSRIs increase the risk of upper gastrointestinal bleeding and this effect is potentiated by concurrent use of NSAIDs or low-dose aspirin. Hospitalizations for upper gastrointestinal bleeding were searched among 26,005 users of antidepressant medications and compared with the number of hospitalizations in those patients who did not receive prescriptions for antidepressants. The amount of upper GI bleeding episodes was 3.6 times more than expected (95% confidence interval, 2.7 to 4.7). Combined use of an SSRI and NSAIDs or low-dose aspirin increased the risk to 12.2 (95% confidence interval, 7.1 to 19.5) and 5.2 (95% confidence interval, 3.2 to 8), respectively. The findings of this study demonstrate an increased risk of upper GI bleeding during the use of SSRIs. Combined use of SSRIs and NSAIDs or low-dose aspirin increased the risk even further (Dalton et al, 2003).

b) Coadministration of ketorolac with psychoactive drugs (such as fluoxetine) has been associated with hallucinations in some patients (Prod Info TORADOL(R) oral tablets, 2007).

3.5.1.FD 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 cohort studies have shown that the combined use of SSRIs and antiplatelet agents has been associated with an increased risk of bleeding. Bleeding events reported have included epistaxis, ecchymosis, hematoma, petechiae, and life-threatening hemorrhages (Prod Info PAXIL(R) oral 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 signs of increased bleeding (Prod Info PAXIL(R) oral tablets, suspension, 2008; Prod Info PROZAC(R) oral capsules, delayed-release capsules, solution, 2008)

7) Probable Mechanism: unknown

3.5.1.FE Sumatriptan

1) Interaction Effect: an increased risk of serotonin syndrome

2) Summary: There have been case reports of weakness, hyperreflexia, incoordination, and persistent paroxysmal dyskinesias following concomitant use of sumatriptan and a serotonin specific reuptake inhibitor (SSRI) (Prod Info Paxil CR(TM), 2003m; Prod Info Imitrex(R), 2004; Abraham et al, 1997a). Concurrent use of a triptan and an SSRI may result in serotonin syndrome which may be life-threatening. Symptoms of serotonin syndrome may include restlessness, hallucinations, loss of coordination, fast heart beat, rapid changes in blood pressure, increased body temperature, overreactive reflexes, nausea, vomiting, and diarrhea. Clinicians should be aware that triptans may be commonly used intermittently and that either the triptan or the SSRI may be prescribed by a different physician. Discuss the risks of serotonin syndrome with patients who are prescribed this combination and monitor them closely for symptoms of serotonin syndrome (US Food and Drug Administration, 2006).

3) Severity: major
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: Coadministration of a triptan, such as sumatriptan, and an SSRI, such as paroxetine, may result in a life-threatening condition called serotonin syndrome. Be aware that triptans may be commonly used intermittently and that either the triptan or the SSRI may be prescribed by a different physician. If these agents are used together, discuss the risks of serotonin syndrome with the patient and monitor closely for symptoms of serotonin syndrome (restlessness, hyperthermia, hyperreflexia, incoordination).
7) Probable Mechanism: additive pharmacologic effects resulting in excessive serotonergic stimulation
8) Literature Reports
a) A 40-year old female with a 9-year history of a bipolar disorder was started on paroxetine therapy, with the dose being increased to 30 mg daily within one week. After seven days of paroxetine 30 mg, she received an injection of sumatriptan for a migraine headache. Within 24 hours, she developed sustained dystonic contractions of her neck muscles, dystonic arching of her back, choreaform rocking of her hips, choreaform up and down movements of her shoulders, and wavelike, athetoid movements of her abdominal muscles. These dyskinesias occurred about five times daily and lasted for 20 to 30 minutes. Following the discontinuation of paroxetine, these abnormal movements decreased in severity but worsened when paroxetine was again initiated. All medications were stopped, and clozapine at a dose of 100 mg daily caused a remission of her paroxysmal dyskinesias. The authors speculated that the combination of paroxetine and sumatriptan may have sensitized the 5-HT autoreceptors and induced postsynaptic receptor supersensitivity (Abraham et al, 1997).

3.5.1.FF 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 cohort studies have shown that the combined use of SSRIs and NSAIDs has been associated with an increased risk of bleeding. Bleeding events have included epistaxis, ecchymosis, hematoma, petechiae, and life-threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension, 2008) (Prod Info Lexapro(TM), 2003; Dalton et al, 2003a; Prod Info CELEXA (R) oral tablet, solution, 2005).
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 increased bleeding.
7) Probable Mechanism: unknown
8) Literature Reports
a) SSRIs increase the risk of upper gastrointestinal bleeding and this effect is potentiated by concurrent use of NSAIDs or low-dose aspirin. Hospitalizations for upper gastrointestinal bleeding were searched among 26,005 users of antidepressant medications and compared with the number of hospitalizations in those patients who did not receive prescriptions for antidepressants. The amount of upper GI bleeding episodes was 3.6 times more than expected (95% confidence interval, 2.7 to 4.7). Combined use of an SSRI and NSAIDs or low-dose aspirin increased the risk to 12.2 (95% confidence interval, 7.1 to 19.5) and 5.2 (95% confidence interval, 3.2 to 8), respectively. The findings of this study demonstrate an increased risk of upper GI bleeding during the use of SSRIs. Combined use of SSRIs and NSAIDs or low-dose aspirin increased the risk even further (Dalton et al, 2003).
b) Coadministration of ketorolac with psychoactive drugs (such as fluoxetine) has been associated with hallucinations in some patients (Prod Info TORADOL(R) oral tablets, 2007).

3.5.1.FG Tamoxifen
1) Interaction Effect: decreased plasma concentrations of the active metabolites of tamoxifen
2) Summary: Tamoxifen is a prodrug metabolized to active metabolites by CYP450 enzymes (Stearns et al, 2003). Paroxetine, a potent inhibitor of CYP2D6, reduces plasma concentrations of the active metabolites. In one study of 12 patients, coadministration with tamoxifen significantly reduced plasma concentrations of the active metabolite 4-hydroxy-N-desmethyl-tamoxifen (Stearns et al, 2003). The patient's CYP2D6 genotype also influences the metabolism of tamoxifen, with the homozygous variant or heterozygous allele having lower plasma concentrations of the potent antiestrogenic metabolite endoxifen than subjects with a homozygous wild-type genotype (Jin et al, 2005). However, one small case control study found that pharmacokinetic alterations in tamoxifen metabolism did not significantly increase tumor recurrence in breast cancer patients (Lehmann et al, 2004).
3) Severity: moderate
4) Onset: delayed
5) Substantiation: established
6) Clinical Management: Coadministration of paroxetine and tamoxifen has resulted in decreased plasma concentrations of 4-hydroxy-N-desmethyl-tamoxifen, an active metabolite of tamoxifen. If administered concurrently, monitor for decreased tamoxifen efficacy.
7) Probable Mechanism: inhibition of CYP2D6-mediated tamoxifen metabolism
8) Literature Reports

a) Concomitant use of paroxetine, a potent inhibitor of CYP2D6, and tamoxifen, which requires activation by CYP2D6 enzymes to the antiestrogenic metabolite (endoxifen), results in substantially reduced plasma concentrations of endoxifen. Eighty newly diagnosed breast cancer patients taking tamoxifen 20 mg/day were genotyped for the common alleles of the CYP2D6, CYP2C9, CYP3A5, and sulfotransferase (SULT) 1A1 genes. After 1 and 4 months of tamoxifen treatment, plasma concentrations of tamoxifen and endoxifen were measured. After 4 months of tamoxifen, plasma endoxifen concentrations were statistically significantly lower in those with a CYP2D6 homozygous variant genotype (20 nM, 95% CI = 11.1 to 28.9) or a heterozygous genotype (43.1 nM, 95% CI = 33.3 to 52.9) than those with a homozygous wild-type genotype (78 nM, 95% CI = 65.9 to 90.1) (both P = 0.003). The mean plasma endoxifen concentration for subjects with a homozygous wild-type genotype who were taking CYP2D6 inhibitors was 58% lower than those not taking such inhibitors (38.6 nM versus 91.4 nM, 95% CI of difference = -86.1 to -19.5, P = 0.0025). Concomitant use of venlafaxine, a weak inhibitor of CYP2D6, resulted in slightly reduced plasma concentrations of endoxifen, while the use of paroxetine, a potent inhibitor of CYP2D6, resulted in substantial reductions in endoxifen concentrations. Plasma concentrations of tamoxifen and metabolites were not altered significantly by genetic variations of CYP2C9, CYP3A5 or SULT1A1 (Jin et al, 2005).
b) A case control study (n = 28) designed to evaluate the effect of CYP isoform inhibitors on therapeutic outcome in women taking tamoxifen for estrogen receptor-positive breast cancer found no significant impact on breast cancer recurrence from chronic exposure (3 months or greater) to CYP2D6, 2C9, or 3A4 inhibitors or substrates. Cases (recurrences of breast cancer) and controls (patients without recurrent breast cancer) were matched by cancer stage, year of diagnosis, and CYP inhibitor or substrate exposure. Selective serotonin reuptake inhibitors, including paroxetine, are inhibitors of CYP2D6, 2C9, and 3A isoforms responsible for the metabolism of tamoxifen to the potent antiestrogen 4-hydroxy metabolite (Lehmann et al, 2004).
c) In a prospective clinical trial involving 12 women of known CYP2D6 genotype with breast cancer taking adjuvant tamoxifen, coadministration of paroxetine decreased the plasma concentration of the tamoxifen active metabolite endoxifen (4-hydroxy-N-desmethyl-tamoxifen). Each patient was maintained on tamoxifen 20 mg/day during treatment with paroxetine 10 mg/day for 4 weeks. Plasma concentrations of endoxifen clinically significantly decreased from a pre-paroxetine mean of 12.4 ng/mL to 5.5 ng/mL after paroxetine administration (difference = 6.9 ng/mL, 95% CI = 2.7 to 11.2 ng/mL; P = 0.004). When analyzed by genotype, reduced levels of endoxifen were more pronounced in women who carried the wild-type CYP2D6, while those with the variant genotype experienced no statistically significant effect of paroxetine on endoxifen levels. However, the authors caution that the results of this small study should not alter current treatment recommendations which include the use of selective serotonin reuptake inhibitors (SSRIs) and selective norepinephrine reuptake inhibitors (SNRIs) to relieve tamoxifen-associated hot flashes (Stearns et al, 2003).

3.5.1.FH Tapentadol

1) Interaction Effect: increased risk of serotonin syndrome (hypertension, hyperthermia, myoclonus, mental status changes)
2) Summary: Concurrent use of tapentadol and a selective serotonin reuptake inhibitor (SSRI) may result in serotonin syndrome, which may be life-threatening. Symptoms of serotonin syndrome may include restlessness, hallucinations, loss of coordination, fast heart beat, rapid changes in blood pressure, increased body temperature, overreactive reflexes, nausea, vomiting, and diarrhea (Prod 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 condition called serotonin syndrome. If these agents are used together, monitor the patient closely for symptoms of serotonin syndrome (restlessness, hyperthermia, hyperreflexia, incoordination), especially during treatment initiation and dose increases (Prod Info tapentadol immediate release oral tablets, 2008).
7) Probable Mechanism: additive serotonergic effect

3.5.1.FI 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 cohort studies have shown that the combined use of SSRIs and NSAIDs has been associated with an increased risk of bleeding. Bleeding events have included epistaxis, ecchymosis, hematoma, petechiae, and life-threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension, 2008) (Prod Info Lexapro(TM), 2003; Dalton et al, 2003a; Prod Info CELEXA (R) oral tablet, solution, 2005).
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 increased bleeding.
7) Probable Mechanism: unknown
8) Literature Reports

a) SSRIs increase the risk of upper gastrointestinal bleeding and this effect is potentiated by concurrent use of NSAIDs or low-dose aspirin. Hospitalizations for upper gastrointestinal bleeding were searched among 26,005 users of antidepressant medications and compared with the number of hospitalizations in those patients who did not receive prescriptions for antidepressants. The amount of upper GI bleeding episodes was 3.6 times more than expected (95% confidence interval, 2.7 to 4.7). Combined use of an SSRI and NSAIDs or low-dose aspirin increased the risk to 12.2 (95% confidence interval, 7.1 to 19.5) and 5.2 (95% confidence interval, 3.2 to 8), respectively. The findings of this study demonstrate an increased risk of upper GI bleeding during the use of SSRIs. Combined use of SSRIs and NSAIDs or low-dose aspirin increased the risk even further (Dalton et al, 2003).
b) Coadministration of ketorolac with psychoactive drugs (such as fluoxetine) has been associated with hallucinations in some patients (Prod Info TORADOL(R) oral tablets, 2007).

3.5.1.FJ 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 cohort studies have shown that the combined use of SSRIs and NSAIDs has been associated with an increased risk of bleeding. Bleeding events have included epistaxis, ecchymosis, hematoma, petechiae, and life-threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension, 2008) (Prod Info Lexapro(TM), 2003; Dalton et al, 2003a; Prod Info CELEXA (R) oral tablet, solution, 2005).
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 increased bleeding.
7) Probable Mechanism: unknown
8) Literature Reports

a) SSRIs increase the risk of upper gastrointestinal bleeding and this effect is potentiated by concurrent use of NSAIDs or low-dose aspirin. Hospitalizations for upper gastrointestinal bleeding were searched among 26,005 users of antidepressant medications and compared with the number of hospitalizations in those patients who did not receive prescriptions for antidepressants. The amount of upper GI bleeding episodes was 3.6 times more than expected (95% confidence interval, 2.7 to 4.7). Combined use of an SSRI and NSAIDs or low-dose aspirin increased the risk to 12.2 (95% confidence interval, 7.1 to 19.5) and 5.2 (95% confidence interval, 3.2 to 8), respectively. The findings of this study demonstrate an increased risk of upper GI bleeding during the use of SSRIs. Combined use of SSRIs and NSAIDs or low-dose aspirin increased the risk even further (Dalton et al, 2003).
b) Coadministration of ketorolac with psychoactive drugs (such as fluoxetine) has been associated with hallucinations in some patients (Prod Info TORADOL(R) oral tablets, 2007).

3.5.1.FK Tetrabenazine

1) Interaction Effect: increased exposure to tetrabenazine
2) Summary: Caution should be used when administering a strong CYP2D6 inhibitor (eg, paroxetine) to a patient taking tetrabenazine (a CYP2D6 substrate), and the daily dose of tetrabenazine should be halved if paroxetine and tetrabenazine are used concomitantly. Following a single 50 mg dose of tetrabenazine given after 10 days of daily administration of paroxetine 20 mg, an increase in tetrabenazine exposure was observed in 25 healthy volunteers. When compared with tetrabenazine alone, coadministration with paroxetine caused an approximately 30% increase in Cmax and a 3-fold increase in the AUC of the alpha-HTBZ metabolite of tetrabenazine. Subjects given paroxetine prior to tetrabenazine alone experienced a 2.4-fold increase in Cmax and a 9-fold increase in the AUC of the beta-HTBZ metabolite of tetrabenazine. The elimination half-life for both metabolites was approximately 14 hours when tetrabenazine was coadministered with paroxetine (Prod Info XENAZINE(R) oral tablets, 2008).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: Use caution when prescribing paroxetine to patients who take tetrabenazine. Patients who are already receiving a stable dose of tetrabenazine should have their daily dose of tetrabenazine decreased by half if coadministration with paroxetine is necessary. Concomitant use of paroxetine and tetrabenazine may cause elevated tetrabenazine levels. Monitor for increased tetrabenazine side effects such as somnolence, fatigue, insomnia, depression, anxiety, akathisia, and nausea (Prod Info XENAZINE(R) oral tablets, 2008).
7) Probable Mechanism: inhibition of CYP2D6-mediated tetrabenazine metabolism by paroxetine

3.5.1.FL Theophylline

1) Interaction Effect: an increased risk of theophylline toxicity
2) Summary: There have been isolated reports of increased theophylline levels during coadministration with paroxetine. Until further study is conducted, monitoring of the theophylline level is recommended when paroxetine therapy is added, changed, or discontinued (Prod Info Paxil CR(TM), 2003o).
3) Severity: moderate
4) Onset: delayed

5) Substantiation: theoretical
6) Clinical Management: Monitor theophylline levels if paroxetine and theophylline are coadministered.
7) Probable Mechanism: unknown

3.5.1.FM Thioridazine

1) Interaction Effect: an increased risk of thioridazine toxicity, cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Paroxetine inhibits the metabolism of thioridazine, possibly through the inhibition of cytochrome P450 2D6 (CYP2D6) resulting in toxicity. The resulting elevated levels of thioridazine would be expected to enhance the prolongation of the QT interval and may increase the risk of serious, potentially fatal, cardiac arrhythmias, such as torsade de pointes-type arrhythmias (Prod Info Paxil(R), 2003b; Prod Info Mellaril(R), 2000a).
3) Severity: contraindicated
4) Onset: rapid
5) Substantiation: probable
6) Clinical Management: Due to the potential for significant, possibly life-threatening, proarrhythmic effects, concurrent administration of thioridazine and paroxetine is contraindicated.
7) Probable Mechanism: inhibition of cytochrome P450 2D6-mediated thioridazine metabolism
8) Literature Reports
a) The metabolism of thioridazine is inhibited by drugs such as paroxetine due to reduced cytochrome P450 2D6 isozyme activity. The elevated levels of thioridazine would be expected to enhance the prolongation of the QTc interval associated with thioridazine. This, in turn, may increase the risk of serious, potentially fatal, cardiac arrhythmias, such as torsade de pointes-type arrhythmias (Prod Info Mellaril(R), 2000).

3.5.1.FN 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 cohort studies have shown that the combined use of SSRIs and NSAIDs has been associated with an increased risk of bleeding. Bleeding events have included epistaxis, ecchymosis, hematoma, petechiae, and life-threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension, 2008) (Prod Info Lexapro(TM), 2003; Dalton et al, 2003a; Prod Info CELEXA (R) oral tablet, solution, 2005).
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 increased bleeding.
7) Probable Mechanism: unknown
8) Literature Reports
a) SSRIs increase the risk of upper gastrointestinal bleeding and this effect is potentiated by concurrent use of NSAIDs or low-dose aspirin. Hospitalizations for upper gastrointestinal bleeding were searched among 26,005 users of antidepressant medications and compared with the number of hospitalizations in those patients who did not receive prescriptions for antidepressants. The amount of upper GI bleeding episodes was 3.6 times more than expected (95% confidence interval, 2.7 to 4.7). Combined use of an SSRI and NSAIDs or low-dose aspirin increased the risk to 12.2 (95% confidence interval, 7.1 to 19.5) and 5.2 (95% confidence interval, 3.2 to 8), respectively. The findings of this study demonstrate an increased risk of upper GI bleeding during the use of SSRIs. Combined use of SSRIs and NSAIDs or low-dose aspirin increased the risk even further (Dalton et al, 2003).
b) Coadministration of ketorolac with psychoactive drugs (such as fluoxetine) has been associated with hallucinations in some patients (Prod Info TORADOL(R) oral tablets, 2007).

3.5.1.FO 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 cohort studies have shown that the combined use of SSRIs and antiplatelet agents has been associated with an increased risk of bleeding. Bleeding events reported have included epistaxis, ecchymosis, hematoma, petechiae, and life-threatening hemorrhages (Prod Info PAXIL(R) oral 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 signs of increased bleeding (Prod Info PAXIL(R) oral tablets, suspension, 2008; Prod Info PROZAC(R) oral capsules, delayed-release capsules, solution, 2008)
7) Probable Mechanism: unknown

3.5.1.FP 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 cohort studies have shown that the combined use of SSRIs and anticoagulants has been associated with an increased risk of bleeding (Wallerstedt et al, 2009; Schalekamp et al, 2008; Prod Info PAXIL(R) oral tablets, suspension, 2008). Bleeding events reported have included epistaxis, ecchymosis, hematoma, petechiae, and life-threatening hemorrhages. Altered anticoagulant effects (including increased bleeding) have been reported with the coadministration of SSRIs with warfarin (Schalekamp et al, 2008; Prod Info PAXIL(R) oral tablets, suspension, 2008).
3) Severity: major
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: When paroxetine and an anticoagulant are given concurrently, monitor patients for signs of increased bleeding. Patients who are taking warfarin should be monitored closely for altered anticoagulant effects, including increased bleeding, when paroxetine therapy is initiated or discontinued (Prod Info PAXIL(R) oral tablets, suspension, 2008).
7) Probable Mechanism: unknown
8) Literature Reports
a) According to a retrospective cohort study (n=234), there was an increased risk of clinically relevant bleeding (hospital admission due to bleeding) in patients receiving warfarin for atrial fibrillation during concomitant SSRI therapy or within 2 weeks following SSRI therapy termination. Patients with a mean age of 72 +/- 7 years receiving warfarin plus SSRI (n=117) were matched with randomly selected patients who received warfarin only (n=117). SSRI included fluoxetine, citalopram, paroxetine, sertraline, fluvoxamine, or escitalopram. Nine patients experienced 11 bleeding episodes during 213.9 treatment years in the warfarin plus SSRI group, and 10 patients experienced 14 bleedings during 586.4 treatment years in the warfarin-only group. The corresponding total incidences of bleedings were 51.4 and 23.9 per 1000 treatment years, respectively. The hazard ratio for first bleedings during treatment with warfarin plus SSRI was 3.49 (95% CI; 1.37 to 8.91, p=0.009) compared with warfarin only. The SSRI implicated in patients experiencing bleeding at the time of concomitant administration were sertraline or citalopram. The addition of an SSRI was not associated with a change in warfarin dose or INR (p=0.48 and p=0.31 respectively). The results of the study may be limited by earlier bleeding events, unknown patient adherence, and exclusion of clopidogrel, dipyridamol, corticosteroids and anticoagulants other than warfarin in the model (Wallerstedt et al, 2009).
b) A population-based, case-controlled study of new coumarin users (acenocoumarol and phenprocoumon) with concomitant selective serotonin reuptake inhibitors (SSRIs) resulted in an increased risk of hospitalization due to nongastrointestinal bleeding. Using national pharmacy and hospitalization records, Netherlands researchers identified 1848 cases that were admitted for abnormal bleeding and compared them with 5818 control subjects also taking coumarins. Median duration of treatment in patients was 220 days (range, 1 to 4690 days). Patients on SSRIs showed greater risk for hospitalization for nongastrointestinal bleeding (adjusted odds ratio (OR) 1.7, 95% confidence interval (CI), 1.1 to 2.5), however, the rate of gastrointestinal bleeding (adjusted OR 0.8, 95% CI, 0.4 to 1.5) was not significantly different (Schalekamp et al, 2008).
c) Preliminary data suggest that there may be a pharmacodynamic interaction (that causes an increased bleeding diathesis with unaltered prothrombin time) between paroxetine and warfarin. The concomitant use of paroxetine and warfarin should be undertaken with caution (Prod Info PAXIL(R) oral tablets, suspension, 2008).
d) In a multiple-dose study, several days of combined therapy with warfarin and paroxetine resulted in mild but clinically significant bleeding in 5 of 27 subjects. This effect occurred in the absence of a significant enhancement in warfarin-induced hypoprothrombinemia or changes in either paroxetine or warfarin disposition (Bannister et al, 1989b).

3.5.1.FQ Tipranavir
1) Interaction Effect: increased paroxetine plasma concentrations
2) Summary: Although the drug interaction between paroxetine and tipranavir/ritonavir has not been studied, coadministration of paroxetine with tipranavir/ritonavir may result in increased paroxetine plasma concentrations. Paroxetine doses may need to be adjusted when tipranavir/ritonavir therapy is initiated (Prod Info APTIVUS(R) oral capsules, solution, 2008).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Concurrent administration of paroxetine and tipranavir/ritonavir may increase paroxetine plasma concentrations. Use caution when these agents are coadministered and consider adjusting the paroxetine dose as needed upon initiation of tipranavir/ritonavir (Prod Info APTIVUS(R) oral capsules, solution, 2008).
7) Probable Mechanism: unknown

3.5.1.FR 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 cohort studies have shown that the combined use of SSRIs and antiplatelet agents has been associated

with an increased risk of bleeding. Bleeding events reported have included epistaxis, ecchymosis, hematoma, petechiae, and life-threatening hemorrhages (Prod Info PAXIL(R) oral 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 signs of increased bleeding (Prod Info PAXIL(R) oral tablets, suspension, 2008; Prod Info PROZAC(R) oral capsules, delayed-release capsules, solution, 2008)
7) Probable Mechanism: unknown

3.5.1.FS 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 cohort studies have shown that the combined use of SSRIs and NSAIDs has been associated with an increased risk of bleeding. Bleeding events have included epistaxis, ecchymosis, hematoma, petechiae, and life-threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension, 2008) (Prod Info Lexapro(TM), 2003; Dalton et al, 2003a; Prod Info CELEXA (R) oral tablet, solution, 2005).
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 increased bleeding.
7) Probable Mechanism: unknown
8) Literature Reports
a) SSRIs increase the risk of upper gastrointestinal bleeding and this effect is potentiated by concurrent use of NSAIDs or low-dose aspirin. Hospitalizations for upper gastrointestinal bleeding were searched among 26,005 users of antidepressant medications and compared with the number of hospitalizations in those patients who did not receive prescriptions for antidepressants. The amount of upper GI bleeding episodes was 3.6 times more than expected (95% confidence interval, 2.7 to 4.7). Combined use of an SSRI and NSAIDs or low-dose aspirin increased the risk to 12.2 (95% confidence interval, 7.1 to 19.5) and 5.2 (95% confidence interval, 3.2 to 8), respectively. The findings of this study demonstrate an increased risk of upper GI bleeding during the use of SSRIs. Combined use of SSRIs and NSAIDs or low-dose aspirin increased the risk even further (Dalton et al, 2003).
b) Coadministration of ketorolac with psychoactive drugs (such as fluoxetine) has been associated with hallucinations in some patients (Prod Info TORADOL(R) oral tablets, 2007).

3.5.1.FT Toloxatone
1) Interaction Effect: CNS toxicity or serotonin syndrome (hypertension, hyperthermia, myoclonus, mental status changes)
2) Summary: Concurrent administration or overlapping therapy with paroxetine and a monoamine oxidase (MAO) inhibitor may result in CNS toxicity or serotonin syndrome, a hyperserotonergic state characterized by symptoms such as restlessness, myoclonus, changes in mental status, hyperreflexia, diaphoresis, shivering, and tremor. Serious, even fatal, reactions have been reported with concomitant use of serotonin specific reuptake inhibitors and MAO inhibitors (Prod Info Paxil(R), 1999b; Lappin & Auchincloss, 1994e; Graber et al, 1994e; Suchowersky & de Vries, 1990e). As a reversible and selective monoamine oxidase inhibitor, toloxatone may not potentiate the effects of selective serotonin reuptake inhibitors to the same frequency, extent, and duration observed with other MAOIs. However, until further studies confirm the safety and efficacy of this combined therapy, concomitant use is contraindicated.
3) Severity: contraindicated
4) Onset: rapid
5) Substantiation: probable
6) Clinical Management: Concurrent use of paroxetine and a MAO inhibitor is contraindicated. Wait at least two weeks after discontinuing a MAO inhibitor before initiating paroxetine, and at least two weeks after discontinuing paroxetine 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 serotonin syndrome (Sternbach, 1991g). Serotonin syndrome is a condition of serotonergic hyperstimulation and manifests as restlessness, myoclonus, changes in mental status, hyperreflexia, diaphoresis, shivering, and tremor. If the syndrome is not recognized and correctly treated, fatality can result.
b) A 26-year old woman who had been taking isocarboxazid for eight weeks stopped taking the drug for 11 days before beginning therapy with sertraline. After a single 100 mg sertraline dose, the patient became restless and developed leg twitches. The patients was later admitted to the emergency room with diaphoresis, tachycardia, hyperreflexia, and various neuromuscular disturbances. After treatment with diazepam and propranolol the patient did not improve. The patient was then given two 4 mg doses of cyproheptadine an hour apart, with notable improvement 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 added to a regimen of lithium, phenelzine, thioridazine, and doxepin. Three hours after taking the first sertraline dose, the patient was found in a semicomatose state, with elevated body temperature, increased pulse, increased respiration rate, and a blood pressure of 140/110 mm Hg. After transportation to the hospital, the patient was misdiagnosed as having neuroleptic malignant syndrome (NMS) which was later changed to serotonin syndrome due to a reaction between sertraline and phenelzine. The authors suggest that monoamine oxidase inhibitor (MAOI) therapy should be discontinued for at least two weeks before initiation of therapy with a selective serotonin reuptake inhibitor (SSRI) and that before starting a MAOI, SSRI therapy should be discontinued for at least five half-lives of the parent drug and any active metabolites (Graber et al, 1994d).

d) Two cases reports suggested a possible interaction between fluoxetine and selegiline (Suchowersky & de Vries, 1990d). One case involved a first episode of mania being observed approximately one month after adding selegiline to fluoxetine. The patient improved two months after both drugs were discontinued, and no further details were provided. The second case involved diaphoresis, vasoconstriction, and cyanosis of the hands which occurred in close temporal relationship to adding fluoxetine to selegiline. Both drugs were discontinued, with relatively quick resolution of symptoms. Rechallenge with fluoxetine alone occurred without incident.

3.5.1.FU Tramadol

1) Interaction Effect: an increased risk of seizures and serotonin syndrome (hypertension, hyperthermia, myoclonus, mental status changes); a decrease in the analgesic effect of tramadol

2) Summary: Seizures and serotonin syndrome have been reported in patients using tramadol. Some medications, including paroxetine, are known to reduce the seizure threshold. The risk of seizures and serotonin syndrome may be enhanced when paroxetine and tramadol therapy are combined (Prod Info Ultram(R), 2004). Paroxetine also inhibits the metabolism of tramadol to its active metabolite M1. This reduces the analgesic effect of tramadol (Laugesen et al, 2005).

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 concomitant paroxetine therapy. If possible, avoid this combination, especially in patients with underlying conditions that might predispose to seizures. Observe the patient closely for signs and symptoms of serotonin syndrome, as well as decreased analgesic effect of tramadol.

7) Probable Mechanism: increased concentration of serotonin in the nervous system and periphery; inhibition of the CYP2D6 -mediated formation of tramadol active metabolites (-)-M1 and (+)-M1 by paroxetine

8) Literature Reports

a) The coadministration of paroxetine with tramadol reduced the analgesic effect of tramadol. In this study, 16 healthy subjects participated in a randomized, double blind, placebo-controlled, 4 way crossover design study to evaluate the effect of paroxetine on the analgesic effect of tramadol. Subjects received treatment with paroxetine 20 mg or equivalent placebo on the 3 days prior to the study days. This was followed by a single oral dose of tramadol 150 mg or the equivalent placebo. The washout period was at least 2 weeks between each treatment. All the subjects were included in one of the following treatment groups: placebo/placebo, placebo/tramadol, paroxetine/placebo, and paroxetine/tramadol. Nociceptive tests were conducted and included pressure pain tolerance threshold, electrical sural nerve stimulation, and the cold pressor test. Pretreatment with paroxetine resulted in a drop in the analgesic effect of tramadol in the cold pressor test mean pain measure (P=0.036) and a change in the discomfort modality (P=0.056). Paroxetine pretreatment did not cause a decrease in the analgesic effect of tramadol that was statistically significant in the other pain tests. The paroxetine/tramadol treatment combination maintained a statistically significant analgesic effect in the pressure pain tolerance threshold (P=0.01) and the single electrical stimulation tolerance threshold (P=0.15) compared with the placebo/placebo treatment group. In comparison with the placebo/tramadol group, the (+)- and (-)- tramadol AUC increased 37% and 32% respectively when paroxetine was administered with tramadol and the AUC of (+)- and (-)-M1 active metabolite decreased 67% and 40% respectively (Laugesen et al, 2005).

3.5.1.FV Tranylcypromine

1) Interaction Effect: CNS toxicity or serotonin syndrome (hypertension, hyperthermia, myoclonus, mental status changes)

2) Summary: Concurrent administration or overlapping therapy with paroxetine and a monoamine oxidase (MAO) inhibitor may result in CNS toxicity or serotonin syndrome, a hyperserotonergic state characterized by symptoms such as restlessness, myoclonus, changes in mental status, hyperreflexia, diaphoresis, shivering, and tremor. Serious, even fatal, reactions have been reported with concomitant use of serotonin specific reuptake inhibitors and MAO inhibitors (Prod Info Paxil(R), 2003; Lappin & Auchincloss, 1994a; Graber et al, 1994a; Suchowersky & de Vries, 1990a). Concomitant use is contraindicated.

3) Severity: contraindicated

4) Onset: rapid

5) Substantiation: theoretical
6) Clinical Management: Concurrent use of selective serotonin reuptake inhibitors, such as paroxetine, and tranylcypromine is contraindicated. Wait at least two weeks after discontinuing an MAO inhibitor before initiating paroxetine, and at least two weeks after discontinuing paroxetine before initiating therapy with an MAOI.
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 serotonin syndrome (Sternbach, 1991a). Serotonin syndrome is a condition of serotonergic hyperstimulation and manifests as restlessness, myoclonus, changes in mental status, hyperreflexia, diaphoresis, shivering, and tremor. If the syndrome is not recognized and correctly treated, fatality can result.
b) A 26-year old woman who had been taking isocarboxazid for eight weeks stopped taking the drug for 11 days before beginning therapy with sertraline. After a single 100 mg sertraline dose, the patient became restless and developed leg twitches. The patient was later admitted to the emergency room with diaphoresis, tachycardia, hyperreflexia, and various neuromuscular disturbances. After treatment with diazepam and propranolol the patient did not improve. The patient was then given two 4 mg doses of cyproheptadine an hour apart, with notable improvement in symptoms after the second dose (Lappin & Auchincloss, 1994).
c) Sertraline 100 mg twice daily was added to a regimen of lithium, phenelzine, thioridazine, and doxepin in a 61-year old woman (Graber et al, 1994). Three hours after taking the first sertraline dose, the patient was found in a semicomatose state, with elevated body temperature, increased pulse, increased respiration rate, and a blood pressure of 140/110 mm Hg. After transportation to the hospital, the patient was misdiagnosed as having neuroleptic malignant syndrome (NMS) which was later changed to serotonin syndrome due to a reaction between sertraline and phenelzine. The authors suggest that monoamine oxidase inhibitor (MAOI) therapy should be discontinued for at least two weeks before initiation of therapy with a selective serotonin reuptake inhibitor (SSRI) and that before starting a MAOI, SSRI therapy should be discontinued for at least five half-lives of the parent drug and any active metabolites.
d) Two cases suggestive of an interaction between fluoxetine and selegiline were reported (Suchowersky & de Vries, 1990). One case involved a first episode of mania being observed approximately one month after adding selegiline to fluoxetine. The patient improved two months after both drugs were discontinued, and no further details were provided. The second case involved diaphoresis, vasoconstriction, and cyanosis of the hands which occurred in close temporal relationship to adding fluoxetine to selegiline. Both drugs were discontinued, with relatively quick resolution of symptoms. Rechallenge with fluoxetine alone occurred without incident.

3.5.1.FW Trazodone
1) Interaction Effect: serotonin syndrome (hypertension, hyperthermia, myoclonus, mental status changes)
2) Summary: There have been several reports of serotonin syndrome due to interactions between selective serotonin reuptake inhibitors and antidepressants, including one case report due to paroxetine and trazodone coadministration (George & Godleski, 1996a; Reeves & Bullen, 1995a; Alderman & Lee, 1996). Serotonin syndrome is a rare but potentially fatal condition of serotonergic hyperstimulation characterized by hypertension, hyperthermia, myoclonus and changes in mental status (Sternbach, 1991d). Further clinical studies or case reports are necessary to determine the incidence and implications of serotonin syndrome associated with this drug combination.
3) Severity: major
4) Onset: rapid
5) Substantiation: probable
6) Clinical Management: Concurrent use of paroxetine and trazodone should be undertaken with caution. Monitor patients for signs and symptoms of serotonin syndrome (hypertension, hyperthermia, myoclonus, mental status changes).
7) Probable Mechanism: additive serotonergic effects
8) Literature Reports
a) Serotonin syndrome was reported in a 29-year old woman taking trazodone and paroxetine. The patient was treated with trazodone 200 mg daily at bedtime for approximately three months for depression and insomnia. The patient's depressive symptoms were unresponsive to this treatment, so trazodone was subsequently decreased to 50 mg daily at bedtime for two weeks before paroxetine 20 mg every morning was added. Within 24 hours after the first dose of paroxetine, the patient became agitated, confused, shaky, and diaphoretic. Upon examination, the patient had impaired concentration, intermittent myoclonus in all extremities, hyperreflexia, tremor, and diaphoresis. After discontinuation of antidepressant medications, the patient's symptoms resolved (Reeves & Bullen, 1995).
b) A 44-year old man developed symptoms characteristic of serotonin syndrome due to a possible interaction between fluoxetine and trazodone. The patient had been taking fluoxetine 40 mg daily and trazodone 100 mg daily for approximately two months before symptoms occurred. The patient experienced disorientation, tremor, diaphoresis, and anxiety, followed by uncontrollable shaking and loss of consciousness. After the patient was treated with cyproheptadine 4 mg orally, symptoms resolved over the next 30 minutes. Trazodone was discontinued and the patient continued to take

fluoxetine 40 mg daily without further complications (George & Godleski, 1996).

3.5.1.FX Trimipramine

1) Interaction Effect: trimipramine toxicity (dry mouth, sedation, urinary retention)
2) Summary: Paroxetine coadministered with desipramine or imipramine produced higher serum concentrations of the tricyclic antidepressant (TCA) in some patients (Hartter et al, 1994e; Brosen et al, 1993m). Although not reported for trimipramine, a similar interaction could occur. Paroxetine's effect on TCAs may resemble that of fluoxetine (another selective serotonin reuptake inhibitor), which is known to inhibit TCA metabolism (Aranow et al, 1989e; Vaughan, 1988e; Goodnick, 1989e). With coadministration, monitor patients for trimipramine toxicity. Trimipramine doses may need to be reduced.
3) Severity: moderate
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: When paroxetine is coadministered with trimipramine, monitor patients for signs and symptoms of trimipramine toxicity (dry mouth, sedation, urinary retention, blurred vision). Trimipramine doses may need to be reduced.
7) Probable Mechanism: decreased trimipramine metabolism
8) Literature Reports
a) The effect of paroxetine on desipramine metabolism was studied in 9 extensive metabolizers (EM) and 8 poor metabolizers (PM) of desipramine. Subjects took a single oral dose of desipramine before starting paroxetine and a second dose after 11 days of paroxetine use. After the addition of paroxetine, EMs experienced a 5-fold decrease in clearance of desipramine, indicating that paroxetine inhibits oxidation reactions catalyzed by CYP2D6. PMs had a slight increase in clearance of desipramine with paroxetine. With concurrent administration of desipramine and paroxetine, interaction of the two drugs may result in a need for dosage adjustments, especially in extensive metabolizers of desipramine (Brosen et al, 1993l).

3.5.1.FY Tryptophan

1) Interaction Effect: serotonin syndrome (hypertension, hyperthermia, myoclonus, mental status changes)
2) Summary: Adverse effects (headache, nausea, sweating, dizziness) have been reported when tryptophan was given concurrently to patients using paroxetine (Prod Info Paxil CR(TM), 2004a). Tryptophan can be metabolized to serotonin (Boyer & Blumhardt, 1992b), and paroxetine, a selective serotonin reuptake inhibitor, acts to increase available serotonin (Caley & Weber, 1993a). It is possible that combining these two serotonin-enhancing agents could result in excessive serotonin leading to a condition known as serotonin syndrome. Effects associated with the serotonin syndrome include confusion, restlessness, mental status changes, tremor, diaphoresis, hypertension, myoclonus, shivering, and hyperreflexia. Concomitant administration of the SSRI fluoxetine with tryptophan was reported to cause signs and symptoms associated with serotonin syndrome (Steiner & Fontaine, 1986).
3) Severity: major
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: Coadministration of tryptophan and paroxetine is not recommended by the manufacturer of paroxetine. Should tryptophan and paroxetine be given concomitantly, monitor patient response and watch for signs of excessive serotonergic activity. It may be necessary to reduce doses of either agent.
7) Probable Mechanism: additive adverse effects

3.5.1.FZ 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 cohort studies have shown that the combined use of SSRIs and NSAIDs has been associated with an increased risk of bleeding. Bleeding events have included epistaxis, ecchymosis, hematoma, petechiae, and life-threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension, 2008) (Prod Info Lexapro(TM), 2003; Dalton et al, 2003a; Prod Info CELEXA (R) oral tablet, solution, 2005).
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 increased bleeding.
7) Probable Mechanism: unknown
8) Literature Reports
a) SSRIs increase the risk of upper gastrointestinal bleeding and this effect is potentiated by concurrent use of NSAIDs or low-dose aspirin. Hospitalizations for upper gastrointestinal bleeding were searched among 26,005 users of antidepressant medications and compared with the number of hospitalizations in those patients who did not receive prescriptions for antidepressants. The amount of upper GI bleeding episodes was 3.6 times more than expected (95% confidence interval, 2.7 to 4.7). Combined use of an SSRI and NSAIDs or low-dose aspirin increased the risk to 12.2 (95% confidence interval, 7.1 to 19.5) and 5.2 (95% confidence interval, 3.2 to 8), respectively. The findings of this study demonstrate

an increased risk of upper GI bleeding during the use of SSRIs. Combined use of SSRIs and NSAIDs or low-dose aspirin increased the risk even further (Dalton et al, 2003).
b) Coadministration of ketorolac with psychoactive drugs (such as fluoxetine) has been associated with hallucinations in some patients (Prod Info TORADOL(R) oral tablets, 2007).

3.5.1.GA 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 cohort studies have shown that the combined use of SSRIs and anticoagulants has been associated with an increased risk of bleeding (Wallerstedt et al, 2009; Schalekamp et al, 2008; Prod Info PAXIL(R) oral tablets, suspension, 2008). Bleeding events reported have included epistaxis, ecchymosis, hematoma, petechiae, and life-threatening hemorrhages. Altered anticoagulant effects (including increased bleeding) have been reported with the coadministration of SSRIs with warfarin (Schalekamp et al, 2008; Prod Info PAXIL(R) oral tablets, suspension, 2008).
3) Severity: major
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: When paroxetine and an anticoagulant are given concurrently, monitor patients for signs of increased bleeding. Patients who are taking warfarin should be monitored closely for altered anticoagulant effects, including increased bleeding, when paroxetine therapy is initiated or discontinued (Prod Info PAXIL(R) oral tablets, suspension, 2008).
7) Probable Mechanism: unknown
8) Literature Reports
a) According to a retrospective cohort study (n=234), there was an increased risk of clinically relevant bleeding (hospital admission due to bleeding) in patients receiving warfarin for atrial fibrillation during concomitant SSRI therapy or within 2 weeks following SSRI therapy termination. Patients with a mean age of 72 +/- 7 years receiving warfarin plus SSRI (n=117) were matched with randomly selected patients who received warfarin only (n=117). SSRI included fluoxetine, citalopram, paroxetine, sertraline, fluvoxamine, or escitalopram. Nine patients experienced 11 bleeding episodes during 213.9 treatment years in the warfarin plus SSRI group, and 10 patients experienced 14 bleedings during 586.4 treatment years in the warfarin-only group. The corresponding total incidences of bleedings were 51.4 and 23.9 per 1000 treatment years, respectively. The hazard ratio for first bleedings during treatment with warfarin plus SSRI was 3.49 (95% CI; 1.37 to 8.91, p=0.009) compared with warfarin only. The SSRI implicated in patients experiencing bleeding at the time of concomitant administration were sertraline or citalopram. The addition of an SSRI was not associated with a change in warfarin dose or INR (p=0.48 and p=0.31 respectively). The results of the study may be limited by earlier bleeding events, unknown patient adherence, and exclusion of clopidogrel, dipyridamol, corticosteroids and anticoagulants other than warfarin in the model (Wallerstedt et al, 2009).
b) A population-based, case-controlled study of new coumarin users (acenocoumarol and phenprocoumon) with concomitant selective serotonin reuptake inhibitors (SSRIs) resulted in an increased risk of hospitalization due to nongastrointestinal bleeding. Using national pharmacy and hospitalization records, Netherlands researchers identified 1848 cases that were admitted for abnormal bleeding and compared them with 5818 control subjects also taking coumarins. Median duration of treatment in patients was 220 days (range, 1 to 4690 days). Patients on SSRIs showed greater risk for hospitalization for nongastrointestinal bleeding (adjusted odds ratio (OR) 1.7, 95% confidence interval (CI), 1.1 to 2.5), however, the rate of gastrointestinal bleeding (adjusted OR 0.8, 95% CI, 0.4 to 1.5) was not significantly different (Schalekamp et al, 2008).
c) Preliminary data suggest that there may be a pharmacodynamic interaction (that causes an increased bleeding diathesis with unaltered prothrombin time) between paroxetine and warfarin. The concomitant use of paroxetine and warfarin should be undertaken with caution (Prod Info PAXIL(R) oral tablets, suspension, 2008).
d) In a multiple-dose study, several days of combined therapy with warfarin and paroxetine resulted in mild but clinically significant bleeding in 5 of 27 subjects. This effect occurred in the absence of a significant enhancement in warfarin-induced hypoprothrombinemia or changes in either paroxetine or warfarin disposition (Bannister et al, 1989b).

3.5.1.GB 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 cohort studies have shown that the combined use of SSRIs and antiplatelet agents has been associated with an increased risk of bleeding. Bleeding events reported have included epistaxis, ecchymosis, hematoma, petechiae, and life-threatening hemorrhages (Prod Info PAXIL(R) oral 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 signs of increased bleeding (Prod Info PAXIL(R) oral tablets, suspension, 2008; Prod Info PROZAC(R) oral

capsules, delayed-release capsules, solution, 2008)
7) Probable Mechanism: unknown

3.5.1.GC Zolmitriptan
1) Interaction Effect: an increased risk of serotonin syndrome
2) Summary: There have been case reports of weakness, hyperreflexia, and incoordination following concomitant use of sumatriptan, a 5-hydroxytryptamine-1 (5HT-1) agonist, and a serotonin specific reuptake inhibitor (SSRI) (Prod Info Imitrex(R), 1998a; Prod Info Zomig(TM), 1997). Because zolmitriptan is a 5HT 1B/1D agonist, a similar interaction between SSRIs and zolmitriptan may occur (Prod Info Zomig(TM), 1997). Concurrent use of zolmitriptan and an SSRI may result in serotonin syndrome which may be life-threatening. Symptoms of serotonin syndrome may include restlessness, hallucinations, loss of coordination, fast heart beat, rapid changes in blood pressure, increased body temperature, overreactive reflexes, nausea, vomiting, and diarrhea. Clinicians should be aware that triptans may be commonly used intermittently and that either the triptan or the SSRI may be prescribed by a different physician. Discuss the risks of serotonin syndrome with patients who are prescribed this combination and monitor them closely for symptoms of serotonin syndrome (US Food and Drug Administration, 2006).
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-threatening condition called serotonin syndrome. Be aware that triptans may be commonly used intermittently and that either the triptan or the SSRI may be prescribed by a different physician. If these agents are used together, discuss the risks of serotonin syndrome with the patient and monitor closely for symptoms of serotonin syndrome (restlessness, hyperthermia, hyperreflexia, incoordination).
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 fluoxetine 20 mg daily pretreatment in healthy volunteers. The effects of zolmitriptan on blood pressure were also not changed by fluoxetine therapy (Prod Info Zomig(R), 2002).

3.5.1.GD 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 cohort studies have shown that the combined use of SSRIs and NSAIDs has been associated with an increased risk of bleeding. Bleeding events have included epistaxis, ecchymosis, hematoma, petechiae, and life-threatening hemorrhages (Prod Info PAXIL(R) oral tablets, suspension, 2008) (Prod Info Lexapro(TM), 2003; Dalton et al, 2003a; Prod Info CELEXA (R) oral tablet, solution, 2005).
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 increased bleeding.
7) Probable Mechanism: unknown
8) Literature Reports
a) SSRIs increase the risk of upper gastrointestinal bleeding and this effect is potentiated by concurrent use of NSAIDs or low-dose aspirin. Hospitalizations for upper gastrointestinal bleeding were searched among 26,005 users of antidepressant medications and compared with the number of hospitalizations in those patients who did not receive prescriptions for antidepressants. The amount of upper GI bleeding episodes was 3.6 times more than expected (95% confidence interval, 2.7 to 4.7). Combined use of an SSRI and NSAIDs or low-dose aspirin increased the risk to 12.2 (95% confidence interval, 7.1 to 19.5) and 5.2 (95% confidence interval, 3.2 to 8), respectively. The findings of this study demonstrate an increased risk of upper GI bleeding during the use of SSRIs. Combined use of SSRIs and NSAIDs or low-dose aspirin increased the risk even further (Dalton et al, 2003).
b) Coadministration of ketorolac with psychoactive drugs (such as fluoxetine) has been associated with hallucinations in some patients (Prod Info TORADOL(R) oral tablets, 2007).

3.5.2 Drug-Food Combinations

3.5.2.A Ethanol
1) Interaction Effect: an increased risk of impairment of mental and motor skills
2) Summary: Paroxetine did not potentiate cognitive or psychomotor effects associated with ethanol consumption (Caley & Weber, 1993b). However, the manufacturer of paroxetine recommends that patients be advised to avoid alcohol while using paroxetine (Prod Info Paxil CR(TM), 2003p).
3) Severity: minor
4) Onset: rapid
5) Substantiation: theoretical
6) Clinical Management: Patients receiving paroxetine should be advised to avoid the use of alcohol.
7) Probable Mechanism: additive central nervous system effects

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) Paroxetine Hydrochloride

1) Therapeutic

a) Laboratory Parameters

1) Steady-state plasma levels of paroxetine have not correlated with clinical efficacy in depressed patients (Tasker et al, 1989b).

b) Physical Findings

1) A reduction in symptoms of depression is indicative of a therapeutic response to paroxetine.

2) Toxic

a) Laboratory Parameters

1) Hepatic and renal function tests, as well as blood pressure and pulse, should be monitored periodically throughout therapy.

2) Steady-state plasma levels of paroxetine have not correlated with toxic effects in depressed patients (Tasker et al, 1989b).

b) Physical Findings

1) Blood pressure and pulse should be monitored.

2) Monitor patients receiving antidepressants for worsening of depression, suicidality, or unusual changes in behavior, especially at the initiation of therapy or when the dose increases or decreases. Such monitoring should include at least weekly face-to-face contact with patients or their family members or caregivers during the initial 4 weeks of treatment, then visits every other week for the next 4 weeks, then at 12 weeks, and then as clinically indicated beyond 12 weeks. Families and caregivers should be advised of the need for close observation (i.e., daily observation) of patients and communication with the prescriber (Anon, 2004; Anon, 2004).

3) Patients who experience symptoms of anxiety, agitation, panic attacks, insomnia, irritability, hostility, impulsivity, akathisia, hypomania, or mania may be at an increased risk for worsening depression or suicidality. If these symptoms are observed, therapy should be re-evaluated and it may be necessary to discontinue medications when symptoms are severe, sudden in onset, or were not part of the patient's initial symptoms (Anon, 2004; Anon, 2004).

4) During discontinuation of treatment (especially when abrupt) patients should be monitored for withdrawal symptoms such as dysphoric mood, irritability, dizziness, agitation, sensory disturbances (i.e., paresthesias), anxiety, confusion, lethargy, headache, insomnia, emotional lability, and hypomania. If these symptoms are observed following a reduction of dose or upon cessation of treatment, the previously prescribed dose may be resumed and subsequently reduced at a more gradual rate (Prod Info Paxil(R), 2004; Prod Info Paxil CR(TM), 2004b).

4.2 Patient Instructions

A) Paroxetine (By mouth)

Paroxetine

Treats depression, obsessive-compulsive disorder (OCD), panic disorder, social anxiety disorder, premenstrual dysphoric disorder (PMDD), generalized anxiety disorder, and posttraumatic stress disorder (PTSD). This medicine is 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 paroxetine, or if you are pregnant. Do not use this medicine if you are also using pimozide (Orap®), thioridazine (Mellaril®), or have taken an MAO inhibitor (Marplan®, Eldepryl®, Parnate®, or Nardil®) within the past 2 weeks. This medicine is not for use in children.

How to Use This Medicine:
Liquid, Tablet, Long Acting Tablet

Your doctor will tell you how much of this medicine to use and how often. Do not use more medicine or use it more often than your doctor tells you to.
You may take this medicine with or without food. This medicine is usually taken in the morning.
Measure the oral liquid medicine with a marked measuring spoon, oral syringe, or medicine cup. Shake the bottle well before measuring each dose.
Swallow the tablet and extended-release tablet whole. Do not crush, break, or chew it. Do not use an extended-release tablet that is cracked or chipped.
This medicine should come with a Medication Guide. Read and follow these instructions carefully. Ask your doctor or pharmacist if you have any questions. Ask your pharmacist for the Medication Guide if you do not have one. Your doctor might ask you to sign some forms to show that you understand this information.

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 dose, wait until then to use the medicine and skip 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 you have finished your treatment. You will also 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, and herbal products.

Make sure your doctor knows if you are using cimetidine (Tagamet®), linezolid (Zyvox®), St. John's wort, sumatriptan (Imitrex®), theophylline (Theo-Dur®), tramadol (Ultram®), tryptophan, medicine for seizures (such as phenobarbital, phenytoin, Dilantin®, Luminal®, or Solfoton®), or any other medicine for depression (such as amitriptyline, desipramine, doxepin, fluoxetine, imipramine, lithium, nortriptyline, Aventyl®, Elavil®, Eskalith®, Lithane®, Lithobid®, Norpramin®, Pamelor®, Prozac®, Sinequan®, or Tofranil®). Tell your doctor if you use a blood thinner (such as warfarin or Coumadin®), diuretics or "water pills" (such as furosemide or Lasix®), or phenothiazine medicine (such as prochlorperazine, Compazine®, Mellaril®, Phenergan®, Thorazine®, or Trilafon®).
Make sure your doctor knows if you are also using atomoxetine (Strattera®), digoxin (Lanoxin®), ketoconazole (Nizoral®), procyclidine (Kemadrin®), risperidone (Risperdal®), or terfenadine (Seldane®). Also tell your doctor if you are using medicine for heart rhythm problems (such as encainide, flecainide, propafenone, quinidine, Enkaid®, Quinaglute®, Rythmol®, or Tambocor®), medicine to treat HIV or AIDS (such as fosamprenavir, ritonavir, Lexiva®, or Norvir®), or any pain or arthritis medicines (NSAIDs) such as aspirin, ibuprofen, naproxen, Advil®, Aleve®, Bextra®, Celebrex®, Ecotrin®, or Motrin®.
Do not drink alcohol while you are using this medicine.

Warnings While Using This Medicine:

Using this medicine while you are pregnant can harm your unborn baby. Use an effective form of birth control to keep from getting pregnant. If you think you have become pregnant while using the medicine, tell your doctor right away.
Make sure your doctor knows if you are breastfeeding, or if you have a recent heart attack, heart disease, kidney disease, liver disease, bleeding problems, epilepsy or seizures, narrow angle glaucoma, or a history of mania or drug abuse.
You may need to take this medicine for up to 4 weeks before you feel better. Keep using this medicine for the full treatment time. If you feel that the medicine is not working well, do not take more than your prescribed dose. Call your doctor for instructions.
For some children, teenagers, and young adults, this medicine can increase thoughts of suicide. Tell your doctor or your child's doctor right away if you or your child start to feel more depressed and have thoughts about hurting yourselves. Report any unusual thoughts or behaviors that trouble you or your child, especially if they are new or are getting worse quickly. Make sure the doctor knows if you or your child have trouble sleeping, get upset easily, have a big increase in energy, or start to act reckless. Also tell the doctor if you or your child have sudden or strong feelings, such as feeling nervous, angry, restless, violent, or scared. Let the doctor know if you, your child, or anyone in your family has bipolar disorder (manic-depressive) or has tried to commit suicide.
Do not stop using this medicine suddenly without asking your doctor. You may need to slowly decrease your dose before stopping it completely.
Make sure any doctor or dentist who treats you knows that you are using this medicine. This medicine may affect the results of certain medical tests.
This medicine may make you dizzy or drowsy. Avoid driving, using machines, or doing anything else that could be dangerous if you are not alert.

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

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, chest tightness, trouble breathing.
Anxiety, agitation, restlessness, or mood or mental changes.
Change in how much or how often you urinate, or problems in urination.
Changes in behavior, or thoughts of hurting yourself or others.
Confusion, weakness, and muscle twitching.
Extreme lightheadedness, or fainting.
Fast, slow, or uneven heartbeat.
Fever, chills, or sore throat.
Numbness, tingling, or burning pain in your hands, arms, legs, or feet.
Seizures or tremors.
Trouble sleeping or unusual dreams.
Unusual bleeding or bruising.

If you notice these less serious side effects, talk with your doctor:
Blurred vision.
Drowsiness or sleepiness.
Headache.
Loss of appetite.
Menstrual cramps.
Nausea, dry mouth, diarrhea, constipation, or upset stomach.
Problems with sex.
Sweating.
Tiredness.
Vaginal pain or discharge.

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) Paroxetine has received approval by the United States Food and Drug Administration for treating depression, generalized anxiety disorder, obsessive compulsive disorder, panic disorder, and social anxiety disorder. Paroxetine has also been evaluated in numerous other psychiatric disorders.

B) DEPRESSION

1) All of the selective serotonin reuptake inhibitors (SSRIs) are effective for treating depression although selected characteristics of each agent may offer greater benefit in some patients. Paroxetine does NOT have any major therapeutic benefits over other SSRIs; however, discontinuation symptoms may be troublesome in patients who stop taking paroxetine. Ultimately, the selection of an SSRI is dependent on clinical judgment and response of patients to previous therapy (Edwards & Anderson, 1999).

2) Paroxetine is a selective serotonin uptake inhibitor which has been effective as once daily therapy in the treatment of major depression. In comparative studies, paroxetine has been as effective as amitriptyline, clomipramine, imipramine, and mianserin. A more favorable adverse effect profile compared to tricyclic antidepressants has been observed in several studies. Paroxetine may have a faster onset of action than fluoxetine; however, both agents are equal in efficacy after six weeks of therapy.

3) Preliminary data suggest that a trial of a second serotonin reuptake inhibitor (SSRI) is a viable clinical alternative in depressed patients who have failed to respond to an adequate trial to the first SSRI used (Joffe et al, 1996). In a retrospective review of 55 patients who had failed to respond to at least five weeks of therapy with either fluoxetine, sertraline, fluvoxamine, or paroxetine (all at therapeutic dosages), 51% did respond to a trial of an alternative agent. The choice of the second agent was based on clinician preference; no difference between response rates of the different drugs was noted.

4.4 Mechanism of Action / Pharmacology

A) MECHANISM OF ACTION

1) Paroxetine is a phenylpiperidine antidepressant agent which selectively inhibits serotonin uptake (Magnussen et al, 1982; Hassan et al, 1985; Lassen, 1978). Similar to other selective inhibitors of serotonin uptake, paroxetine was developed as an alternative to tricyclic antidepressants which have effects on the reuptake of both serotonin and other neurotransmitters. More specific and more potent serotonin uptake inhibitors may result in more effective antidepressant therapy in the absence of adverse effects associated with norepinephrine uptake inhibition (Laursen et al, 1985; Raptopoulos et al, 1989a; Mertens & Pintens, 1988). Other selective serotonin reuptake inhibitors are fluoxetine, zimeldine, femoxetine, citalopram, and 2-nitro-imipramine (Mellerup et al, 1983).

2) In vitro and in vivo studies have demonstrated that paroxetine is a selective serotonin uptake inhibitor with minimal effects on uptake of norepinephrine (Lassen, 1974; Magnussen et al, 1982; Hassan et al, 1985). Potent

and long-lasting inhibition of serotonin uptake into platelets and synaptosomes, leading to depletion of blood serotonin, has been reported in man and animals, and potentiation of 5-hydroxytryptophan-induced central effects has been observed in mice (Mellerup et al, 1983; Lassen, 1978; Raptopoulos et al, 1989a; Magnussen et al, 1982). These effects are attributed to long-lasting binding of the drug to a serotonin uptake mechanism in neurons and platelets (Mellerup et al, 1983).

B) REVIEW ARTICLES

1) A comparison of selective serotonin reuptake inhibitors with a guide to selection is provided (Edwards & Anderson, 1999a).

2) Two reviews provide a discussion of the efficacy of selective serotonin reuptake inhibitors and other antidepressants for treatment of severe depression (Schatzberg, 1999; Hirschfeld, 1999).

3) The efficacy of antidepressants in reducing panic attack frequency, symptoms of depression, social avoidance, and overall impairments from panic disorder are addressed (den Boer, 1998).

4) A review article described the treatment of panic disorder, including the place of selective serotonin reuptake inhibitors for this disorder (DeVane, 1997).

5) Treatment of elderly patients with selective serotonin reuptake inhibitors is discussed with emphasis on improved tolerability compared to other antidepressants (Skerritt et al, 1997).

6) Drug-interactions of antidepressants are reviewed in German language (Zapotoczky & Simhandl, 1995).

4.5 Therapeutic Uses

4.5.A Paroxetine Hydrochloride

Bipolar disorder, depressed phase

Compulsive gambling

Diabetic neuropathy

Difficulty controlling emotions

Drug-induced depressive state

Fibromyalgia

Generalized anxiety disorder

Headache

Hot sweats

Insomnia

Kleptomania

Major depressive disorder

Myocardial infarction; Prophylaxis

Nocturnal sleep-related eating disorder

Obsessive-compulsive disorder

Panic disorder

Posttraumatic stress disorder

Premature ejaculation

Premenstrual dysphoric disorder

Pruritus, Non-dermatological

Schizophrenia, Negative symptoms

Social phobia

Somatization disorder

Trichotillomania

Vasovagal syncope

4.5.A.1 Bipolar disorder, depressed phase

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:

When given with lithium, no better than placebo unless serum lithium concentration is low

c) Adult:

1) Neither paroxetine nor imipramine was more effective than placebo in treating BIPOLAR DEPRESSION in patients stabilized on lithium if their serum lithium levels were above 0.8 milliequivalents per liter (meq/L). However, patients whose serum lithium concentration was less than 0.8 meq/L showed greater improvement with 8 weeks of antidepressant treatment than with placebo treatment (p=0.05 for paroxetine, p=0.04 for imipramine). In a double-blind study, patients were stratified according to serum lithium concentration and then randomized to receive paroxetine (n=35), imipramine (n=39), or placebo (n=43) for 10 weeks. Among all completers of the study, therapeutic response (Hamilton depression scale scores of 7 or less) was achieved by 56%, 48%, and 54% of patients receiving paroxetine, imipramine, and placebo, respectively. Adverse events accounted for study discontinuation in 1 patient in the paroxetine group (3%), 12 in the imipramine group (30%), and 5 in the placebo group (12%). No patient in the paroxetine group experienced induction to mania, whereas 3 patients treated with imipramine and 1 treated with placebo developed treatment-emergent mania (Nemeroff et al, 2001a).

4.5.A.2 Compulsive gambling

a) Overview

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

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:

Paroxetine was effective in the treatment of pathological gambling in patients without concomitant mood, anxiety, or substance use disorders.

c) Adult:

1) Paroxetine (mean dose 51.7 milligrams per day (mg/d)) was effective in the treatment of pathological gambling for patients without concomitant mood, anxiety, or substance use disorders. In this 8-week, double-blind, placebo- controlled study, 45 patients who fulfilled the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) criteria for pathological gambling and scored at least 5 on the South Oaks Gambling Screen (SOGS) were randomly assigned to either a paroxetine or placebo treatment group. For the paroxetine group, an initial dosage of 20 mg/d was administered. This dose could be gradually increased, in increments of 10 mg per week, to a maximum of 60 mg/d, based on tolerability and efficacy. Patients' clinical status was assessed weekly using the Clinical Global Impressions (CGI) scale, (including the Pathological Gambling CGI), and both the total score and gambling urge subscale score of the Gambling Symptom Assessment Scale (G-SAS). By the study endpoint, there was a significant difference between the treatment groups in the reduction of the mean G-SAS scores, with a 52% decrease in the paroxetine group compared to a 23% decrease in the placebo group. Assessment using the CGI scale also showed significant differences in the degree of improvement in the two treatment groups. In the paroxetine group, 47.8% were very much improved (score of 1), 13% were much improved (score of 2), and 13% had no change; in the placebo group, the values were 4.5%, 18.2%, and 27.3%, respectively. There was not a significant difference between the paroxetine and placebo groups until patients completed at least 6 weeks of treatment. The most

common side effects of paroxetine were nausea (26.1%), headache (17.4%), and sweating (17.4%). A key limitation of these results is that patients in this study are not representative of the larger population of patients with pathological gambling; most of the study participants were women (30 women, 15 men), and did not have comorbid mood, anxiety, and substance use disorders (Kim et al, 2002).

4.5.A.3 Diabetic neuropathy

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:

Paroxetine 10 to 60 milligrams per day (median 40 milligrams/day) was effective in relieving symptoms of diabetic neuropathy in a single-blind, dose-escalation study in 19 diabetic patients. Patients conducted daily self-ratings on a visual analog scale for the following symptoms: pain, paresthesia, dysesthesia, nightly aggravation, and sleep disturbances. The most commonly reported adverse effects were fatigue, sweating, and nausea (Sindrup et al, 1991).

4.5.A.4 Difficulty controlling emotions

a) Overview

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

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:

In 2 case reports, paroxetine 20 milligrams daily was effective for relieving pathological crying related to a stroke.

c) Adult:

1) Pathologic crying resolved within 24 hours after beginning paroxetine 20 milligrams daily in a 55-year-old man following a left anterior choroidal artery infarct. Although the patient was NOT depressed, 5 to 8 crying episodes were reported daily; they generally occurred in response to a trivial environmental stimuli. Three episodes daily were still reported at 30 days at which time paroxetine was started. Definitive data are not available; however, serotonergic neurotransmission may be damaged during a stroke with the result of pathologic crying (Derex et al, 1997).

2) A 65-year-old man developed frequent (50 per day), uncontrolled episodes of crying which were effectively treated with paroxetine 20 milligrams daily (Tan & Dorevitch, 1996). Within a week, the episodes of crying had disappeared completely. The PATHOLOGIC CRYING episodes began after the man suffered a stroke. Interaction with the staff at the rehabilitation hospital and family or friends caused crying. Before the stroke, the man was emotionally reserved; he was not depressed after the stroke. Based on this and other cases treated with a selective serotonin reuptake inhibitor, these agents should be considered for treating emotional incontinence, a condition characterized by uncontrolled laughing or crying, which is common in stroke patients or patients with multiple sclerosis or pseudobulbar palsy.

4.5.A.5 Drug-induced depressive state

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:

Reduced the occurrence of depression in patients receiving high-dose interferon alfa for treatment of malignant melanoma

c) Adult:

1) Paroxetine treatment, given 2 weeks before and throughout interferon alfa treatment, resulted in a lower rate of occurrence and lower severity of depression than occurred with placebo administration. In a double-blind, randomized trial, 40 patients with resected malignant melanoma that was estimated to have a greater than 50% likelihood of recurrence were to be treated with high-dose interferon alfa, which is known to cause depression. Two weeks before starting interferon alfa treatment, half of the patients were given paroxetine and half were given placebo. The paroxetine dose increased from 10 milligrams (mg) per day in the first week to 20 mg/day in the second week. Thereafter, dose could be increased at the discretion of the study psychiatrist to a maximum of 40 mg/day. Interferon alfa-2b was given intravenously at 20 million units per square meter 5 days per week for the first 4 weeks and subcutaneously at 10 million units per square meter 3 days per week for the remaining 8 weeks. The incidence of major depression was significantly lower with paroxetine than with placebo (p=0.04; 11%

vs 45%, relative risk=0.24). Severity of depressive symptoms, anxiety, and neurotoxicity were all significantly less among patients receiving paroxetine than among those receiving placebo (p less than 0.001 for each parameter). Paroxetine also decreased the likelihood that interferon alfa therapy would need to be discontinued because of depression or neurotoxicity (p=0.03). The effect of paroxetine on the therapeutic efficacy of interferon alfa was not assessed (Musselman et al, 2001).

4.5.A.6 Fibromyalgia

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:

In a 12-week, randomized, double-blind, placebo-controlled trial in adults with fibromyalgia without current mood or anxiety disorders (n=124), treatment with controlled-release paroxetine improved overall symptomatology but did not yield significant reduction in pain (Patkar et al, 2007).

c) Adult:

1) General Information

a) Treatment with paroxetine has demonstrated efficacy in the treatment of fibromyalgia in adults. In a 12-week, randomized, double-blind, placebo-controlled trial, treatment with controlled-release (CR) paroxetine led to improvement in overall fibromyalgia symptomatology in adults meeting the American College of Rheumatology diagnostic criteria for fibromyalgia (Patkar et al, 2007). The study excluded patients with mood or anxiety disorders. A higher proportion of paroxetine CR-treated patients (mean dose, 39.1 milligrams (mg)) had a 25% or greater reduction in Fibromyalgia Impact Questionnaire (FIQ) scores compared to placebo-treated patients. However, there was no significant difference from placebo for reduction in pain (based on FIQ subscale and Visual Analog Scale (VAS) scores) or tender point count. In another 12-week, randomized, single-blind study in patients with fibromyalgia syndrome (n=40), treatment with paroxetine 20 mg/day led to statistically significant improvements in overall condition as well as yielded significant improvements in pain, stiffness, and mood based on VAS scores and reductions in mean tender point scores compared to placebo (Giordano et al, 1999). Long-term studies in populations representative of fibromyalgia in the real world setting are warranted.

2) Clinical Trial

a) Treatment with controlled-release (CR) paroxetine improved overall symptomatology in adults with fibromyalgia without current mood or anxiety disorders in a 12-week, randomized, double-blind, placebo-controlled trial; however, there was no significant reduction of pain. Patients (n=124; aged, 18 to 65 years; 94% female) meeting the American College of Rheumatology diagnostic criteria for fibromyalgia were included. Prior to initiation of study drug, patients were required to have a Visual Analog Scale (VAS) pain score of 5 or higher and a Beck Depression Inventory score of 23 or less. Patients with inflammatory disease or current depressive or anxiety disorders were excluded. Randomization was preceded by a 1-week, single-blind, placebo run-in phase to identify and exclude patients displaying a 25% or greater reduction from baseline on the 10-item, self-reported Fibromyalgia Impact Questionnaire (FIQ) scores (range, 0 to 100). Study patients were randomized to receive either paroxetine CR (n=58; mean age, 47.9 years) or placebo (n=58; mean age, 49.1 years) for 12 weeks. Paroxetine was initiated at 12.5 milligrams (mg)/day and force-titrated in weekly 12.5-mg increments to the maximum tolerated dose up to 62.5 mg/day and maintained through week 12 (mean study dose, 39.1 mg/day). This was followed by a 2-week taper. The primary outcome was response, defined by a 25% or greater reduction on the FIQ total score from randomization to end of therapy. Baseline FIQ scores were 53 and 49 in the paroxetine CR and placebo groups, respectively. Approximately half of the patients had a greater than 5-year fibromyalgia duration (paroxetine CR, 28 (49%); placebo, 31 (53%)). An intention-to-treat analysis revealed significantly more responders in the paroxetine CR group compared to the placebo group (56.8% vs 32.7%; p=0.016). These results were consistent with a complete analysis (65.7% (n=25/38) vs 33.3% (n=16/48); p less than 0.01). Although a higher proportion of patients in the paroxetine CR group achieved a 50% or greater reduction in baseline FIQ scores, the difference compared to placebo was not statistically significant (25.8% vs 13.7%; p=0.08). Among secondary outcomes, paroxetine CR treatment led to a significant reduction in FIQ total score compared to placebo (F(1,113)=25.28; p=0.015). The mean treatment difference in FIQ scores was -6.4 (95% confidence interval (CI), -11.4 to +0.9; p less than 0.05) in favor of paroxetine CR. Among the FIQ subscales, paroxetine CR had better outcomes than placebo on fatigue, anxiety, and days the patient felt good (p less than 0.05 for all). However, the difference between the groups for pain (p=0.07) and depression (p=0.08) were not statistically significant. The groups did non differ significantly in the mean change in VAS pain scores (paroxetine CR -12.2 vs placebo -8.8; p=0.16). Additionally, improvements on other secondary outcomes measures, including changes in tender point count, tender point index, or the Sheehan Disability Scale scores, were not significantly different between the groups. For the paroxetine CR group, adverse events reported commonly and at a higher frequency than the placebo group included drowsiness (26% vs 7%), dry mouth

(36% vs 9%), female genital disorders (9% vs 2%), ejaculatory problems (66% vs 2%), impotence (33% vs 0%), insomnia (17% vs 9%), anxiety (14% vs 7%), and nausea (14% vs 9%) (Patkar et al, 2007).

4.5.A.7 Generalized anxiety disorder

FDA Labeled Indication

a) Overview

FDA Approval: Adult, yes ((regular-release)); 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:

Paroxetine was found to be effective in patients without comorbid depression
Improved symptoms and social functioning in patients with generalized anxiety disorder

c) Adult:

1) Paroxetine was more effective than placebo in the treatment of generalized anxiety disorder. In a randomized, double-blind trial, 324 patients were given placebo or paroxetine 10 milligrams (mg) per day for the first week, 20 mg/day for the second, and, thereafter, up to 50 mg/day on an individual basis. Patients in both treatment groups showed improvement in scores of the Hamilton Rating Scale for Anxiety anxious mood item, but improvement was significantly greater for the paroxetine group as early as week one (p less than 0.05) and at every point thereafter (p less than 0.01). According to the Clinical Global Impressions-Severity of Illness scale, patients in the paroxetine group had a significantly greater reduction in illness severity. At the end of the trial, 40% of paroxetine patients and 27% of placebo patients were reported to be "not ill" or to have only "borderline illness" (p less than 0.01). A patient-rated anxiety scale also showed improvement in both groups but significantly greater improvement in patients receiving paroxetine (p less than 0.001 at week 8). In the intent-to-treat population, 62 percent of patients who received paroxetine were responders vs 36% of patients who received placebo. Improvement in social life and family life were significantly greater among patients treated with paroxetine (p less than 0.01). Adverse events were more frequent among patients taking paroxetine than among those taking placebo, with the most common events associated with paroxetine treatment being asthenia, constipation, abnormal ejaculation, decrease in libido, nausea, and somnolence. Approximately 80% of each group completed the study (Pollack et al, 2001).

2) In an 8-week multicenter study, paroxetine 20 milligrams (mg) daily and paroxetine 40 mg daily were significantly (p less than 0.001 and p less than 0.001, respectively) better than placebo at improving Hamilton Rating Scale for Anxiety (HAM-A) total, HAM-A anxiety item, HAM-A tension item, and Clinical Global Impression Severity of Illness and Improvement scores. Five-hundred and sixty-six patients with DSM-IV diagnosed generalized anxiety disorder WITHOUT current depression were randomized to receive either placebo, paroxetine 20 mg daily, or paroxetine 40 mg daily for 8 weeks. At study conclusion, patients receiving both doses of paroxetine had significantly improved HAM-A and CGI scores compared to patients receiving placebo. Drug related adverse events that occurred at rates greater than patients receiving placebo included asthenia, constipation, decreased appetite, dry mouth, nausea, libido decreases, somnolence, sweating and abnormal ejaculation (Bellew et al, 2000).

4.5.A.8 Headache

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:

Paroxetine has been effective for treating migraine and tension headaches in small studies. In a case report, it was also useful for prophylaxis of migraine headache.

c) Adult:

1) Three patients with preexisting classical migraine, who received paroxetine for depression, had total elimination of or a decrease in headaches after starting paroxetine. In 2 patients, headaches returned when the patients missed a dose or discontinued paroxetine. Although prospective clinical trials are needed to verify these reports, paroxetine may prevent migraine headache when taken routinely (Hays, 1997).

2) In a case report, paroxetine was effective for MIGRAINE PROPHYLAXIS (Black & Sheline, 1995). A 48-year-old woman with a long history of depression and migraine headaches was started on paroxetine 20 mg/day for her depression. She had been experiencing approximately 50 migraine headaches a year. Sumatriptan was being used to alleviate her migraines. After six weeks of paroxetine therapy her depression scores demonstrated marked improvement. She also indicated that she had a 2-week period with no migraine headaches, the first time in over a year; her usage of sumatriptan was also greatly reduced. Well controlled, double-blind trials are needed to further evaluate the role of paroxetine in migraine prophylaxis.

3) Paroxetine may be useful in treating chronic daily headache (Foster & Bafaloukos, 1994). In an open study involving 60 patients with mixed migraine/tension-type headache who had failed at least two other medications, paroxetine was started at 10 mg/day and titrated up to 50 mg/day in 2 to 4 week intervals. Patients were followed for 3 to 9 months. Forty-eight patients completed the study. A reduction of at least 50% in the number of headaches per month were reported in 92% of the patients. The most common adverse effects were fatigue and insomnia. Double-blind controlled trials are needed to validate these findings.

4) Headache decreased significantly compared to baseline in patients receiving paroxetine 20 to 30 milligrams per day for 8 weeks during a randomized, double-blind, cross-over study with sulpiride. Fifty patients with chronic tension headache were randomized to receive either sulpiride 200 to 400 milligrams/day or paroxetine for 8 weeks. Headache was recorded by the patients on a 5-point verbal score. Comparison between the 2 treatment groups after the first 8 weeks demonstrated no statistical differences in headache scores; however, both treatments did reduce headaches when compared to base line. Following crossover, patients switched to sulpiride demonstrated a reduction in headache scores, while those switched to paroxetine did not. It should be noted that there was no washout period between the crossover and paroxetine is known to have a relatively long half-life. More controlled, large scale clinical trials are necessary to determine paroxetine's role in the treatment of chronic tension headache (Langemark et al, 1989).

4.5.A.9 Hot sweats

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:

Paroxetine reduced hot flash severity and frequency in menopausal women.

c) Adult:

1) Treatment with paroxetine reduced hot flash severity and frequency in menopausal women. In a double-blind, placebo-controlled, multicenter, parallel-group study, menopausal women (n=165) experiencing at least 2 to 3 hot flashes daily or at least 14 hot flashes per week received paroxetine controlled-release (CR) 12.5 milligrams (mg)/day, paroxetine CR 25 mg/day, or placebo for 6 weeks. Patients recorded frequency and severity of hot flashes in diaries each day and hot flash composite scores (frequency x severity) were calculated from these ratings. Following six weeks of treatment, mean placebo-adjusted reductions in the daily composite hot flash scores were -4.7 (95% CI, -8.1 to -1.3; p=0.007) for paroxetine CR 12.5 mg and -3.6(95% CI, -6.8 to -0.4; p=0.03) for paroxetine CR 25 mg as compared with placebo. The median reduction from baseline in the hot flash composite score was 62.2% for patients taking paroxetine CR 12.5 mg and 64.6% for patients taking paroxetine CR 25 mg as compared with 37.8% for placebo. Headache, nausea, and insomnia were the most commonly reported adverse events (Stearns et al, 2003a).

4.5.A.10 Insomnia

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:

A preliminary study suggests that paroxetine may be useful in patients with primary insomnia

c) Adult:

1) Patients with primary insomnia improved during treatment with paroxetine. In this 6-week study (n=15), patients received paroxetine 10 milligrams (mg) within 1 hour of bedtime; dose titration to 30 mg daily was allowed. For the primary outcome measure, Clinical Global Impressions-Improvement scale (CGI-I), 11 of 14 patients were much improved or very much improved. In addition, 7 patients no longer met criteria for primary insomnia. However, improvement was NOT consistent for other parameters including sleep quality, daytime well-being, daytime mental functioning that were determined from patient diaries and polysomnography. One patient left the study due to side effects. Results of this small, uncontrolled study support the need for a longer, randomized, placebo-controlled clinical trial (Nowell et al, 1999).

4.5.A.11 Kleptomania

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:

Effective for treating kleptomania in a single patient

c) Adult:

1) In a single patient, paroxetine was effective for treating depression and compulsive kleptomania. This patient initially presented with depression but also mentioned a long history of compulsive stealing that resulted in loss of several jobs. He typically stole items with little value about twice weekly. Treatment with paroxetine 30 milligrams daily for 3 months resulted in remission of depressive symptoms and absence of all stealing. Although he had fleeting thoughts about stealing, he easily controlled this behavior. This report suggests that paroxetine similar to other selective serotonin reuptake inhibitors may be useful for treating kleptomania (Kraus, 1999).

4.5.A.12 Major depressive disorder

FDA Labeled Indication

a) Overview

FDA Approval: Adult, yes (Regular and controlled-release formulations); 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:

Paroxetine 10 to 50 mg daily was effective in uncontrolled (Gagiano et al, 1989) and controlled studies
Paroxetine was comparable to amitriptyline, clomipramine, imipramine, and mianserin
Paroxetine did not provide more symptomatic improvement than placebo in elderly nursing home residents with non-major depression
Paroxetine was effective in the treatment of late-life depression in non-nursing home residents with major depressive disorder

c) Adult:

1) COMBINATION THERAPY

a) The addition of PINDOLOL enhanced the antidepressant efficacy of PAROXETINE in patients with recurrent major depression, and longer-duration combination therapy appeared to be more beneficial compared with shorter-duration therapy (Zanardi et al, 1997). In a double-blind study, 63 patients who had not received psychotropic drugs in the previous two weeks were randomized to one of three groups: paroxetine plus placebo for 4 weeks (N=21), paroxetine plus pindolol for 1 week, followed by paroxetine plus placebo for 3 weeks (N=21), or paroxetine plus pindolol for 4 weeks (N=21). Paroxetine was given as 20 milligrams (mg) once daily; pindolol (2.5 mg) or placebo was given three times daily. An additional 10 patients were treated in an open-label manner with paroxetine 20 mg once daily plus metoprolol 25 mg twice daily for 4 weeks. After 1 and 2 weeks, the presence of pindolol significantly increased the effectiveness of paroxetine, based on the lower depression ratio of Hamilton Rating Scale for Depression scores obtained in the two groups receiving pindolol compared to the paroxetine plus placebo group. The response to 4 weeks of combined therapy was greater than that of paroxetine plus 1 week of pindolol, indicating the value of longer combination therapy. The response to metoprolol was similar to the paroxetine plus placebo group, which indicates that the mechanism of this additive effect is not beta blockade, but probably the ability of pindolol to block 5-HT1A.

2) COMPARATIVE DATA

a) Paroxetine has not been convincingly superior to any other antidepressant in available clinical studies. Several controlled trials lasting 6 to 7 weeks reported similar efficacy for paroxetine and amitriptyline (Byrne, 1989a; Kuhs & Rudolf, 1989b; Laursen et al, 1985c; Battegay et al, 1985b), although in some studies amitriptyline has been either superior to paroxetine, or exhibited a definite trend toward superiority, after 3 weeks of treatment (Laursen et al, 1985c; Kuhs & Rudolf, 1989b). Paroxetine has also been comparable to clomipramine (Guillibert et al, 1989a) and mianserin (Mertens & Pintens, 1988c) and at least as effective as imipramine in depression (Feighner & Boyer, 1989a). A safety advantage in favor of paroxetine, particularly with regard to anticholinergic effects, was reported in some, but not all, of these comparative studies.

3) SINGLE-AGENT THERAPY

a) Both paroxetine immediate-release (IR) and paroxetine controlled release (CR) were more effective than placebo in the treatment of late- life depression in elderly patients. In a flexible-dose, multi-center, randomized, double-blind, placebo-controlled trial (n=319), elderly patients (mean age, 70 years) with major depressive disorder and a score of at least 18 on the Hamilton Rating Scale for Depression (HAM- D) received paroxetine CR (12.5 to 50 milligrams (mg)/day; mean dose, 30.4 mg/day), paroxetine IR (10 to 40 milligrams (mg)/day; mean dose, 25.7 mg/day), or placebo for 12 weeks. From baseline to endpoint, there was a significantly greater reduction in the HAM-D total score for both paroxetine CR and paroxetine IR as compared with placebo (p=0.007 and p=0.003, respectively). Response was defined as a score of 1 ("much improved") or 2 ("very much improved") on the Clinical Global Impression-Improvement (CGI-I) scale. Seventy-two percent of paroxetine CR-treated patients (p less than 0.002) and 65% of paroxetine IR-treated patients were

rated as responders as compared with 52% of patients in the placebo group. Remission (defined as an endpoint HAM-D total score of 7 or less) was also significantly higher in the paroxetine CR (43%) and paroxetine IR (44%) groups as compared with placebo (26%) (p=0.009 and p=0.01, respectively). Paroxetine CR and paroxetine IR were well tolerated with somnolence, dry mouth, diarrhea, headache, abnormal ejaculation, nausea, dyspepsia, constipation, asthenia, and decreased appetite reported most commonly as adverse events (Rapaport et al, 2003).

b) An 8-week course of PAROXETINE did not show superiority over placebo for improvement of depression (non-major) in very old nursing home residents, according to a randomized, double-blind trial (n=24, mean age 87.9 years). Excluded from the trial were residents with major depression or psychosis, those who were suicidal, and those with scores less than 10 on the Mini Mental State Exam (MMSE). Subjects were chosen based on interviews with residents (videotaped), interviews with their primary nurses, and review of the videotapes by 2 investigators; interview questions were derived from the Hamilton Depression Rating Scale (HDRS) and the Cornell Scale for Depression (CS). Starting doses of PAROXETINE were 10 milligrams (mg) daily, with weekly titration in 10-mg increments (maximum 30 mg). Mean final dose of paroxetine was 23.3 mg. After 8 weeks of study medication, there were no significant differences between the paroxetine- and placebo- treated subjects using an intent-to-treat analysis (n=24). Comparing subjects who completed at least 6 weeks of treatment (n=20), 5 of 9 paroxetine subjects (56%) were rated by their nurses as 'much improved' or 'very much improved' (Clinical Global Impression of Change 1 or 2 points) compared with 4 of 11 (36%) of the control group (p=0.39). HDRS and CS scores from nurse and subject interviews both improved over time, with no significant differences between the paroxetine group and the placebo group. Overall placebo response rate was 45%. Two members of the paroxetine group had to be withdrawn due to development of delirium (which resolved after paroxetine was stopped). Cognitive ratings (MMSE scores) dropped significantly more often in the paroxetine group (7 of 8) compared with controls (4 of 11; p=0.03). No differences were seen in serum anticholinergic levels across the 2 groups. A sub-group analysis of the more symptomatic subjects at baseline (n=15) found that greater improvement occurred among the paroxetine-treated subjects in this sub-group (p=0.06). The investigators noted that there was not good correlation between subject-derived and nurse-derived measures of change (Burrows et al, 2002).

c) Pharmacotherapy with paroxetine decreased scores on the Hopkins Symptom Checklist Depression Scale (HSCL-D-20) an average of 0.61 points compared to a decrease of 0.40 points with placebo (p=0.004) in older primary care patients with minor depression or dysthymia (n=415). Inclusion criteria included: diagnosis of dysthymia or minor depression, 60 years of age or older, 3 or 4 symptoms for at least 4 weeks, and a score of at least 10 on the Hamilton Depression Rating Scale (HDRS). Patients were randomized to receive paroxetine at a target dose of 20 mg/day (n=137), placebo (n=140), or problem-solving treatment-primary care (PST-PC; n=138) for 11 weeks. HSCL-D-20 scores in patients receiving PST-PC decreased 0.52 points, not significantly different from either placebo (p=0.13) or paroxetine (p=0.17). Effects of paroxetine were similar in patients with dysthymia and minor depression (Williams et al, 2000).

d) Paroxetine 40 milligrams (mg) was more effective than paroxetine 20 mg daily for preventing recurrence of depression (Franchini et al, 1998). For all patients, the current depressive episode abated during treatment with paroxetine 40 mg daily which was continued for 4 months. During the maintenance phase, patients (n=68) were randomly assigned to blinded treatment with paroxetine 20 or 40 mg daily for 28 months. After 28 months, 51.5% and 23.5% of patients treated with paroxetine 20 and 40 mg, respectively, had 1 recurrence; 1 patient in paroxetine 20 mg group was excluded due to noncompliance with therapy. The Mantel-Cox survival analysis showed a significant survival advantage for paroxetine 40 mg versus 20 mg (p=0.018). Treatment was tolerated well with no new adverse effects reported during the maintenance phase. Based on this study, the maintenance dose should be individualized since lower doses than the one used in treatment may not be effective in all patients.

e) Increasing paroxetine from 20 milligrams (mg) to 40 mg did NOT result in a statistically significant improvement in depressive symptoms; however, there was a trend toward greater improvement in patients with major depression treated with paroxetine 40 mg (Benkert et al, 1997). In this randomized, double-blind, parallel-group study, patients (n=544) were assigned to receive paroxetine 20 mg or maprotiline 100 mg for 3 weeks. If, after 3 weeks, the Hamilton Depression Rating Scale (HAMD) failed to decrease by at least 50% or more, then the dosage of paroxetine was increased to 40 mg (n=50) or was continued at 20 mg (n=36) for an additional 3 weeks. When patients with major depression were analyzed separately, the response (reduction in HAMD greater than 50%) was 75% for paroxetine 40 mg versus 61% for paroxetine 20 mg; however, results were similar with both doses for patients with minor depression. New adverse effects occurred in 18% of patients when the dose of paroxetine was increased to 40 mg. Patients receiving maprotiline 100 mg initially were treated similarly if they had an inadequate response after 3 weeks. Results of this study are limited by the relatively small number of patients who were treated with higher doses, the inclusion of patients with major and minor depression, and lack of a placebo control. Larger studies which include patients with major depression are needed to better evaluate the efficacy of higher doses of paroxetine.

f) Significantly greater reductions in symptoms of depression were achieved with paroxetine

compared to placebo after 2 weeks of treatment, with improvements being even greater after 6 weeks of therapy. Paroxetine was evaluated for treating major depression (DSM-III) in a 6-week, placebo-controlled, double-blind study involving 111 outpatients (Rickels et al, 1989a). Patients were randomized to receive either placebo or paroxetine 20 milligrams once daily initially, followed by dosing adjustments over the subsequent 2 weeks based upon efficacy and adverse effects (range, 10 to 50 milligrams/day). All doses were given in the morning. Paroxetine was superior to placebo in reducing total scores on the Hamilton Depression Rating Scale (HAMD), the Montgomery-Asberg Depression Rating Scale (MADRS), the Raskin depression scale, and the Clinical Global Impression (CGI) scale of depression. Patients improving during this first 6-week period were allowed to enter a second 6-week treatment period; the clinical status of all patients treated during this second phase (18 paroxetine, 9 placebo) remained unchanged, with paroxetine remaining superior to placebo. Diaphoresis, diarrhea, somnolence, and nausea occurred to a significantly greater degree with paroxetine compared to placebo; laboratory parameters were not significantly affected during therapy.

g) Paroxetine was more effective than placebo in reducing psychic anxiety. The efficacy of paroxetine in treating symptoms of anxiety and/or agitation associated with depression were examined in 2963 patients (Sheehan et al, 1993).

4.5.A.13 Myocardial infarction; Prophylaxis

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 confer a protective effect against first MI

c) Adult:

1) In a case-control study comprised of 653 cases of first myocardial infarction (MI) and 2990 control subjects, results indicated that selective serotonin reuptake inhibitors (SSRIs) may confer a protective effect against first MI. The subjects in this study were smokers, between the ages of 30 to 65 years, with a first MI hospitalized between September 1995 and December 1997. The four SSRIs investigated in this study were fluoxetine, fluvoxamine, paroxetine, and sertraline; doses taken by participants were not stated. The odds ratio of patients who were taking SSRIs having a first MI compared to controls (after adjustment for potential confounders) was 0.35 (95% CI 0.18, 0.68; p less than 0.01). The authors suggested that this effect was possibly attributable to an inhibitory effect on serotonin-medicated platelet activation or amelioration of other factors associated with increased risk for MI in depression (Sauer et al, 2001).

4.5.A.14 Nocturnal sleep-related eating 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:

Resolved symptoms of nocturnal eating/drinking syndrome in three patients

c) Adult:

1) Paroxetine therapy resolved symptoms of nocturnal eating/drinking syndrome (NEDS) in three female patients. A 40-year-old, 28-year-old, and 38-year-old suffering from NEDS were treated with paroxetine 20 or 30 milligrams (mg) daily. All patients were conscious during uncontrollable nocturnal eating which sometimes occurred multiple times throughout the night. Following paroxetine administration, the number of awakenings due to NEDS was reduced within a few days and approximately 2 weeks after initiation of therapy, symptoms had completely resolved. Treatment was continued at 20 mg/day (Miyaoka et al, 2003).

4.5.A.15 Obsessive-compulsive disorder

FDA Labeled Indication

a) Overview

FDA Approval: Adult, yes ((regular-release formulation)); 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:

Considered a first-line agent for treating obsessive-compulsive disorder (OCD)
Effective as a crossover therapy in patients with obsessive compulsive disorder non-responsive to

initial SSRI treatment
Venlafaxine extended-release (XR) and paroxetine were equally effective in the treatment of patients with OCD

c) Adult:

1) GENERAL INFORMATION

a) Venlafaxine extended-release (XR) was as effective as paroxetine in the treatment of patients with obsessive compulsive disorder (OCD). In a randomized, double-blind, comparative study, patients (n=150) with OCD and a score of at least 18 (or at least 12, if only obsessions or only compulsions were present) on the Yale-Brown Obsessive Compulsive Scale (Y-BOCS) received either venlafaxine XR (initial, 75 milligrams (mg)/day, titrated to 300 mg/day by week 7) or paroxetine (initial, 15 milligrams (mg)/day, titrated to 60 mg/day by week 7) for 12 weeks. Both paroxetine and venlafaxine XR treatments were effective, producing mean reductions of 7.8 and 7.2 points, respectively, in the Y-BOCS score from baseline to endpoint. A significant decrease in the total Y-BOCS score from baseline was seen at week 3 for venlafaxine XR- treated patients (p=0.008) and at week 5 for patients in the paroxetine group (p=0.018). There were no significant differences in responder rates between treatment groups. In the venlafaxine XR group, 37% and 25% of patients were partial responders and full responders, respectively. Similarly, in the paroxetine group, 44% and 22% of patients were partial responders and full responders, respectively. Additionally, no significant differences were observed between the two treatments with regard to reduction of anxious or depressive symptoms (as measured by the Hamilton Anxiety Scale and the Hamilton Rating Scale for Depression, respectively). For both treatments, most adverse effects were of mild or moderate severity and included somnolence, sweating, insomnia, and nausea (Denys et al, 2003a).

2) PRIMARY THERAPY

a) Of the selective serotonin reuptake inhibitors (SSRIs) (ie, fluoxetine, sertraline, paroxetine, fluvoxamine) with U.S. Food and Drug Administration approval for treating OCD, all are effective. Limited clinical studies also suggest that the SSRIs are comparable to clomipramine; however, results of a meta-analysis found that clomipramine may be more effective than the SSRIs (Flament & Bisserbe; Leonard). Selection of initial treatment is often based on the side effect profile of the individual drug; in general, the SSRIs are tolerated better than clomipramine (Leonard). Early studies used near maximal doses of an SSRI which resulted in a high incidence of adverse effects; however, initial low doses with gradual dose adjustment result in a good response in some patients and better tolerance in most (Leonard). While the optimal duration of treatment has NOT been defined, most patients require long-term treatment. A few small studies have shown relapse rates between 65% and 90% when pharmacologic treatment was stopped (Rasmussen & Eisen). Patients who do NOT respond to 10 to 12 weeks of maximum doses of an SSRI and/or behavioral therapy are considered refractory to treatment. In about 20% of this group, a trial of a second SSRI will be effective. In the remaining patients, augmentation therapy with haloperidol or clonazepam may be beneficial (Rasmussen & Eisen).

b) In a 12-week, comparative study, paroxetine was as effective as clomipramine for treating obsessive compulsive disorder. Patients were randomly assigned to receive placebo (n=99), paroxetine 10 milligrams (mg) (n=201), or clomipramine 25 mg daily (n=99); the dose of active treatments was titrated to a maximum of 60 mg and 250 mg for paroxetine and clomipramine, respectively. No statistically significant differences were found in the primary efficacy measures, the Yale-Brown Obsessive-Compulsive Scale or the National Institute of Mental Health Obsessive-Compulsive Scale, between paroxetine or clomipramine; however, both drugs were significantly better than placebo. Adverse effects requiring treatment withdrawal occurred in fewer patients treated with paroxetine (9%; p=0.033) than clomipramine (17%). Limitations of the study are the relatively short duration, and the potential loss of blinding due to differences in adverse effects (Zohar et al, 1996).

c) Paroxetine was effective in at least two 12-week trials in patients suffering from obsessive compulsive disorder (OCD) (Anon, 1996). Patients studied had moderate to severe OCD (mean baseline scores on the Yale Brown Obsessive Compulsive Scale of between 23 and 26). Patients treated with paroxetine 40 mg or 60 mg daily significantly improved (mean reduction of 6 and 7 points, respectively) compared to those patients treated with either paroxetine 20 mg daily or placebo.

3) CROSSOVER THERAPY

a) Patients with obsessive-compulsive disorder (OCD) refractory to initial treatment with a selective serotonin reuptake inhibitor (SSRI) responded to crossover therapy with another SSRI. In a double-blind switch study, patients (n=150) with primary OCD received venlafaxine (titrated to 300 milligrams (mg)/day) or paroxetine (titrated to 60 mg/day) for 12 weeks and then non-responders (n=43) were switched to the opposite therapy (venlafaxine, n=16; paroxetine, n=27) for an additional 12 weeks following a 4-week washout period between phases. Non-response was defined as a reduction in the Yale-Brown Obsessive- Compulsive Scale (Y-BOCS) below 25%. Following crossover, the Y-BOCS total score decreased in both groups from baseline (week 16) to endpoint, however the score was significantly reduced in paroxetine- treated patients (p less than 0.000), but not in venlafaxine-treated patients (p=ns). Paroxetine was statistically superior as compared with venlafaxine (p=0.017). The response rate during phase II of the study was 42%

(18/43) overall, with a 16% (3/16) response rate in the venlafaxine group and a 56% (15/27) response rate in the paroxetine group (p=0.01). At the end of both phases 73% (109/150) of patients had responded to treatment. Adverse effects were similar between treatment groups including somnolence, sweating, headache, constipation, insomnia, nausea, change in mood, loss of libido, and dry mouth (Denys et al, 2004).

4.5.A.16 Panic disorder

FDA Labeled Indication

a) Overview

FDA Approval: Adult, yes ((regular and controlled-release formulations)); Pediatric, no
Efficacy: Adult, Effective; Pediatric, Evidence is inconclusive
Recommendation: Adult, Class IIa; Pediatric, Class IIb
Strength of Evidence: Adult, Category B; Pediatric, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:

In short-term and long-term studies, effective for treating panic disorder in adults
Effective in children in one open study

c) Adult:

1) In a 12-week randomized, double-blind, placebo-controlled study of patients (n=367) with panic disorder (with or without agoraphobia), paroxetine was as effective as clomipramine in reducing the number of panic attacks; both agents were significantly more effective than placebo. The dose of each agent was titrated upwards from an initial dose of 10 milligrams (mg) daily to a maximum of 60 mg for paroxetine and 150 mg for clomipramine based on tolerance and clinical response. Paroxetine appeared to have a more rapid onset of action with a greater number of patients reporting no full attacks at weeks 6 and 9 compared to clomipramine or placebo. At the endpoint, 76.1% of paroxetine-treated patients showed a greater than 50% reduction in the total number of full panic attacks compared to 64.5% and 60% in the clomipramine- and placebo-treated groups, respectively. Significantly more patients in the clomipramine group compared to the paroxetine group experienced adverse effects; twice as many patients in the clomipramine group (18) withdrew from the study due to adverse effects (Lecrubier et al, 1997).

2) Although there was no significant difference in efficacy between paroxetine and clomipramine in the 36-week continuation study, the number of full panic attacks continued to decrease in the active treatment groups. One hundred and seventy-six patients continued long-term treatment at the same dose received in the initial 12-week study. Clinic visits and evaluations of patients' panic diaries occurred every 6 weeks. One hundred and sixteen patients completed the study with 42% of the placebo group withdrawing for lack of efficacy and 19% of the clomipramine group withdrawing due to adverse effects. A higher percentage of patients in the clomipramine group (76.2%) experienced at least 1 adverse effect during the continuation phase compared to 61.8% in the paroxetine- and 51.1% in the placebo-treated groups, respectively; these differences did not reach statistical significance. Efficacy in maintaining reduction in panic attacks and continued reduction of attacks throughout the study period suggests that treatment of panic disorder may be beneficial on a long-term basis (Lecrubier et al, 1997a).

3) In a 10-week, randomized, placebo-controlled trial, paroxetine 40 milligrams (mg) daily was significantly more effective than placebo for treating panic attacks; however, differences between paroxetine 10 and 20 mg were NOT significantly different from placebo. At 10 weeks, 86%, 65.2%, 67.4%, and 50%, respectively, of patients taking paroxetine 40 mg, 20 mg, 10 mg, or placebo had a complete response. Patients enrolled in the study met DSM-III criteria for panic disorder with or without agoraphobia and had at least 2 full panic attacks during the 2 weeks before study entry. Of the 278 patients entered into the study, 188 (67.6%) completed 10 weeks of treatment. Withdrawal was due primarily to adverse effects and lack of efficacy which decreased with increasing paroxetine dose. Paroxetine 40 mg daily is an effective treatment for panic attacks (Ballenger et al, 1998).

4) Paroxetine 20 to 60 mg/day was significantly more effective than placebo in reducing the number of panic attacks in patients with panic disorders. Patients (n=120) were randomly assigned to placebo or paroxetine after a three-week washout period; therapy was continued for a total of 12 weeks. Paroxetine was given as an initial dose of 20 mg daily and then adjusted at two-week intervals to 40 mg and then 60 mg daily, depending on efficacy and tolerability. The majority of patients (75%) required doses of 40 or 60 mg. After 12 weeks of therapy, 82% of patients treated with paroxetine had at least a 50% reduction in number of panic attacks compared to 50% of patients treated with placebo; 36% of paroxetine-treated patients became almost free of panic attacks. Paroxetine was generally well tolerated at all three dose levels (Oehrberg et al, 1995).

d) Pediatric:

1) A retrospective analysis of the records of 18 children with panic disorder who were treated with paroxetine showed favorable response in 15 children (83%). Children aged 7 to 16 years and unequivocally meeting the DSM-IV criteria for panic disorder were treated with paroxetine, beginning at an average of 8.9 milligrams (mg) per day and progressing to an average of 24 mg/day. Children were treated for 2 to 24 months (mean 12 months). With last- observation-carried-forward analysis, significant improvement was shown on the Clinical Global Impressions (CGI) Severity score: from an average initial score of 5.2 to an average final score of 1.8 (p less than 0.0001). Responders (83% of subjects)

were defined as those who had a CGI-Improvement score of 1 (marked improvement) or 2 (moderate improvement). Side effects were minimal or mild and transient, with no patient requiring a reduction in dosage due to side effects. The most common side effects were nausea (39%), tension-agitation (39%), sedation (33%), insomnia (22%), palpitations (22%), and headache (22%) (Masi et al, 2001).

4.5.A.17 Posttraumatic stress disorder

FDA Labeled Indication

a) Overview

FDA Approval: Adult, yes ((regular-release formulation)); 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:

Paroxetine (20 to 50 mg/day) effectively treated all three components of posttraumatic stress disorder

c) Adult:

1) Paroxetine in doses of 20 to 50 milligrams (mg) per day effectively treated all three components of posttraumatic stress disorder (PTSD) (reexperiencing, avoidance/numbing and hyperarousal) when compared to a matched patient group receiving placebo. In this 12-week, double-blind, multi-center trial, 323 patients were divided into paroxetine and placebo treatment groups. Assessments using the Clinician- Administered PTSD Scale, part 2 (CAPS-2), at 4, 8, and 12 weeks, showed a statistically significant decrease (p less than 0.001) in PTSD symptoms that began at 4 weeks and showed the maximum fraction of improvement by week 8. Response, defined as very much improved or much improved on the Clinical Global Impressions-Global Improvement Scale (CGI-I), at 12 weeks was 60% in the paroxetine group and 40% in the placebo group. The proportion of patients achieving remission (CAPS-2 total score less than 20) was 29.4 % and 16.5% for paroxetine and placebo respectively (p = 0.008). CAPS-2 results showed, in the sub-group analysis, that both males and females experienced comparable decreases in PTSD symptoms by study endpoint and that patients whose index trauma occurred more than 5 years prior to this study had a greater decrease in symptom score (p=0.037) than other paroxetine-treated patients. There was also a greater proportion of responders in the trauma-type category of seeing someone hurt or die (p=0.019), compared to the other trauma types of physical or sexual attack, serious accident or injury, or exposure to combat. The mean paroxetine dose during the study was 27.6 +/- 6.72 mg/day with 22% taking 20 mg/day, 24% taking 30 mg/day, 28% taking 40 mg/day, and 25% taking 50 mg/day at study end. Patients treated with paroxetine experienced asthenia, abnormal ejaculation, dry mouth, nausea, and somnolence at an incidence of at least 10% (and at least twice the placebo rate) and approximately 60% of patients in both groups completed the 12-week study (Tucker et al, 2001).

2) Paroxetine in doses of 20 or 40 milligrams (mg) per day effectively treated all three components of posttraumatic stress disorder (PTSD) (reexperiencing, avoidance/numbing and hyperarousal) when compared to a matched patient group receiving placebo. In this 12-week, double-blind, multi-center trial, 551 patients were divided into three groups: paroxetine 20 mg/day, paroxetine 40 mg/day or placebo. Assessments using the Clinician-Administered PTSD Scale, part 2, at 1, 2, 4, 6, 8, and 12 weeks, showed a statistically significant decrease in PTSD symptoms that began at 4 weeks and continued through the remaining 12 weeks of the trial. Response at endpoint was 62% in the paroxetine 20 mg group, 54% in the paroxetine 40 mg group and 37% in the placebo group. There was no difference in response due to trauma type, time since trauma, severity of baseline PTSD, depressive symptoms or gender. Asthenia, diarrhea, abnormal ejaculation, impotence, nausea, and somnolence occurred with an incidence of at least 10% (and at least twice the placebo rate) in the paroxetine groups (Marshall et, al, 2001). This study confirms the results of an earlier, small open trial, where 65% of patients had a 48% decrease in PTSD symptoms and were rated as very much improved or much improved on the Clinical Global Impression Scale (Marshall et al, 1998).

4.5.A.18 Premature ejaculation

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:

Selective serotonin reuptake inhibitors fluoxetine, paroxetine, and sertraline have been effective in the symptomatic treatment of PREMATURE EJACULATION. Objective results are usually seen after 2 weeks treatment, with prolongation to ejaculation time ranging between 6 to 10 minutes compared to less than 1 minute at baseline. Significant subjective changes included increased sexual desire, partner satisfaction, and decreased anxiety. However, over 90% will relapse to baseline functional status within 2 to 3 weeks after discontinuing medication (Ludovico et al, 1996; Kara et al, 1996; Lee et al, 1996; Mendels et al, 1995; Waldinger et al, 1994).

c) Adult:

1) Paroxetine was effective for treatment of PREMATURE EJACULATION (McMahon & Touma, 1999). Paroxetine 20 milligrams 3 to 4 hours before planned intercourse delayed ejaculation from 0.3 minutes at baseline to 3.5 minutes at the end of study; paroxetine was superior to placebo in this single-blind, randomized crossover study of 26 men (p less than 0.001). In the second study, 42 men were randomly assigned to receive paroxetine 10 milligrams daily for 3 weeks followed by paroxetine 20 milligrams as needed 3 to 4 hours before planned intercourse or placebo in a crossover design. Ejaculatory latency increased during daily treatment with paroxetine compared to placebo at 2 weeks (p less than 0.05); however, the greatest benefit was achieved after daily followed by as needed paroxetine (baseline mean 0.5 minutes to week 7 mean 5.8 minutes; p less than 0.05). Based on the second study, daily followed by as needed treatment with paroxetine is likely more effective than as needed treatment only.
2) PAROXETINE is an effective treatment for premature ejaculation. In an open-label trial of 32 men, all of the subjects experienced a delay in ejaculation with paroxetine 20 milligrams daily at bedtime. Generally, benefit occurred after approximately two weeks of therapy. After paroxetine was discontinued, premature ejaculation resumed in 90% of patients. The most common side effects reported were sleepiness and mild sensory confusion which tended to subside after about 15 days of therapy (Ludovico et al, 1996).
3) Paroxetine 40 milligrams daily significantly improved premature ejaculation in a double-blind, placebo-controlled trial (Waldinger et al, 1994). Both patients and partners were questioned before and during the trial regarding time to ejaculation. Prior to treatment the median time to ejaculation was 30 seconds or less for both groups. Following 6 weeks of paroxetine therapy, placebo-treated patients had no change while treated patients had increased time to ejaculation to a median of 10 minutes.

4.5.A.19 Premenstrual dysphoric disorder

FDA Labeled Indication

a) Overview

FDA Approval: Adult, yes (controlled-release formulation)); 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:

Reduced symptoms related to PDD in an open study and in controlled trials

c) Adult:

1) Treatment with paroxetine controlled-release (CR) tablets effectively reduced symptoms associated with premenstrual dysphoric disorder (PDD). In two placebo- controlled trials, patients (n=672) with PDD and a mean symptom history of 11 years received paroxetine CR 12.5 milligrams (mg)/day, paroxetine CR 25 mg/day, or placebo continuously throughout 3 menstrual cycles. Patients taking systemic hormonal contraceptives were excluded before the trials began. Treatment response was assessed using a patient-rated visual analog scale (VAS)-total score, which measured mood, physical symptoms and other symptoms. Patients in both paroxetine treatment groups showed significantly greater improvements on the luteal phase VAS-total score from baseline to endpoint as compared with placebo (Prod Info Paxil CR (TM), 2003).
2) In an open study (n=14), paroxetine reduced symptoms of premenstrual dysphoric disorder (PDD). Patients with a Clinical Global Impression (CGI) score greater than 3 during 1 cycle using placebo received paroxetine 10 milligrams (mg) daily with adjustment to a maximum dose of 30 mg daily during subsequent cycles; the average dose was 22 mg/day. Daily symptom scores for mood swings, anger/irritability, interpersonal difficulties, and behavioral control showed significant (p less than 0.05) decreases from baseline to the final cycle although luteal phase levels were NOT quite as low as follicular phase levels. Between 8 and 10 women were considered responders to paroxetine based on the following: (1) 50% decrease in luteal phase worsening of 5 symptoms (n=10), (2) absolute Hamilton Rating Scale for Depression (HAM-D) reduction of 50% (n=9), (3) luteal phase HAM-D score less than or equal to 8 (n=9), (4) luteal phase HAM-D less than or equal to follicular phase HAM-D score (n=9), and (5) absolute CGI less than or equal to 2 (n=8). Like other selective serotonin reuptake inhibitors, paroxetine reduces symptoms associated with PDD but additional controlled trials are needed (Yonkers et al, 1996).

4.5.A.20 Pruritus, Non-dermatological

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, paroxetine was effective in the treatment of severe, non-dermatological pruritus

c) Adult:

1) Paroxetine therapy was effective in the treatment of severe, non- dermatological pruritus in patients with advanced cancer and other systemic diseases. In a randomized, double-blind, placebo-controlled,

crossover study, patients (n=26) with severe pruritus not associated with primary skin disease received placebo or paroxetine (20 milligrams/day) for 7 days and then switched over to the opposite treatment arm for 7 days. Patients assessed pruritus intensity via a numerical analogue scale. On the 7 days average, paroxetine-treated patients had lower mean pruritus intensity scores as compared with patients in the placebo group (mean difference, 0.78 (95% CI=0.37 to 1.19); p=0.001). This effect was even stronger when measured over the last 3 days average (mean difference, 1.35 (95% CI=0.61 to 2.08); p=0.002). A significantly higher percentage of patients treated with paroxetine exhibited clinical response (defined as a pruritus reduction of at least 50% in the last 3 days of the period as compared to the last 3 days of the run-in period) as compared with placebo (37.5% vs 4.2%, respectively; p=0.027). Paroxetine treatment was associated with a higher incidence of nausea and sleepiness as compared with placebo. Because this study population was composed mostly of patients with pruritus associated with advanced neoplastic disease, these findings cannot be extrapolated to all patients with severe pruritus. Additional studies are needed to explore the efficacy of paroxetine in the treatment of pruritus in more diverse patient populations (Zylicz et al, 2003).

4.5.A.21 Schizophrenia, Negative symptoms

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:

Reduced negative symptoms of schizophrenia when added to antipsychotic therapy in small open study

c) Adult:

1) Paroxetine treatment added to antipsychotic treatment brought sustained improvement in negative symptoms of schizophrenia patients in a small, open study. Six patients with chronic schizophrenia and with a score of at least 20 on the negative subscale of the Positive and Negative Syndrome Scale (PANNS) took paroxetine 30 milligrams per day for 12 weeks and were followed up for 30 months. Patients were not depressed, as shown by a score of 8 or less on the Hamilton-Depression scale. The mean score on the PANNS negative subscale decreased significantly from 29.3 to 20.3 (p=0.043) by week 12. The most notable effects were on blunted affect and stereotyped thinking. One patient improved during the 12 weeks but deteriorated after stopping paroxetine. He improved again after restarting paroxetine and continued taking it thereafter. One patient did not respond within the 12-week study period but responded at 16 weeks and maintained that improvement through the following 30 months. The other 4 did not change medication and maintained their initial improvement throughout the follow-up period (Jockers-Scherubl et al, 2001).

4.5.A.22 Social phobia

FDA Labeled Indication

a) Overview

FDA Approval: Adult, yes ((regular and controlled-release formulations)); 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 SOCIAL PHOBIA

c) Adult:

1) Controlled-release (CR) paroxetine was more effective than placebo in improving the symptoms of social anxiety disorder. In a randomized, double-blind, placebo-controlled, multicenter study (n=370), patients with social anxiety disorder received paroxetine 12.5 to 37.5 milligrams (mg) (mean dose, 32.3 mg/day) or placebo daily for 12 weeks following a 1 week single-blind placebo run-in period. Changes in Liebowitz Social Anxiety Scale (LSAS) scores from baseline to endpoint significantly favored treatment with paroxetine CR as compared with placebo (adjusted mean difference= -13.33, 95%CI= -18.25 to -8.41; p less than 0.001). From baseline to week 12, mean LSAS scores for paroxetine CR-treated patients decreased from 78.3 to 47.1, while mean scores of patients in the placebo group were reduced from 78.6 to 60.5. A significantly higher percentage of patients treated with paroxetine CR achieved remission (defined as at least a 70% reduction in the LSAS total score) as compared with patients in the placebo group (24.3% vs 8.2%, respectively; 95%CI= 1.92 to 6.85; p less than 0.001). From baseline to endpoint, there were significantly more responders (defined as very much improved or much improved on the Clinical Global Impression-Improvement scale) in the paroxetine CR group as compared with the placebo group (57% vs 30.4%, respectively; p less than 0.001). The most commonly observed adverse events in paroxetine CR-treated patients included nausea, asthenia, abnormal ejaculation, sweating, impotence, somnolence, insomnia, and decreased libido (Lepola et al, 2004).

2) Paroxetine 20 milligrams (mg) per day was more effective than placebo in improving the symptoms of generalized social anxiety disorder; higher doses of paroxetine were not more efficacious. In a double-blind, placebo-controlled trial, 384 patients with a minimum of 4 interactional and performance

phobias were randomly assigned to receive paroxetine 20, 40, or 60 mg/day or placebo for 12 weeks. Using last-observation- carried-forward analysis, scores on the Liebowitz Social Anxiety Scale (LSAS) were reduced significantly more by paroxetine 20 mg than by placebo (p less than 0.001). Mean improvement in the LSAS total score was twice as great with paroxetine 20 mg as with placebo. The significant difference between paroxetine and placebo appeared at the beginning of week 8 and continued to the end of the study. Improvements in LSAS scores with paroxetine 40 mg and 60 mg approached statistical significance when compared to placebo. The percentage of responders (defined as a score of either 1 or 2 on the Clinical Global Impressions-Global Improvement scale) ranged from 43% to 47% in the paroxetine groups, compared to 28% in the placebo group. In comparison to placebo-treated patients, patients treated with paroxetine 20 mg showed greater improvements on the LSAS fear and avoidance subscales at endpoint (p=0.001 and p less than 0.001, respectively), on the Social Avoidance and Distress Scale, and on the Sheehan Disability Scale. Although scores for those taking higher doses of paroxetine were in some cases better than for those taking placebo, they were not generally superior to those with paroxetine 20 mg. Adverse effects were typical of those reported for selective serotonin reuptake inhibitors: insomnia, somnolence, asthenia, nausea, dizziness, decreased libido, dry mouth, nervousness. The only adverse events that showed a linear dose response were delayed ejaculation and constipation. More patients withdrew from paroxetine groups than from the placebo because of adverse events, whereas more withdrew from placebo treatment than from paroxetine treatment because of lack of efficacy. The authors acknowledged that the response rate in this study is lower than in some other studies, perhaps because of the fixed dosage regimens. Although flexible dosing may increase response rate, the authors suggested that the initial target dose of paroxetine should be 20 mg/day (Liebowitz et al, 2002).

3) Paroxetine was effective for treating social anxiety disorder in a 12-week, controlled study. Patients were randomly assigned to receive placebo (n=151) or paroxetine (n=139) 20 milligrams (mg) daily for 2 weeks followed by dosage titration to 50 mg daily, if needed. At 12 weeks, the mean dosage of paroxetine was 34.7 mg/day. Thirty-five (25%) and 42 (28%) patients withdrew from the paroxetine and placebo groups, respectively; no patient withdrew due to a serious drug-related adverse effect. The Liebowitz Social Anxiety Scale score was reduced by 29.4 and 15.6 in the paroxetine and placebo groups, respectively (p less than or equal to 0.001); 26.3% versus 9% of patients were rated as very much improved on the Clinical Global Impression (CGI) scale after receiving paroxetine versus placebo. The percentage of responders on the CGI scale was also higher after paroxetine treatment (p less than 0.001). This study confirms the short-term effectiveness of paroxetine for social phobia, and studies are underway that will assess long-term effectiveness (Baldwin et al, 1999).

4) In a smaller study with a similar design, paroxetine was effective and tolerated well during treatment of social anxiety disorder (Allgulander, 1999). After diagnosing social phobia by DSM-IV criteria, patients (n=96) were randomly assigned to receive paroxetine 20 to 50 milligrams daily or placebo for 3 months. Beginning after 4 weeks, the Clinical Global Impression (CGI) scale showed a significantly higher proportion of responders with paroxetine (70.5%) than placebo (8.3%; p less than 0.0001). The difference in total Liebowitz Social Anxiety Scale score was also significantly different between treatments beginning at 4 weeks (mean decrease 33.4 versus 8.6; p=0.0001). Eight patients treated with paroxetine withdrew from treatment due to adverse effects compared to 3 patients treated with placebo.

5) Paroxetine was effective for treating generalized social phobia in a 12-week, double-blind trial. Patients were randomly assigned to receive paroxetine 20 milligrams (mg) daily (n=91) or placebo (n=92). After 2 weeks of treatment, paroxetine treated patients not achieving a clinical response were increased to paroxetine 30 mg daily. Further dose titration upwards (to a maximum daily dose of 50 mg) and downwards were used to facilitate response and avoid adverse reactions. Fifty (55%) patients treated with paroxetine achieved a clinical response determined by mean changes from baseline in Liebowitz Social Anxiety Scale scores and by Clinical Global Improvement scores of very much improved or much improved. Twenty-two (23.9%) of those treated with placebo demonstrated a clinical response, a statistically significant difference from the paroxetine treated group. Paroxetine was tolerated well with 14 discontinuations due to adverse effects. Only 3 of the patients treated with placebo discontinued the study due to adverse effects. Although this study demonstrated the efficacy of paroxetine in the treatment of generalized social phobia, further studies addressing dose and duration of therapy are needed (Stein et al, 1998).

6) Of 30 patients with the generalized subtype of social phobia, 23 (76.7%) were rated as responders to paroxetine. During the double-blind, randomized discontinuation phase, 1 (13%) and 5 (63%) patients treated with paroxetine and placebo, respectively, relapsed; the difference was not significant. All patients (n=36) were initially treated with paroxetine 10 milligrams (mg) daily with titration to 50 mg daily during the open phase. Responding patients as determined by a Clinical Global Impressions scale score of much or very much improved were asked to participate in the discontinuation study where paroxetine was stopped over 1 week. Side effects were mild and tolerable. This study suggests that paroxetine is effective for treating generalized social phobia; however, long-term, placebo-controlled trials are needed (Stein et al, 1996).

4.5.A.23 Somatization 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:
Paroxetine was an effective treatment for somatization disorder in one patient

c) Adult:
1) Somatization disorder was successfully treated with paroxetine in one female patient. A 38-year-old woman with a 16-year history of joint pain was given paroxetine (initial, 10 milligrams (mg)/day titrated to 40 mg/day over 6 weeks) after being diagnosed with somatization disorder. Her joint pain improved within 3 weeks of treatment and following 8 weeks, she was able to climb and descend stairs. She was maintained on paroxetine 30 mg/day and diazepam 4 mg/day during outpatient therapy (Okugawa et al, 2002).

4.5.A.24 Trichotillomania

a) Overview
FDA Approval: Adult, no; Pediatric, no
Efficacy: Pediatric, Evidence is inconclusive
Recommendation: Pediatric, Class IIb
Strength of Evidence: Pediatric, Category C
See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:
Produced major improvement in trichotillomania in adolescent

c) Pediatric:
1) A 16-year-old woman had clinically significant improvement in HAIR PULLING but not depression after treatment with paroxetine 10 milligrams (mg) daily for 2 weeks. She had a history of trichotillomania since 2 years of age. Depressive symptoms finally improved after several weeks of therapy with paroxetine 20 mg alternating with paroxetine 30 mg daily. This case is interesting due to the rapid, clinically significant decrease in trichotillomania with paroxetine 10 mg compared to the higher dose and longer duration of treatment required before depression responded. Additional study of paroxetine is needed for this use (Block et al, 1998).

4.5.A.25 Vasovagal syncope

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:
In a small study, paroxetine reduced the number of syncopal episodes

c) Adult:
1) Significantly fewer episodes of vasovagal syncope occurred in patients treated with paroxetine than placebo. Sixty-eight consecutive patients with a positive head-up tilt test and lack of response to other therapies were randomly assigned to blinded treatment with paroxetine 20 milligrams/day or placebo. One month after initiating paroxetine, a repeat tilt test revealed syncope in 38.2% and 61.8% of patients treated with paroxetine and placebo, respectively (p=0.001). During at least 24 months of follow-up, spontaneous syncope was reported by 52.9% and 17.6% of patients in the placebo and paroxetine groups, respectively (p less than 0.0001). Patients treated with paroxetine also reported a decrease in syncopal episodes from 8.1 to 5.9/year during treatment. Treatment was discontinued in 1 patient receiving paroxetine due to severe recurrent headaches. While paroxetine appears effective, larger and longer study is needed (Di Girolamo et al, 1999).

4.6 Comparative Efficacy / Evaluation With Other Therapies

Amisulpride

Amitriptyline

Aprepitant

Bupropion

Citalopram

Clomipramine

Delorazepam

Doxepin

Duloxetine

Escitalopram

Fluoxetine

Fluvoxamine

Imipramine

Maprotiline

Mianserin

Mirtazapine

Nortriptyline

Risperidone

Sertraline

Sildenafil

Sulpiride

Venlafaxine

4.6.A Amisulpride

4.6.A.1 Burning mouth syndrome

a) Amisulpride, sertraline, and paroxetine were all effective in reducing the symptoms of burning mouth syndrome (BMS), but response was achieved earlier with amisulpride than with the selective serotonin reuptake inhibitors (SSRIs). In a randomized, single-blind study, 76 patients with BMS and without major depression were given amisulpride 50 milligrams (mg) per day, paroxetine 20 mg/day, or sertraline 50 mg/day for 8 weeks. Pain scores decreased significantly in all groups, as did depression (Hamilton Rating Scale for Depression) and anxiety (Hamilton Rating Scale for Anxiety), by week 8. The only difference among treatments was the shorter latency to response in the amisulpride group (22% of patients responding at 2 weeks with amisulpride vs 0% with paroxetine and 6% with sertraline) (Maina et al, 2002a).

4.6.B Amitriptyline

4.6.B.1 Depression

a) SUMMARY: Paroxetine and amitriptyline have been comparable in the treatment of depression; adverse effects have occurred to a lesser degree with paroxetine.

b) Paroxetine and amitriptyline were equally efficacious for the treatment of depression in women with BREAST CANCER in an 8- week, double-blind, parallel-group, randomized study. After a 3 to 7 day washout period, breast cancer patients diagnosed with mild to severe depression were randomized to receive either paroxetine (n=88) 20 to 40 milligrams (mg) per day, or amitriptyline (n=87) 75 to 150 mg per day. There was no statistically significant difference in depressive symptomatology between the treatment groups, but both groups improved significantly compared to baseline by the end of the 8-week trial. At endpoint, both groups had about a 10 point reduction (paroxetine 10.5, amitriptyline 9.4) on the Montgomery Asberg Depression Rating Scale (MADRS) and this corresponded to an overall response rate (50% or

greater reduction in MADRS) of 43.7% and 37.9%, respectively Both groups showed improvement on the Clinical Global Impression (CGI) severity of illness scale (from moderately/mildly ill to borderline ill) and on the CGI improvement and Patient's Global Evaluation (PGE) rating scales (minimally to much improved). Each group also demonstrated a steady improvement in quality of life as measured by the Functional Living Index: Cancer (FLIC) scale. There was no statistically significant difference between the paroxetine- and amitriptyline-treated groups in regards to adverse drug reactions with somnolence most frequently reported in both groups and dry mouth most frequently reported in the amitriptyline group. Six patients in the amitripyline group and 6 in the paroxetine group withdrew from the study due to adverse experiences considered by the investigators to be possibly related or related to the study medications (Pezzella et al, 2001).

c) Paroxetine and amitriptyline were equally efficacious for the treatment of depression in patients with RHEUMATOID ARTHRITIS (RA); paroxetine was associated with fewer adverse effects. After a 2-week washout period, RA patients with mild to severe depression were randomized to receive either paroxetine 20 milligrams (n=94) and an amitriptyline-matched placebo or amitriptyline 75 mg (n=97) and a paroxetine-matched placebo for the first 2 weeks. At week 2 or week 4, doses could be increased to paroxetine 40 mg or amitriptyline 150 mg, depending on the patients' response. Improvements, according to a depression rating scale, were similar for the 2 groups at 4, 8 and 12 weeks (endpoint). At week 8, 65% of the paroxetine group and 56% of the amitriptyline group considered themselves "much improved" or "very much improved" (p=0.4). Improvements in RA symptom severity were similar for the 2 groups (Bird & Broggini, 2000).

d) Paroxetine and amitriptyline provided comparable benefit when added to maintenance lithium therapy for treating a major depressive episode; however, improvement was more rapid in the paroxetine-lithium than the amitriptyline-lithium group (Bauer et al, 1999). In this double-blind, parallel-group study, patients (n=42) were randomly assigned to receive paroxetine 20 milligrams (mg) daily or amitriptyline 50 mg daily increased to 75 mg on the fourth day. The study protocol permitted dose titration to paroxetine 40 mg daily and amitriptyline 150 mg daily. All patients were on a stable lithium regimen with documented serum lithium levels between 0.5 and 0.8 millimoles/liter. At 6 weeks, a statistically significant difference was NOT noted between treatments on the Hamilton Rating Scale for Depression (HAM-D) or the Clinical Global Impression Scale (CGI). As expected, adverse effects differed between paroxetine (ie, nausea, headache, increased motor activity) and amitriptyline (ie, dry mouth, blurred vision, tremor, hypotension, constipation). Serum lithium levels did NOT change significantly after addition of paroxetine or amitriptyline.

e) Several controlled trials of 6 to 7 weeks duration have reported the similar efficacy of paroxetine and amitriptyline in the treatment of major depression (Bascara, 1989; Byrne, 1989; Kuhs & Rudolf, 1989; Laursen et al, 1985a; Battegay et al, 1985; Gagiano et al, 1989). Based upon these data, paroxetine 30 mg once daily appears to be as effective as amitriptyline 150 mg once daily. However, in some of these studies, amitriptyline has been either superior to paroxetine, or exhibited a definite trend toward superiority, after 3 weeks of treatment (Laursen et al, 1985a; Kuhs & Rudolf, 1989). Due to these findings, some investigators recommend higher doses of paroxetine (30 to 50 mg daily) in future clinical comparisons with antidepressants. Anticholinergic effects, such as dry mouth and constipation, have been less with paroxetine compared to amitriptyline in some studies (Hassan et al, 1985a; Kuhs & Rudolf, 1989; Laursen et al, 1985a) but no significant difference was observed in others (Bascara, 1989; Battegay et al, 1985). Cardiovascular effects (increase in heart rate, decrease in left ventricular ejection time index) have also been less with paroxetine as compared to amitriptyline (Kuhs & Rudolf, 1989; Warrington et al, 1989a). However, in some studies, the cardiovascular adverse effects have occurred to a similar degree (Byrne, 1989).

f) The comparable efficacy of paroxetine and amitriptyline were reported in the treatment of DSM-III major depression in a randomized, double-blind study involving 53 patients (Bascara, 1989). Mean ages were 37 years in the paroxetine group and 31 years in the amitriptyline group. Paroxetine was administered in doses of 20 mg once daily for 3 days, then 30 mg once daily for the remainder of the 6-week study; amitriptyline was given in an initial dose of 50 mg once daily, with the dose being increased to 75 mg once daily after 3 days. All doses were administered in the morning. Both drugs produced similar reductions in the 21-item Hamilton Depression Rating Scale (HAMD) and physician's global assessment ratings. The incidence of adverse effects was similar with both agents, with the exception of sweating, which occurred to a greater degree with paroxetine. Among 50 evaluable patients, adverse effects accounted for 2 withdrawals in the paroxetine group (nausea, vomiting) and 3 in the amitriptyline group (sweating, chest pain, drowsiness in 2; daytime drowsiness in 1).

4.6.C Aprepitant

4.6.C.1 Depression

a) In a 6-week, placebo-controlled comparison, paroxetine 20 mg and aprepitant 300 mg, each given once daily, were similarly effective in patients with major depression (score of 22 of higher on the 17-item Hamilton Rating Scale for Depression (HAM-D17)) and moderately-high anxiety (at least 15 on the Hamilton Rating Scale for Anxiety (HAM-A)). Improvement in the 21-item HAM-D scale (primary endpoint) after 6 weeks was similar in the paroxetine and aprepitant groups; each agent was significantly superior to placebo. Complete response, defined as an HAM-D17 score of less than 10, was achieved in 33%, 43%, and 17% of patients treated with paroxetine, aprepitant, and placebo, respectively. Improvement in the HAM-A score was significantly greater with aprepitant (but not paroxetine) versus placebo. No adverse effect occurred more commonly with aprepitant compared to paroxetine (Krishnan, 2002; De Vane, 2001).

4.6.C.2 Adverse Effects

a) In one relatively large study (n=213), paroxetine 20 mg daily tended to produce a higher incidence of adverse effects than aprepitant 300 mg daily in depressed patients, including nausea, fatigue, anorexia, sweating, and sexual dysfunction; however, the only one of these effects which was statistically significantly higher in the paroxetine group was sexual dysfunction (26 versus 3%) (Krishnan, 2002).

4.6.D Bupropion

4.6.D.1 Depression, Elderly

a) Both bupropion sustained release (SR) and paroxetine were found to be safe and effective for the treatment of depression in the elderly (greater than or equal to 60 years of age). In a 6-week, multicenter, double-blind study, 100 patients were randomized to receive bupropion SR (100 to 300 milligrams/day) or paroxetine (10 to 40 milligrams/day). After 6 weeks, the patients had improved scores on all depression rating scales and both treatments were similarly effective, with no statistically significant differences between the 2 treatment groups. With the exception of headache (occurring in 25% of bupropion SR- treated patients versus 19% of paroxetine-treated patients), the occurrence of other side effects was generally higher with paroxetine compared with bupropion SR. The data suggests that bupropion SR may provide a safe and effective alternative to serotonergic agents in the treatment of depression in the elderly (Weihs et al, 2000).

4.6.E Citalopram

4.6.E.1 Late ejaculation

a) Paroxetine significantly increased the latency time of ejaculation in men with life-long premature ejaculation, whereas citalopram had very little effect. Thirty men with intravaginal ejaculation times (IELT) of less than 1 minute were given either paroxetine 20 milligrams (mg) per day or citalopram 20 mg/day for 5 weeks after receiving half-doses for a week. The geometric mean of IELT increased from 20 to 170 seconds in the paroxetine group and from 20 to 44 seconds in the citalopram group (p less than 0.001 for group differences; p less than 0.001 for change from baseline for paroxetine; and p=0.07 for change from baseline for citalopram). Neither drug had clinically relevant effects on sexual desire, arousal, erectile dysfunction, or penile rigidity, although 3 patients in the paroxetine group reported a slight decrease in sexual desire and penile rigidity. The authors suggested that paroxetine may be useful for treating premature ejaculation and that citalopram may be useful for treating patients in need of a selective serotonin reuptake inhibitor who do not want ejaculation delay (Waldinger et al, 2001).

4.6.F Clomipramine

Depression

Obsessive-compulsive disorder

4.6.F.1 Depression

a) In a large (n=1002) clinical trial, treatment with paroxetine or clomipramine produced similar decreases in anxiety and depression scores; however, adverse effects occurred in significantly (p=0.025) more patients treated with clomipramine than paroxetine (Ravindran et al, 1997). Statistically significant differences between treatments were NOT found on the Montgomery-Asberg Depresssion Rating Scale (MADRS) or Clinical Anxiety Scale (CAS), but a trend in favor of paroxetine was observed for the Clinical Global Impressions (CGI) score at 6 and 12 weeks (p=0.015). Patients entered into this trial had depression with anxiety which was treated in a primary care setting. Paroxetine 20 milligrams (mg) daily was used initially but the protocol permitted an increase to 40 mg daily, if needed, after 4 weeks. Clomipramine titration proceeded as follows: (1) 25 mg in the evening for 3 days; (2) 50 mg in the evening for 4 days; (3) 75 mg daily (25 mg in the morning and 50 mg in the evening); and (4) after 4 weeks, the dose could be increased to 150 mg/day. Based on this study, paroxetine and clomipramine have comparable efficacy but the incidence of adverse effects (AE) including serious AE is lower in patients treated with paroxetine.

b) Paroxetine 30 milligrams once daily was as effective as clomipramine 25 milligrams three times daily in the treatment of major depressive disorder in a 6-week, double-blind study involving 79 elderly patients (60 years of age or older) (Guillibert et al, 1989). Anticholinergic effects and somnolence occurred to a greater degree with clomipramine, whereas nausea and vomiting were observed more frequently with paroxetine.

c) Clomipramine demonstrated a significantly better therapeutic effect than paroxetine using categorical response measures and group averages of rating scores during a double-blind, randomized, inpatient study of 120 depressed patients (Anon, 1990). Patients were randomized to receive either paroxetine 30 milligrams/day or clomipramine 150 milligrams/day for this 6-week study. At the end of week 4, 27 patients were rated as nonresponders and were terminated from the study. Of thses 27 patients, 23 were in the paroxetine group.

4.6.F.2 Obsessive-compulsive disorder

a) In a 12-week, comparative study, paroxetine was as effective as clomipramine for treating obsessive compulsive disorder. Patients were randomly assigned to receive placebo (n=99), paroxetine 10 milligrams (mg) (n=201), or clomipramine 25 mg daily (n=99); the dose of active treatments was titrated to a maximum of 60 mg and 250 mg for paroxetine and clomipramine, respectively. No statistically significant differences were found in the primary efficacy measures, the Yale-Brown Obsessive-Compulsive Scale or the National Institute of Mental Health Obsessive-Compulsive Scale, between paroxetine or clomipramine; however, both drugs were significantly better than placebo. Adverse effects requiring treatment withdrawal occurred in fewer patients treated with paroxetine (9%; p=0.033) than clomipramine (17%). Limitations of the study are the relatively short duration, and the potential loss of blinding due to differences in adverse effects (Zohar et al, 1996).

4.6.G Delorazepam

4.6.G.1 Anxiety

a) Delorazepam was compared to imipramine and paroxetine in 81 patients with generalized anxiety disorders according to DSM-IV criteria. Approximately 70% of all patients who completed the study showed great or moderate improvement. Delorazepam produced the greatest improvement in anxiety ratings during the first two weeks of treatment, but both paroxetine and imipramine were more effective by the fourth week of treatment. Delorazepam affects predominantly somatic symptoms, whereas paroxetine and imipramine affect psychic symptoms (Rocca et al, 1997a).

4.6.H Doxepin

4.6.H.1 Depression

a) Paroxetine was at least as effective as doxepin in the treatment of major depression in 272 geriatric patients in a double-blind, randomized trial. After a washout-period of 4 to 14 days, patients over 60 years of age received either paroxetine 10 to 40 milligrams (mg) (mean 23.4 mg) as a single daily dose or doxepin (up to 200 milligrams (mg), mean 105.2 mg/day) divided in two doses. Therapy continued for 42 days. Paroxetine was as effective as doxepin by several measures and more effective by others. Doxepin caused more sedation, confusion, and anticholinergic effects, and less nausea and headache compared with paroxetine (Dunner et al, 1992).

4.6.I Duloxetine

4.6.I.1 Major depressive disorder

a) Duloxetine therapy was more effective than placebo and non-inferior to paroxetine therapy in the treatment of psychological and physical symptoms of depression. In a randomized, double-blind, placebo-controlled, multi-center study, patients (n=353) with major depressive disorder, a Hamilton Depression Rating Scale (HAM-D) total score of at least 15, and a moderate Clinical Global Impression (CGI) Severity rating (score of at least 4) received oral duloxetine 80 milligrams (mg) daily (in divided doses), duloxetine 40 mg daily (in divided doses), paroxetine 20 mg daily, or placebo for 8 weeks. Response was defined as at least a 50% reduction from baseline in the HAM-D total score and remission was defined as a HAM-D score of 7 or less. At week 8, both the 80 and 40 mg dosing regimens of duloxetine produced significantly greater reductions in HAM-D scores from baseline as compared with placebo (mean difference, 3.62 points, 95% CI 1.38, 5.86; p=0.002 and 2.34 points, 95% CI 0.19, 4.66; p=0.034, respectively). A significantly greater reduction in HAM-D total scores was also observed with duloxetine 80 mg therapy as compared with paroxetine treatment (mean difference, 2.39 points, 95% CI 0.14, 4.65; p=0.037). Paroxetine therapy was not significantly different from placebo at week 8, however at weeks 2, 4, and 6; paroxetine treatment was superior to placebo. The response rate at endpoint was significantly higher in patients treated with duloxetine 80 mg as compared with placebo (51% vs 31%, p=0.009, respectively). Additionally, the remission rate in the duloxetine 80 mg group (50%) was significantly higher at endpoint as compared with remission rates for patients in the duloxetine 40 mg group (35%; p=0.045) and the placebo group (30%; p=0.008), but was not superior to patients in the paroxetine group (37%; p=ns). Significant reductions from baseline to endpoint in overall pain severity were observed in patients treated with duloxetine 80 mg (reduction from baseline, 47%; -7.5 points on VAS scale, 95%CI -25, 1; p=0.005), as compared with placebo, however significant reductions were not seen with paroxetine or duloxetine 40 mg therapy as compared with placebo. Both duloxetine and paroxetine were generally well tolerated and only insomnia was reported significantly more often in duloxetine-treated (80 mg) patients as compared with paroxetine-treated patients (19.8% vs 8%, respectively; p=0.031) (Goldstein et al, 2004).

4.6.J Escitalopram

4.6.J.1 Generalized anxiety disorder

a) In a randomized, double-blind, multi-center trial involving patients (mean age, approximately 37 years) with moderate to severe generalized anxiety disorder (GAD), treatment with either escitalopram (10 to 20 milligrams (mg) per day), or paroxetine (20 to 50 mg per day) lead to improvements over time in all efficacy measures; however, escitalopram was better tolerated. The primary efficacy endpoint was change in Hamilton Anxiety Scale (HAMA) total score from baseline to week 24 for the intent -to-treat (ITT) population.

Mean baseline HAMA scores were 23.7 +/- 0.5 standard error of the mean (SEM) for the escitalopram-treated patients (n=60) and 23.4 +/- 0.4 SEM for the paroxetine-treated patients (n=61). Upon analysis of efficacy data, there were no statistically significant differences between treatment groups at week 8 or week 24. At week 24, mean changes in HAMA scores were -15.3 +/- 0.8 SEM and -13.3 +/- 1 SEM for the escitalopram and paroxetine groups, respectively. The proportions of patients who met the response criterion (Clinical Global Impressions of Improvement (CGI-I) of 1 or 2) at week 8 were 65% for escitalopram and 55.7% for paroxetine and at week 24 were 78.3% and 62.3%, respectively. These differences were not statistically significant. A greater proportion of patients treated with paroxetine withdrew from the study due to adverse events compared to those receiving escitalopram (22.6% vs. 6.6%, respectively; p=0.02). While no single adverse event was reported as the reason for discontinuation of escitalopram therapy by more than one patient, headache, insomnia, and nausea each lead to the discontinuation of paroxetine in 2 or more patients. Upper respiratory tract infections and diarrhea were reported more frequently with escitalopram than with paroxetine (14.8% vs. 4.8% and 21.3% vs. 8.1%, respectively). Insomnia (25.8% vs. 14.8%), constipation (14.5% vs. 1.6%), ejaculation disorder (30% vs. 14.8%), anorgasmia (26.2% vs. 5.9%) and decreased libido (22.6% vs. 4.9%) occurred more frequently in the paroxetine group compared to the escitalopram group, respectively. Overall, the incidence of treatment emergent adverse events was 88.7% for paroxetine and 77% for escitalopram (Bielski et al, 2005).

4.6.K Fluoxetine

4.6.K.1 Depression

a) Paroxetine, fluoxetine, and sertraline were equally effective for the treatment of depression and for improving quality of life in patients in a primary care setting. In a 9-month, randomized, open-label trial (the ARTIST trial), depressed patients, whose symptoms warranted antidepressant treatment, according to their primary care physicians (PCP), were given paroxetine (n=180), fluoxetine (n=184) or sertraline (n=182). Starting doses were paroxetine 20 milligrams (mg), fluoxetine hydrochloride 20 mg, and sertraline 50 mg. The PCP could adjust the dose on the basis of clinical response and could switch the treatment to one of the other study drugs. Final average doses were 23.5 mg for paroxetine, 23.4 mg for fluoxetine, and 72.8 mg for sertraline. All 3 groups showed substantial improvement in depressive symptoms and quality of life. Overall, the percentage of patients categorized as having major depression dropped from 74% at baseline to 32% at 3 months, and 26% at 9 months. No significant differences were evident among the 3 groups. When data from subgroups (patients with major depression, patients who completed the trial on the drug initially assigned) were analyzed separately, still no differences among the drug treatments was evident. Patient satisfaction did not differ for the 3 groups. Changes in sexual function were small but tended to show improvement for all drug treatments. The drugs were associated with similar incidences of adverse effects and discontinuation rates (Kroenke et al, 2001a).

b) Paroxetine and fluoxetine demonstrated similar efficacy following 6 weeks of treatment in depressed patients (De Wilde et al, 1993). However, the paroxetine-treated patients had a statistically significant difference in terms of reduction of Hamilton Rating Scale for depression after three weeks of treatment. This suggests that paroxetine may have a faster onset of activity than fluoxetine. The most commonly reported adverse effects were nausea and vomiting for both drugs.

4.6.L Fluvoxamine

4.6.L.1 Depression

a) Fluvoxamine and paroxetine produced similar improvements in depressive symptoms in patients with an initial or recurrent episode of major depression. Adverse effects occurred in 100% and 97% of patients treated with paroxetine and fluvoxamine, respectively. Fluvoxamine was associated with a higher incidence of asthenia, dry mouth, somnolence, and insomnia; whereas, paroxetine caused a higher incidence of headache, nausea, diarrhea, sweating, abnormal dreams, and sexual dysfunction. In this 7-week, randomized, double-blind study, 58 patients were assigned to receive fluvoxamine 50 milligrams(mg)/day or paroxetine 20 mg/day initially; the protocol allowed for dosage titration to fluvoxamine 150 mg/day or paroxetine 50 mg/day. An additional 10 fluvoxamine- and 8 paroxetine-treated patients dropped out of the study for various reasons, but all of the patients were included in the intent-to-treat efficacy analysis. Due to the small sample size of this study, only large differences between treatments would be detectable; therefore, larger studies are needed to detect differences in treatment effects between these drugs (Kiev & Feiger, 1997).

b) The pharmacology, pharmacokinetics, adverse effects, drug interactions, efficacy, and dosage and administration of fluvoxamine (FVX), sertraline (SRT) and paroxetine (PRX) were compared in a comprehensive review (Grimsley & Jann, 1992). All three agents have large volumes of distribution and are highly protein-bound. In contrast to fluoxetine, FVX, SRT, and PRX all have shorter elimination half-lives (approximately 24 hours) and are metabolized to clinically-inactive compounds. Nausea was the most commonly reported adverse effect for all three agents. Other reported adverse effects include sedation, headache, dry mouth, insomnia, sexual dysfucntion, and constipation. FVX has been found to be superior to placebo and equivalent to imipramine, clomipramine, desipramine, mianserin, and maprotiline in the treatment of depression and both FVX and SRT have been shown to be superior to placebo in the treatment of obsessive-compulsive disorder (OCD). PRX has been found to be superior to placebo and equivalent to amitriptyline, imipramine, clomipramine, and doxepin in the treatment of depression while SRT has been

found to be superior to placebo and equivalent to amitriptyline. Clinical experience has demonstrated all three drugs to be effective in the treatment of depression. They may be especially useful in elderly patients, in those who cannot tolerate alternate treatments, and in those who do not respond to adequate trials of other antidepressant therapies.

4.6.M Imipramine

Anxiety

Bipolar disorder, depressed phase

Depression

4.6.M.1 Anxiety

a) In an uncontrolled trial, paroxetine and imipramine were as effective as 2- chlordesmethyldiazepam, a benzodiazepine, for treating generalized anxiety disorder (Rocca et al, 1997). Patients (n=81) received paroxetine 20 milligrams(mg)/day, imipramine 50 to 100 mg/day, or 2-chlordesmethyldiazepam 3 to 6 mg/day for 8 weeks. Over the first 2 weeks, patients treated with 2-chlordesmethyldiazepam showed greater improvement; however, after 4 weeks for paroxetine and 8 weeks for imipramine, the anti-depressants were more effective. Adverse effects consisted primarily of anticholinergic effects for imipramine, nausea for paroxetine, and drowsiness for 2-chlordesmethyldiazepam. Larger, blinded, controlled clinical trials are needed to confirm the results of this study.

4.6.M.2 Bipolar disorder, depressed phase

a) Neither paroxetine nor imipramine was more effective than placebo in treating BIPOLAR DEPRESSION in patients stabilized on lithium if their serum lithium levels were above 0.8 milliequivalents per liter (meq/L). However, patients whose serum lithium concentration was less than 0.8 meq/L showed greater improvement with 8 weeks of antidepressant treatment than with placebo treatment (p=0.05 for paroxetine, p=0.04 for imipramine). In a double-blind study, patients were stratified according to serum lithium concentration and then randomized to receive paroxetine (n=35), imipramine (n=39), or placebo (n=43) for 10 weeks. Among all completers of the study, therapeutic response (Hamilton depression scale scores of 7 or less) was achieved by 56%, 48%, and 54% of patients receiving paroxetine, imipramine, and placebo, respectively. Adverse events accounted for study discontinuation in 1 patient in the paroxetine group (3%), 12 in the imipramine group (30%), and 5 in the placebo group (12%). No patient in the paroxetine group experienced induction to mania, whereas 3 patients treated with imipramine and 1 treated with placebo developed treatment-emergent mania (Nemeroff et al, 2001).

4.6.M.3 Depression

a) SUMMARY: Paroxetine, a selective serotonin reuptake inhibitor, and imipramine appear to be similarly effective in the treatment of major depression. The decision as to which drug to use should be based on patient-related characteristics (eg, anxiety disorders, sleep disturbances, cardiovascular disease), potential drug interactions, and side effects.

b) Paroxetine, imipramine, and placebo were compared in 120 outpatients with moderate-to-severe major depression (DSM-III) (Feighner & Boyer, 1989). Following a 4- to 14-day single-blind, placebo washout period, patients were assigned to receive either paroxetine, imipramine, or placebo for 6 weeks. The dose of paroxetine and imipramine could be increased to a maximum of 50 milligrams and 275 milligrams daily, respectively. Paroxetine was superior to placebo in 5 of 6 measures evaluated (HAMD scale, Raskin depression scale, MADRS, CGI scale, Covi anxiety scale); no improvement was observed as compared to placebo in the 56-item Symptom Checklist (SCL-56). Imipramine was also statistically superior to placebo on HAMD, Raskin, MADRS, and the CGI scale, but not on the Covi anxiety scale or the SCL-56. The only outcome measure that improved to a significantly greater degree with paroxetine was the HAMD total score. A high number of patients discontinued therapy (approximately 50%), which limits evaluation of efficacy. If only the patients completing the study are considered, imipramine and paroxetine appear to be equally effective. Based upon the number of dropouts due to adverse effects, paroxetine appeared to be better tolerated than imipramine: 10% versus 30%. The most common adverse effects with paroxetine were sedation and gastrointestinal effects, whereas anticholinergic adverse effects (dry mouth, constipation, urinary symptoms) were the most common with imipramine. However, a detailed incidence of all adverse effects was not provided, making it difficult to fully compare these agents.

c) Paroxetine was more effective than placebo in the short-term (6-week) treatment of depression; however, paroxetine was less effective than imipramine. The study was double-blinded and 122 patients with a major depressive disorder were randomized to receive either paroxetine (dose range 20 to 50 milligrams/day), imipramine (dose range 65 to 275 milligrams/day) or placebo. At the end of the study, the imipramine-treated patients demonstrated consistently better scores, both objective and subjective, on all depression rating scales when compared to paroxetine. Overall there was a 64% response rate to imipramine, a 48% response rate to paroxetine, and a 33% response rate to placebo (Peselow et al, 1989).

d) A multicenter, double-blind, placebo-controlled evaluation of paroxetine and imipramine in the outpatient treatment of major depression was conducted (Dunbar et al, 1991a). After a 4- to 14-day placebo run-in period, patients were randomized to their treatment groups; 240 to the paroxetine group, 237 to the imipramine group, and 240 to the placebo group. Therapy was started at 20 milligrams paroxetine and 80 milligrams imipramine. Dosage adjustment, if necessary, was done at weekly intervals over the six-week treatment phase. Drop-out rates were high for all groups; paroxetine 42.5%, imipramine 53.3%, and placebo 53.6%. Lack of efficacy (10%, 7%, and 33%, respectively) and side effects (23%, 36%, and 9%, respectively) were the most common reasons stated for dropping out of the study. Imipramine and paroxetine were equally superior to placebo and produced similar efficacy results. However, paroxetine therapy was associated with less sedation, cardiovascular, and anticholinergic side effects.
e) Newer clinical trials have continued to support the previous findings that imipramine and paroxetine are similar in effectiveness. The major differences between the two compounds are the frequency of side effects, types of side effects, and frequency of patients withdrawing from the clinical trials secondary to side effects from the study medications. In all cases paroxetine therapy is better tolerated and associated with lower withdrawal rates (Ohrberg et al, 1992; Feighner et al, 1993); (Arminen et al, 1994).
f) A 6-week, double-blind study was continued for 1 year by crossing over all patients who had failed to respond to initial treatment to the other drug (Peselow et al, 1989a). Patients first treated with placebo were crossed over to paroxetine (n=19). A total of 15 patients initially treated with paroxetine switched to imipramine, while 10 imipramine patients were switched to paroxetine. Of the patients who initially failed on paroxetine, 73% responded to imipramine, while 50% of the patients who initially failed on imipramine responded to paroxetine. Similar studies have shown paroxetine to be at least as effective as imipramine with fewer side effects (Fabre, 1992a; Cohn & Wilcox, 1992; Shrivastava et al, 1992; Feighner & Boyer, 1992).

4.6.N Maprotiline

Chronic pain

Depression

Premenstrual dysphoric disorder

4.6.N.1 Chronic pain

a) SUMMARY: MAPROTILINE proved more efficacious for relief of chronic back pain than PAROXETINE, in a double-blind, randomized trial.
b) MAPROTILINE, a noradrenergic antidepressant, provided more effective analgesia than did PAROXETINE, a serotonergic antidepressant, or DIPHENHYDRAMINE (placebo) in non-depressed adult patients with chronic low back pain, according to an 8-week, randomized, double-blind trial (n=74). Pain intensity was measured on the Descriptor Differential Scale (DDS; Gracely & Kwilosz, 1988). Pain intensity scores dropped by 45%, 26%, and 27% for maprotiline-, paroxetine-, and placebo-treated patients, respectively (p=0.013, maprotiline vs paroxetine; p=0.023, maprotiline vs placebo). Decreases in pain unpleasantness were also significantly greater for maprotiline compared with placebo (p=0.009), but were similar to the reductions for paroxetine (NS). Dosing of maprotiline was 50 milligrams (mg) per day for 3 days, followed by 100 mg for 3 days and then an increase to the target dose of 150 mg/day. Paroxetine was started at 10 mg/day for 3 days, followed by 20 mg/day for 3 days and then an increase to the target dose of 30 mg/day. The target dose (or maximum tolerable dose) was taken once daily at 2100 hours. Overall, 15 patients dropped out of the study due to adverse effects (9, maprotiline; 6, paroxetine); 1 patient in the paroxetine group discontinued due to lack of efficacy. The authors suggest that noradrenergic agents or combined noradrenergic/serotonergic agents may be preferable therapy for chronic back pain than serotonergic agents (Atkinson et al, 1999).

4.6.N.2 Depression

a) Paroxetine and maprotiline are similarly effective in the treatment of major depression. In a double-blind study involving a relatively small number of patients (n=71), treatment with either paroxetine (20 to 40 milligrams daily) or maprotiline (50 to 150 milligrams daily) resulted in comparable improvement in symptoms of depression as measured by the Hamilton Psychiatric Rating Scale for Depression (HAMD), the Montgomery-Asberg Depression Rating Scale, the Clinical Global Impression, and the Hopkins Symptoms Checklist. Patients treated with paroxetine experienced fewer side effects; however, this difference was not statistically significant (Schnyder & Koller-Leiser, 1996).

4.6.N.3 Premenstrual dysphoric disorder

a) Paroxetine was more effective than maprotiline or placebo for treating premenstrual symptoms. Following assessment of symptom severity for 2 months, patients were randomly assigned to placebo (n=22), maprotiline (n=21), or paroxetine (n=22). The initial dose of maprotiline and paroxetine was 25 milligrams (mg) and 10 mg, respectively. The maximum dose allowed by the study protocol was 150 mg for maprotiline

and 30 mg for paroxetine. Efficacy was assessed by determining the percentage reduction from baseline for 6 symptoms observed with PDD. All symptoms (ie, irritability, depressed mood, anxiety, increased appetite, bloating, and breast tenderness) were significantly reduced by paroxetine compared to maprotiline and placebo; there were no significant changes between maprotiline and placebo. While paroxetine, a selective serotonin reuptake inhibitor, was more effective than maprotiline, a noradrenaline reuptake inhibitor, the criteria for assessment were less stringent than in other similar trials (Eriksson et al, 1995).

4.6.O Mianserin

4.6.O.1 Depression

a) Paroxetine 30 mg once daily in the morning was as effective as mianserin 30 mg twice daily (morning and night) in the treatment of unipolar or bipolar depression in a controlled inpatient/outpatient study involving 70 patients (Mertens & Pintens, 1988a). Significantly greater reductions in subscales for cognitive disturbance and retardation were observed with paroxetine at some, but not all, time points during the 6-week study. Adverse effects occurred to a similar degree with each agent, with the most common being nausea and headache with paroxetine and somnolence with mianserin.

4.6.P Mirtazapine

4.6.P.1 Major depressive disorder

a) Paroxetine and mirtazapine demonstrated similar efficacy in the treatment of major depressive disorder, with mirtazapine demonstrating a potentially faster onset of action. In a double-blind study, patients with major depression randomly received mirtazapine (n=127) or paroxetine (n=123) for 6 weeks. Patients receiving mirtazapine received 15 milligrams/day (mg) for 2 days then 30 mg thereafter; an increase to 45 mg daily was allowed after 2 weeks in nonresponders. Initial paroxetine doses were 20 mg daily increased to 40 mg daily in nonresponders after 2 weeks. During the study, mean daily doses of mirtazapine and paroxetine were 32.7 mg and 22.9 mg, respectively. The percentage of patients responding to therapy after 1 week as measured by the Hamilton Depression Rating Score-17 (HAM-D-17) was significantly greater in the mirtazapine group (23.2%) as compared to the paroxetine group (8.9%, p=0.002). At endpoint, the patients achieving complete remission, defined as a score of less than 7 on the HAM-D-17, was 40.9% in the mirtazapine group and 34.1% in the paroxetine group (p not significant). Both treatments also produced decreases in anxiety as measured by the Hamilton Rating Scale for Anxiety. Dropouts due to adverse events occurred in 8.6% of mirtazapine patients and 7.4% of paroxetine patients. Adverse events in the paroxetine group included nausea, vomiting, tremor, and increased sweating. Adverse events in the mirtazapine patients included weight increase and influenza-like symptoms (Benkert et al, 2000).

4.6.Q Nortriptyline

4.6.Q.1 Depression

a) Paroxetine was as effective as nortriptyline and caused fewer adverse effects when used in depressed cardiac patients. Outpatients with moderate depression and ischemic heart disease randomly received paroxetine (n=41) or nortriptyline (n=40) for 6 weeks. Patients receiving paroxetine were initially prescribed 20 milligrams (mg) (except for those over 65 years old who received 10 mg) and increased to a maximum of 40 mg/day based on response. Patients prescribed nortriptyline received 25 mg and increased as needed to achieve a blood level between 50 and 150 nanograms/milliliter. A response was defined as a 50% or greater improvement in the Hamilton depression scale score. Mean final doses were paroxetine 22 mg/day and nortriptyline 73 mg/day. Both drugs were efficacious with responses of 73% in the paroxetine group and 92% in the nortriptyline group (p not significant). Significantly more patients assigned to nortriptyline discontinued treatment than with paroxetine (p less than 0.02). With paroxetine, adverse effects causing discontinuation in 2 patients included diarrhea and angina. With nortriptyline, adverse effects causing discontinuation in 10 patients included 4 with sinus tachycardia, 1 with severe angina associated with ST changes on electrocardiogram, 2 with an increase in ventricular ectopy, 1 with persistent myoclonic jerks, and 2 with constipation (Nelson et al, 1999).

b) In a small, 6-week study (n=80), nortriptyline and paroxetine appeared to have comparable efficacy and tolerability (Mulsant et al, 1999). In this double-blind study, elderly (mean age, 75 years) patients with DSM-IV major depression were randomly assigned to nortriptyline or paroxetine. For outpatients, the initial dosage of nortriptyline and paroxetine was 25 milligrams(mg)/day and 10 mg/day, respectively; whereas, inpatients received nortriptyline 50 mg/day and paroxetine 20 mg/day initially. Dosage titration to achieve nortriptyline plasma levels between 50 and 150 ng/mL was permitted, and an increase to paroxetine 30 mg/day was also allowed. Discontinuation of medication due to adverse effects was reported in 5 (14%) and 8 (19%) patients treated with nortriptyline and paroxetine, respectively. The Hamilton Rating Scale for Depression score decreased from 22.4 to 8.8 with nortriptyline and from 20.9 to 9.6 with paroxetine; the difference between treatments was NOT statistically significant. Using intent-to-treat analysis, a higher response rate was achieved in the nortriptyline versus paroxetine group (57% versus 44%; p=0.26).

c) In an open, preliminary study, paroxetine was useful for long-term maintenance therapy of depression in elderly patients (Walters et al, 1999). After completion of a 12-week efficacy study, 25 of 27 and 15 of 16 patients with a response to paroxetine (mean dose, 24.5 milligrams(mg)/day) and nortriptyline (mean dose, 51.3 mg/day), respectively, elected to continue treatment. During a mean follow-up of 11.9 months, relapse

occurred in 1 of 15 subjects treated with nortriptyline versus 5 of 25 subjects treated with paroxetine. A survival plot also suggested similar efficacy for the 2 agents; however, about half of the patients in each treatment group discontinued treatment for a variety of reasons. A larger, controlled clinical study is needed.

4.6.R Risperidone

4.6.R.1 Panic attack

a) In an 8-week, randomized, single-blind, comparative trial (n=56) of low-dose risperidone and paroxetine in the treatment of panic attacks, both treatments were effective in reducing the occurrence and severity of panic attacks but there was no difference in the efficacy of each to improve anxiety associated with panic disorders. Thirty-three (8 men, 25 women) subjects were randomized to risperidone and 23 (8 men, 15 women) to paroxetine. The average age of the group was 40.36 +/- 12.37 years. Risperidone was initiated at 0.25 mg/day, adjusted as necessary for lack of response or sedation (maximum dose of 16 mg/day). Paroxetine was initiated at 30 mg/day, increased to a maximum of 60 mg/day if needed. The average risperidone dose was 0.53 mg (range 0.125 mg to 1 mg). All subjects in the paroxetine group received 30 mg/day except for one who required a dose of 40 mg. Subject assessments were conducted by a clinical rater blinded to medication status, using the 17-item Hamilton Depression Rating Scales (Ham-D-17), the Hamilton Anxiety Rating Scale (Ham-A), the Panic Disorder Severity Scale (PDSS), the Sheehan Panic Anxiety Scale-Patient (SPAS-P) and the Clinical Global Impressions Scale (CGI). Twenty subjects in the risperidone group and 9 in the paroxetine group completed all study visits. A significant decrease in CGI score was demonstrated in all subjects (p less than 0.001), but there was no significant difference between the groups. The CGI score improved from 4.4 +/- 0.6 at baseline to 2.84 +/- 1.02 at final assessment in the risperidone arm. Similarly, paroxetine resulted in a CGI score improvement from 3.81 +/- 1.33 to 2.67 +/- 0.71 at final assessment. All subjects, regardless of treatment, demonstrated a significant decrease in outcome scores for the PDSS total score, PDSS item 1, PDSS item 2, Ham-A and Ham-D. There was no statistical difference between treatment groups by the end of the study, and there was no significant change in SPAS-p scores over time (Prosser et al, 2009).

4.6.S Sertraline

Burning mouth syndrome

Depression

Weight gain

4.6.S.1 Burning mouth syndrome

a) Amisulpride, sertraline, and paroxetine were all effective in reducing the symptoms of burning mouth syndrome (BMS), but response was achieved earlier with amisulpride than with the selective serotonin reuptake inhibitors (SSRIs). In a randomized, single-blind study, 76 patients with BMS and without major depression were given amisulpride 50 milligrams (mg) per day, paroxetine 20 mg/day, or sertraline 50 mg/day for 8 weeks. Pain scores decreased significantly in all groups, as did depression (Hamilton Rating Scale for Depression) and anxiety (Hamilton Rating Scale for Anxiety), by week 8. The only difference among treatments was the shorter latency to response in the amisulpride group (22% of patients responding at 2 weeks with amisulpride vs 0% with paroxetine and 6% with sertraline) (Maina et al, 2002).

4.6.S.2 Depression

a) Paroxetine, fluoxetine, and sertraline were equally effective for the treatment of depression and for improving quality of life in patients in a primary care setting. In a 9-month, randomized, open-label trial (the ARTIST trial), depressed patients, whose symptoms warranted antidepressant treatment, according to their primary care physicians (PCP), were given paroxetine (n=180), fluoxetine (n=184) or sertraline (n=182). Starting doses were paroxetine 20 milligrams (mg), fluoxetine hydrochloride 20 mg, and sertraline 50 mg. The PCP could adjust the dose on the basis of clinical response and could switch the treatment to one of the other study drugs. Final average doses were 23.5 mg for paroxetine, 23.4 mg for fluoxetine, and 72.8 mg for sertraline. All 3 groups showed substantial improvement in depressive symptoms and quality of life. Overall, the percentage of patients categorized as having major depression dropped from 74% at baseline to 32% at 3 months, and 26% at 9 months. No significant differences were evident among the 3 groups. When data from subgroups (patients with major depression, patients who completed the trial on the drug initially assigned) were analyzed separately, still no differences among the drug treatments was evident. Patient satisfaction did not differ for the 3 groups. Changes in sexual function were small but tended to show improvement for all drug treatments. The drugs were associated with similar incidences of adverse effects and discontinuation rates (Kroenke et al, 2001).

b) Sertraline and paroxetine were equally effective in treating major depression, although side effects may be less with sertraline. In a double-blind study, 353 outpatients meeting the DSM-III_R criteria for major depression and having a score of at least 21 on the Montgomery-Asberg Depression Rating Scale (MADRS)

that did not improve at least 25% during a 1-week washout period were randomized to receive 24 weeks of treatment with either sertraline 50 milligrams (mg) or paroxetine 20 mg. Dose adjustments were allowed after 2 weeks based on response to a maximum of 150 mg sertraline and 40 mg paroxetine. No significant differences were observed in the improvement of MADRS and Clinical Global Impression (CGI) scores between the sertraline and paroxetine group. Of the 176 patients taking sertraline, 64% completed 24 weeks of treatment, and 65 % of 177 treated with paroxetine completed 24 weeks. Of those who completed therapy, remission (MADRS score less than 7)was achieved in 80.2% of the sertraline and in 73.7% of the paroxetine-treated patients. Quality of life measures improved with no significant differences between the two groups. Comparable improvements also occurred for the 2 groups in measures of personality. Both treatments were well-tolerated, with diarrhea reported significantly more often with sertraline, and constipation, fatigue, decreased libido in women, and micturition problems significantly more common with paroxetine. A significantly greater weight gain was observed with paroxetine (2.9 pound) compared with sertraline (1.3 pound) (Aberg-Wistedt et al, 2000)

4.6.S.3 Weight gain

a) Weight gain is a common complaint during antidepressant therapy, and weight gain was significantly greater with paroxetine than either sertraline or fluoxetine after 32 weeks of treatment. Patients meeting DSM-IV criteria for major depressive disorder were randomized to double-blind treatment with sertraline 50 milligrams (mg) daily (n=96) fluoxetine 20 mg daily (n=20), or paroxetine 20 mg daily (n=96) for 4 weeks. Patients responding to this dose continued for an additional 6 weeks, and those not responding had their doses titrated based on response up to a dose of 200 mg sertraline, 60 mg fluoxetine, and 60 mg paroxetine, and then maintained at their optimal doses for 6 weeks. After this treatment phase, responders (Clinical Global Impressions-Improvement score of 1 or 2 for 2 consecutive weeks) continued for 16 additional weeks. The number of responders participating in the 16 additional weeks were similar for the 3 treatments: 48 sertraline, 44 fluoxetine, and 47 paroxetine. However, among these responders, the mean increase in weight in the paroxetine group (3.6%) was significant compared to the mean increase with sertraline (1.0%) and mean decrease with fluoxetine (-0.2%). A gain of 7% or greater in weight occurred in 25.5% of paroxetine patients, 4.2% of sertraline patients, and 6.8% of fluoxetine patients; this difference was significant (Fava et al, 2000).

4.6.T Sildenafil

4.6.T.1 Premature ejaculation

a) In a 6-month, prospective, randomized clinical trial (n=180), the use of sildenafil was more effective than paroxetine and squeeze technique in alleviating primary premature ejaculation . Male adults aged between 19 and 52 years (mean 33 years) with a history of primary premature ejaculation (defined as ejaculation before vaginal penetration or within 2 minutes after vaginal penetration) were randomly divided into 3 treatment groups: sildenafil 50 milligrams (mg) as needed an hour before intended intercourse, paroxetine 20 mg once daily, and squeeze technique daily. Participants and their female partners were assessed before treatment began, and followed 3 and 6 months post-treatment. Compared with pretreatment, all treatment groups resulted in marked improvement in participant- and partner-reported intravaginal ejaculation latency (IELT), premature ejaculation grade, and intercourse satisfactory scores (ISS) 3 and 6 months after treatment initiation (p=0). Patient-reported mean IELT from baseline to 6 months post-treatment was 1.09 +/- 0.32 minutes (min) to 6.21 +/- 1.86 min for the sildenafil group, 1.11 +/- 0.45 min to 4.93 +/- 1.36 min for the paroxetine group, and 1.06 +/- 0.36 min to 2.62 +/- 0.69 min for the squeeze technique group (p=0 among groups and from baseline). The magnitude of improvement was comparable at the 3- and 6-month follow-up. At the end of the study, 1.7%, 18.3%, and 36.7% patients in the sildenafil, paroxetine, and squeeze technique group, respectively, withdrew from the study secondary to lack of effect or adverse reaction (p=0). Sildenafil was associated with higher incidence of headache (11.7% vs 3.3%), nasal congestion (8.3% vs 0%), and flushing (8.3% vs 0%) compared with paroxetine. On the other hand, paroxetine was associated with more frequent nausea (10% vs 3.3%), dizziness (3.3% vs 0%), fatigue (5% vs 0%), and constipation (6.7% vs 0%) compared with sildenafil (Wang et al, 2007).

b) According to a double-blind, randomized, cross-over study (n=31), as-needed SILDENAFIL was superior in the treatment of premature ejaculation compared with CLOMIPRAMINE, PAROXETINE, SERTRALINE, and PAUSE-SQUEEZE technique. Clomipramine, paroxetine, and sertraline had generally similar efficacy and safety. Paroxetine exhibited improved efficacy and satisfaction over pause-squeeze, while efficacy and satisfaction were similar to pause-squeeze for clomipramine and sertraline. Median intravaginal ejaculation latency time (IELT) increased significantly to 4 minutes (min), 4 min, 3 min, 15 min, and 3 min from baseline 1 min for clomipramine, paroxetine, sertraline, sildenafil, and pause-squeeze, respectively (all p less than 0.0001). Paroxetine was superior to pause-squeeze with respect to IVELT (p=0.04) and sexual satisfaction (p=0.025). A significant positive correlation occurred between ejaculation latency and sexual satisfaction. No significant differences in adverse effects were found among the 4 drugs. Three patients dropped out due to side effects, including sildenafil (2) and clomipramine (1; also lack of efficacy in this patient). Three additional patients dropped out due to lack of efficacy related to clomipramine, paroxetine, sertraline, and/or pause-squeeze. Medications were administered as needed 3 to 5 hours before planned intercourse and not more than twice a week. Doses were clomipramine 25 milligrams (mg), paroxetine 20 mg, sertraline 50 mg, and sildenafil 50 mg (Abdel-Hamid et al, 2001).

4.6.U Sulpiride

4.6.U.1 Tension-type headache

a) Headache was significantly reduced compared with baseline in patients receiving paroxetine 20 to 30 milligrams per day for 8 weeks during a randomized, double-blind, crossover study with sulpiride (Langemark & Olesen, 1994). Fifty patients with chronic tension headache received either sulpiride 200 to 400 milligrams/day or paroxetine for 8 weeks. Headache was recorded by the patients on a 5-point verbal score. Comparison between the 2 treatment groups after the first 8 weeks demonstrated no statistical differences in headache scores; however, both treatments did reduce headaches when compared to baseline. Following crossover, patients switched to sulpiride demonstrated a reduction in headache scores, while those switched to paroxetine did not. It should be noted that there was no washout period between the crossover and paroxetine is known to have a relatively long half-life. More controlled, large scale clinical trials are necessary to determine sulpiride's role in the treatment of chronic tension headache.

4.6.V Venlafaxine

Bipolar disorder, depressed phase

Obsessive-compulsive disorder

4.6.V.1 Bipolar disorder, depressed phase

a) Paroxetine and venlafaxine had similar efficacy in the treatment of depression in bipolar patients taking concomitant mood stabilizers. This randomized, single-blind (rater blind), comparative, 6-week study demonstrated that paroxetine and venlafaxine produced responses in 43% and 48% of the patients, respectively. At the end of the 6-week trial, both treatment groups showed significant improvement in the Hamilton Rating Scale for Depression (HAM-D) and the Clinical Global Impressions (CGI) for severity rating scores, with a mean HAM-D change of -6.9 for the paroxetine group and -9.0 for the venlafaxine group. These responses were significantly different compared to baseline, but not among treatment groups. At baseline, patients (n=60) were assessed using CGI ratings, the HAM-D, the Structured Clinical Interview for Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV), Axis I Disorders (SCID-I), and the Young Mania Rating Scale (YMRS). All patients were being treated with 1 or more mood stabilizers for at least 6 months prior to onset of the current major depressive episode, and had not taken antidepressant or antipsychotic medication for at least 3 months prior to the start of the study. During the study, doses were adjusted for efficacy and tolerability. The starting dose of venlafaxine was 37.5 milligrams (mg) twice a day, which could be increased in increments of 75 mg per day (mg/d) every week. The starting dose of paroxetine was 20 mg/d, which could be adjusted in increments of 10 mg/d every week. The mean doses of venlafaxine and paroxetine were 179 mg/d and 32 mg/d, respectively. There were no significant differences in reported adverse events (43% for paroxetine, 50% for venlafaxine); the most common adverse events were nausea (20% of all patients), and dizziness (8.3% of all patients). One patient (3%) in the paroxetine group had a switch to hypomania during treatment, 4 patients (13%) in the venlafaxine group switched to either hypomania (2 patients) or full mania (2 patients). Limitations of the study include concomitant use of several different mood stabilizing drugs, no placebo group, a single-blind study design, and a short follow up period (Vieta et al, 2002).

4.6.V.2 Obsessive-compulsive disorder

a) Venlafaxine extended-release (XR) was as effective as paroxetine in the treatment of patients with obsessive compulsive disorder (OCD). In a randomized, double-blind, comparative study, patients (n=150) with OCD and a score of at least 18 (or at least 12, if only obsessions or only compulsions were present) on the Yale-Brown Obsessive Compulsive Scale (Y-BOCS) received either venlafaxine XR (initial, 75 milligrams (mg)/day, titrated to 300 mg/day by week 7) or paroxetine (initial, 15 milligrams (mg)/day, titrated to 60 mg/day by week 7) for 12 weeks. Both paroxetine and venlafaxine XR treatments were effective, producing mean reductions of 7.8 and 7.2 points, respectively, in the Y-BOCS score from baseline to endpoint. A significant decrease in the total Y-BOCS score from baseline was seen at week 3 for venlafaxine XR- treated patients (p=0.008) and at week 5 for patients in the paroxetine group (p=0.018). There were no significant differences in responder rates between treatment groups. In the venlafaxine XR group, 37% and 25% of patients were partial responders and full responders, respectively. Similarly, in the paroxetine group, 44% and 22% of patients were partial responders and full responders, respectively. Additionally, no significant differences were observed between the two treatments with regard to reduction of anxious or depressive symptoms (as measured by the Hamilton Anxiety Scale and the Hamilton Rating Scale for Depression, respectively). For both treatments, most adverse effects were of mild or moderate severity and included somnolence, sweating, insomnia, and nausea (Denys et al, 2003).

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