DRUGDEX® Evaluations

FLUOXETINE

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) Fluoxetine Hydrochloride

1) Adult

a) Bulimia nervosa

1) 60 mg ORALLY once daily in the morning (Prod Info PROZAC(R) oral pulvule, oral solution, oral tablet, oral delayed-release capsule, 2005)

b) Major depressive disorder

1) initial, 20 mg ORALLY once daily in the morning (Prod Info PROZAC(R) oral pulvule, oral solution, oral tablet, oral delayed-release capsule, 2005)

2) maintenance, may increase daily dose after several weeks if inadequate response (maximum dose 80 mg daily) OR 90 mg ORALLY once a week (weekly capsule), starting 7 days after after the last daily dose of 20 mg (Prod Info PROZAC(R) oral pulvule, oral solution, oral tablet, oral delayed-release capsule, 2005)

c) Obsessive-compulsive disorder

1) initial, 20 mg ORALLY once daily in the morning (Prod Info PROZAC(R) oral pulvule, oral solution, oral tablet, oral delayed-release capsule, 2005)

2) maintenance, 20-60 mg ORALLY daily (single or divided doses) after several weeks if inadequate response; maximum dose 80 mg daily (Prod Info PROZAC(R) oral pulvule, oral solution, oral tablet, oral delayed-release capsule, 2005)

d) Panic disorder

1) 10 mg ORALLY once daily for 1 week, then increase to 20 mg per day; dosage increases up to 60 mg daily may be considered after several weeks if there is no clinical response (Prod Info PROZAC(R) oral pulvule, oral solution, oral tablet, oral delayed-release capsule, 2005)

e) Premenstrual dysphoric disorder

1) 20 mg ORALLY once daily continuously OR 20 mg ORALLY once daily intermittently (start 14 days prior to the anticipated onset of menstruation and continue daily through the first full day of menses); maximum dosage 80 mg daily (Prod Info SARAFEM(R) Oral Capsule, 2005)

2) Pediatric

a) safety and effectiveness in pediatric patients younger than age 8 (major depressive disorder) and younger than age 7 (obsessive compulsive disorder) have not been established (Prod Info PROZAC(R) oral pulvule, oral solution, oral tablet, oral delayed-release capsule, 2005)

1) Major depressive disorder

a) 8 years and older, 10-20 mg ORALLY once daily (Prod Info PROZAC(R) oral pulvule, oral solution, oral tablet, oral delayed-release capsule, 2005)

2) Obsessive-compulsive disorder

a) adolescents and higher weight children 7 years and older, initiate at 10 mg ORALLY once daily; may increase to 20 mg ORALLY once daily after 2 weeks; recommended dose range, 20-60 mg daily (Prod Info PROZAC(R) oral pulvule, oral solution, oral tablet, oral delayed-release capsule, 2005)

b) lower weight children 7 years and older, initiate at 10 mg ORALLY once daily; may increase dose after several weeks if inadequate response; recommended dose range, 20-30 mg daily (Prod Info PROZAC(R) oral pulvule, oral solution, oral tablet, oral delayed-release capsule, 2005)

3) Contraindications

a) Fluoxetine Hydrochloride

1) concomitant use of monoamine oxidase inhibitors (MAOIs), pimozide, or thioridazine (Prod Info PROZAC(R) delayed-release capsules, oral capsules, solution, 2009)

2) hypersensitivity to fluoxetine or any components of the product (Prod Info PROZAC(R) delayed-release capsules, oral capsules, solution, 2009)

3) use of MAOIs within 5 weeks after fluoxetine discontinuation (Prod Info PROZAC(R) delayed-release capsules, oral capsules, solution, 2009)

4) use of fluoxetine within 14 days of MAOI discontinuation (Prod Info PROZAC(R) delayed-release capsules, oral capsules, solution, 2009)

4) Serious Adverse Effects

a) Fluoxetine Hydrochloride

1) Bleeding

2) Depression, worsening
3) Hyponatremia
4) Mania
5) Prolonged QT interval
6) Seizure
7) Serotonin syndrome
8) Suicidal thoughts

5) Clinical Applications
a) Fluoxetine Hydrochloride
1) FDA Approved Indications
a) Bulimia nervosa
b) Major depressive disorder
c) Obsessive-compulsive disorder
d) Panic disorder
e) Premenstrual dysphoric disorder

1.0 Dosing Information

Drug Properties

Storage and Stability

Adult Dosage

Pediatric Dosage

1.1 Drug Properties

A) Information on specific products and dosage forms can be obtained by referring to the Tradename List (Product Index)
B) Synonyms
Fluoxetine
Fluoxetine HCl
Fluoxetine Hydrochloride
C) Orphan Drug Status
1) Fluoxetine Hydrochloride
a) Fluoxetine has been designated an orphan product for use in the treatment of autism.
D) Physicochemical Properties
1) Fluoxetine Hydrochloride
a) Molecular Weight
1) Fluoxetine: 309.33 (Canada, 1997); Fluoxetine hydrochloride: 345.79 (Canada, 1997; Prod Info PROZAC(R) oral capsules, delayed-release capsules, solution, 2008)
b) pKa
1) 9.5 (Taddio et al, 1996)
c) Solubility
1) Soluble at 14 mg per mL in water (Prod Info PROZAC(R) oral capsules, delayed-release capsules, solution, 2008)

1.2 Storage and Stability

A) Fluoxetine Hydrochloride
1) Oral route
a) Capsule/Capsule, Delayed Release/Solution
1) Store at controlled room temperature, between 15 and 30 degrees Celsius (59 to 86 degrees Fahrenheit). Protect from light (Prod Info Sarafem(TM), 2002; Prod Info PROZAC(R) oral capsules, delayed-release capsules, solution, 2008).

1.3 Adult Dosage

Normal Dosage

Dosage in Renal Failure

Dosage in Hepatic Insufficiency

Dosage in Geriatric Patients

Dosage Adjustment During Dialysis

1.3.1 Normal Dosage

Important Note

Fluoxetine

Fluoxetine Hydrochloride

1.3.1.A Important Note

At least 14 days should elapse between the discontinuation of a monoamine oxidase (MAO) inhibitor and the initiation of fluoxetine, and at least 5 weeks should elapse between discontinuation of fluoxetine and initiation of treatment with MAO inhibitors. Cases of serious, sometimes fatal reactions have been reported in patients receiving fluoxetine in combination with an MAO inhibitor, and in patients who have recently discontinued fluoxetine and are then started on an MAO inhibitor. Reactions have been characterized by hyperthermia, rigidity, myoclonus, autonomic instability with possible rapid fluctuations of vital signs, and mental status changes that include extreme agitations progressing to delirium and coma. Some reports resembled cases of neuroleptic malignant syndrome (Prod Info PROZAC(R) oral pulvule, oral solution, oral tablet, oral delayed-release capsule, 2005; Prod Info SARAFEM(R) Oral Capsule, 2005).

1.3.1.B Fluoxetine

1.3.1.B.1 Cataplexy - Narcolepsy

See Drug Consult reference: NARCOLEPSY AND CATAPLEXY - DRUG THERAPY

1.3.1.C Fluoxetine Hydrochloride

Oral route

Tinnitus

1.3.1.C.1 Oral route

Bulimia nervosa

Major depressive disorder

Obsessive-compulsive disorder

Panic disorder

Premenstrual dysphoric disorder

1.3.1.C.1.a Bulimia nervosa

1) The recommended dose for bulimia nervosa is 60 milligrams (mg) once daily, administered in the morning. For some patients, it may be appropriate to titrate up to 60 mg over several days. Studies in which lower doses (ie, 20 mg daily) were used did not demonstrate efficacy. Patients who have responded to fluoxetine 60 mg daily in an 8-week acute treatment phase continued to show benefit for up to 52 weeks in clinical trials. Patients should be periodically reassessed to determine the need for maintenance treatment (Prod Info PROZAC(R) oral pulvule, oral solution, oral tablet, oral delayed-release capsule, 2005).

2) Continued fluoxetine treatment (60 milligrams/day), relative to placebo treatment, was associated with a significant reduction of relapse in patients who had responded acutely to treatment with fluoxetine for bulimia nervosa. The fluoxetine group had fewer relapses in the first 3

months (p less than 0.04). Thereafter, the difference between the groups remained at 14% to 18% but was not statistically significant due to high attrition rates. By the end of 52 weeks, 33% of the fluoxetine group and 51% of the placebo group had relapsed (Romano et al, 2002).

1.3.1.C.1.b Major depressive disorder

1) The recommended starting dose of fluoxetine in patients with major depressive disorder is 20 milligrams (mg) orally once daily, administered in the morning. Studies suggest that doses of 20 mg daily may be sufficient to obtain a satisfactory antidepressant response. If no clinical improvement is observed after several weeks, the dosage can be increased at intervals of several weeks, not to exceed a maximum dose of 80 mg daily. The full effect may be delayed until 4 weeks of treatment or longer. Efficacy has been maintained up to 38 weeks following 12 weeks of treatment with fluoxetine 20 mg daily in clinical trials. Due to the long elimination half lives of both parent drug and metabolites, the full effect of a dosage change may not be observed for several weeks. Doses greater than 20 mg daily may be administered once or twice daily (morning and noon) (Prod Info PROZAC(R) oral pulvule, oral solution, oral tablet, oral delayed-release capsule, 2005).

2) Once weekly dosing of 90 milligrams (mg) enteric-coated capsules was shown to be safe, effective, and well tolerated for the long-term treatment of depression. After responding to 20 mg daily for acute treatment of depression, patients were successfully treated with the once weekly formulation for up to 25 weeks. The weekly dosing should be initiated 7 days after the last daily dose of fluoxetine. It is unknown if weekly dosing provides the same protection from relapse as does daily dosing. If weekly dosing with fluoxetine capsules does not maintain a satisfactory response, consider reestablishing daily dosing (Prod Info PROZAC(R) oral pulvule, oral solution, oral tablet, oral delayed-release capsule, 2005; Schmidt et al, 2000).

Weekly dosage	Daily dosage equivalent
90 mg	12.8 mg
180 mg	25.6 mg
270 mg	38.4 mg
360 mg	51.2 mg
540 mg	76.8 mg

(Buongiorno et al, 2002)

3) Results of a randomized double-blind study demonstrated that continuation phase treatments of major depressive disorder (MDD) with fluoxetine 20 milligrams (mg) per day (n=21), 60 mg/week (n=28), or placebo (n=21) did not differ in their ability to affect the Hamilton Rating Scale for Depression (HAM-D) (Burke et al, 2000). One hundred fourteen subjects with a diagnosis of unipolar MDD and a HAM-D score of greater than or equal to 18 were enrolled in an open label trial. After 7 weeks of open label therapy with fluoxetine 20 mg/day, subjects with HAM-D scores of 12 or less were enrolled in the double blind study. Seventy subjects were randomized to receive continuation phase therapy for 7 weeks. Repeat measures of HAM-D scores and blood levels of fluoxetine and norfluoxetine showed no group effects in the open label study. Similar results were demonstrated during double- blind therapy. No significant differences in drop out rates were observed across treatment groups. No significant correlations between HAM-D scores and serum concentrations of fluoxetine or norfluoxetine were demonstrated at randomization or at the end of the double-blind study. The authors suggest that weekly dosing is well tolerated and possibly as effective as daily dosing for maintenance of MDD treatment response.

4) Some clinical trials have utilized doses of fluoxetine in the treatment of depression of 60 to 80 milligrams orally daily, either as a single daily dose or in divided doses twice a day to three times a day. However, many patients respond adequately to doses of 20 or 40 milligrams daily (Stark & Hardison, 1985b; Fabre & Crismon, 1985a; Cohn & Wilcox, 1985b; Bremner, 1984c; Chouinard, 1985c). Many of the early clinical trials used protocols that required titration of the fluoxetine dose from 20 milligrams/day to 80 milligrams/day within 2 weeks. The adverse effect profile of fluoxetine suggests that a dose-dependent relationship exists. A more recent multicenter study utilized daily fluoxetine doses of 20 milligrams, 40 milligrams and 60 milligrams without titration (Wernicke et al, 1987). The 3 fixed-dose regimens were equally effective in controlling depression and the 2 lower dose regimens resulted in fewer patient withdrawals due to adverse effects. In a similar trial utilizing daily fluoxetine doses of 5 milligrams, 20 milligrams, and 40 milligrams, it was found that endpoint and weekly analyses of outcome variables resulted in a flat dose-response curve and superiority of all doses compared to placebo (Wernicke et al, 1987). There were differences seen on individual measures: the 5-milligram dose was superior in improving the HAM-D Sleep Disturbance factor; the 20-milligram dose was superior on the CGI severity scale; and the 40-milligram dose was more effective in improving the HAM-D Retardation factor. However, these latter differences appeared dose related; statistical analyses to support stronger conclusions were not presented. A later trial identified patients without significant response within three weeks of initiation of fluoxetine 20 milligrams/day (Dornseif et al, 1989); these patients were randomized to further treatment with 20 milligrams/day or 60 milligrams/day on a double-blind basis. Although the 60-milligram dose provided greater improvements on some measures, the differences were considered of little clinical significance and should be weighed against higher discontinuation rates and more frequent reports

of adverse events (diarrhea and abdominal pain). Further analyses of the dose-response relationship have been provided and suggest that 5 mg and 60 mg per day, respectively, are the lower and upper ends of the therapeutic range for fluoxetine (Beasley et al, 1990).
5) Beneficial effects have been observed in patients receiving fluoxetine 5 milligrams(mg)/day for depression or panic disorder (Louie et al, 1993). However, the majority of patients treated for depression respond to fluoxetine 20 to 30 mg/day (Altamura et al, 1988); (Fabre & Putnam, 1987). The dosage range for fluoxetine is 20 to 80 mg/day (Benfield et al, 1986). The effectiveness of fluoxetine 40, 60, or 80 mg is similar whether doses are administered once or twice daily (Rickels et al, 1985).
6) A trial addressing the optimal length of continuation therapy in depression suggested that therapy with fluoxetine should be continued at least 26 weeks to prevent relapse, after an initial 12 weeks of acute treatment with fluoxetine (Reimherr et al, 1998).

1.3.1.C.1.c Obsessive-compulsive disorder

1) The recommended starting dose of fluoxetine in patients with obsessive-compulsive disorder (OCD) is 20 milligrams (mg) orally once daily, administered in the morning. If a sufficient clinical response is not observed after several weeks, the dose may be increased. The full effect may be delayed until 5 weeks of treatment or longer. The recommended dose range of fluoxetine for treatment of OCD is 20 mg to 60 mg daily. The maximum dose of fluoxetine is 80 mg daily. Due to the long elimination half lives of both parent drug and metabolites, the full effect of a dosage change may not be observed for several weeks. Doses greater than 20 mg daily may be administered once or twice daily (morning and noon) (Prod Info PROZAC(R) oral pulvule, oral solution, oral tablet, oral delayed-release capsule, 2005).
2) Efficacy of fluoxetine after 13 weeks of therapy for obsessive-compulsive disorder has not been documented in clinical trials. Patients have been continued for up to an additional 6 months without loss of benefit. Dosage adjustments should be made to maintain the patient on the lowest effective dosage. Patients should be periodically reassessed to determine the need for treatment (Prod Info PROZAC(R) oral pulvule, oral solution, oral tablet, oral delayed-release capsule, 2005).

1.3.1.C.1.d Panic disorder

1) The recommended starting dose of fluoxetine for the treatment of panic disorder is 10 milligrams (mg) orally once per day. After 1 week the dose should be increased to 20 mg daily. Dosage increases up to 60 mg daily may be considered after several weeks if there is no clinical response. In 2 clinical trials, most patients received 20 mg daily. Doses above 60 mg per day have not been evaluated. Due to the long elimination half lives of both parent drug and metabolites, the full effect of a dosage change may not be observed for several weeks. Patients should be periodically reassessed to determine the need for continued treatment (Prod Info PROZAC(R) oral pulvule, oral solution, oral tablet, oral delayed-release capsule, 2005).
2) Fluoxetine in doses up to 80 milligrams daily was reported effective in the treatment of panic attacks in 7 of 16 patients in an open study (Gorman et al, 1987a). Mean doses in the responding patients were 27 milligrams daily (range, 10 to 70 milligrams daily).

1.3.1.C.1.e Premenstrual dysphoric disorder

1) The starting dose of fluoxetine (Sarafem(R)) in patients with premenstrual dysphoric disorder (PMDD) is 20 milligrams (mg) orally once daily given either continuously or on an intermittent schedule (initiate 14 days prior to the anticipated onset of menstruation and continue daily through first full day of menses and then repeating with each new cycle). Doses of 60 mg daily are also effective, however, no significant added benefit compared to 20 mg daily is obtained. Due to the long elimination half lives of both parent drug and metabolites, the full effect of a dosage change may not be observed for several weeks. Efficacy has been demonstrated for up to 6 months with continuous dosing and for 3 months with intermittent dosing. Reevaluate patients periodically to determine the need for continued treatment. The maximum dose should not exceed 80 mg daily (Prod Info SARAFEM(R) Oral Capsule, 2005).

1.3.1.C.2 Tinnitus

See Drug Consult reference: DRUG THERAPY OF TINNITUS

1.3.1.C.3 MAXIMUM DOSE

a) The maximum dose of fluoxetine is 80 milligrams per day (Prod Info PROZAC(R) oral pulvule, oral solution, oral tablet, oral delayed-release capsule, 2005; Prod Info SARAFEM(R) Oral Capsule, 2005).

1.3.2 Dosage in Renal Failure

A) Fluoxetine Hydrochloride

1) Dosage adjustments for renal impairment are not routinely necessary (Prod Info PROZAC(R) oral pulvule, oral solution, oral tablet, oral delayed-release capsule, 2005; Prod Info SARAFEM(R) Oral Capsule, 2005).
2) Only 2.5% to 5% of an oral dose of fluoxetine is excreted unchanged in the urine, with 10% appearing as the active metabolite (norfluoxetine). Studies have demonstrated no correlation between the degree of renal dysfunction and the rate of elimination, volume of distribution, or protein binding of fluoxetine when given in

single doses (Aronoff et al, 1984b; Lemberger et al, 1985b).

1.3.3 Dosage in Hepatic Insufficiency

A) Fluoxetine Hydrochloride

1) Fluoxetine is metabolized in the liver (Lemberger et al, 1985b) and dosing adjustments may be required in hepatic disease. A lower dose or less frequent dosage schedule is recommended with fluoxetine in patients with hepatic insufficiency (Prod Info PROZAC(R) oral pulvule, oral solution, oral tablet, oral delayed-release capsule, 2005; Prod Info SARAFEM(R) Oral Capsule, 2005).

2) A significant reduction in plasma clearance and an increase in the elimination half-life of fluoxetine were observed in stable alcoholic cirrhosis patients (Schenker et al, 1988a). The formation of norfluoxetine was also decreased, and its clearance reduced, in these patients compared to normal volunteers. It is recommended that a lower or less frequent dose of fluoxetine be given to patients with cirrhosis; in patients with compensated cirrhosis (without ascites), an approximately 50% reduction is suggested; whereas patients with decompensated cirrhosis may require greater adjustments in dosage, due to the possibility of a greater reduction in the rate of fluoxetine elimination.

1.3.4 Dosage in Geriatric Patients

A) Fluoxetine Hydrochloride

1) A lower dose or less frequent dosage schedule is recommended with fluoxetine in elderly patients (Prod Info PROZAC(R) oral pulvule, oral solution, oral tablet, oral delayed-release capsule, 2005).

1.3.5 Dosage Adjustment During Dialysis

A) Fluoxetine Hydrochloride

1) Fluoxetine 20 milligrams once daily for 2 months, administered to patients with depression and on dialysis (n=12), produced steady-state fluoxetine and norfluoxetine plasma concentrations that were comparable to those found in patients with normal renal function. While it is possible that renally excreted metabolites may accumulate in patients with severe renal dysfunction, dose reduction is usually not necessary in patients with renal impairment (Prod Info PROZAC(R) oral pulvule, oral solution, oral tablet, oral delayed-release capsule, 2005; Prod Info SARAFEM(R) Oral Capsule, 2005).

2) The large volume of distribution for fluoxetine and norfluoxetine (over 1,000 liters) and fluoxetine's high plasma protein binding (94%) suggest a low degree of clearance by extracorporeal extraction. Plasma levels of fluoxetine and its active metabolite (norfluoxetine) were not affected significantly by hemodialysis and indicated that dosing adjustments are not required in this setting (Aronoff et al, 1984b).

1.4 Pediatric Dosage

Normal Dosage

Dosage in Renal Failure

Dosage in Hepatic Insufficiency

Dosage Adjustment During Dialysis

1.4.1 Normal Dosage

Important Note

Fluoxetine

Fluoxetine Hydrochloride

1.4.1.A Important Note

At least 14 days should elapse between the discontinuation of a monoamine oxidase (MAO) inhibitor and the initiation of fluoxetine, and at least 5 weeks should elapse between discontinuation of fluoxetine and initiation of treatment with MAO inhibitors. Cases of serious, sometimes fatal reactions have been reported in patients receiving fluoxetine in combination with an MAO inhibitor, and in patients who have recently discontinued fluoxetine and are then started on an MAO inhibitor. Reactions have been characterized by hyperthermia, rigidity, myoclonus, autonomic instability with possible rapid fluctuations of vital signs, and mental status changes that include extreme agitations progressing to delirium and coma. Some reports resembled cases of neuroleptic malignant syndrome (Prod Info PROZAC(R) oral pulvule, oral solution, oral tablet, oral delayed-release capsule, 2005; Prod Info SARAFEM(R) Oral Capsule, 2005).

1.4.1.B Fluoxetine

1.4.1.B.1 Anorexia nervosa
See Drug Consult reference: ANOREXIA NERVOSA - DRUG THERAPY

1.4.1.C Fluoxetine Hydrochloride

1.4.1.C.1 Oral route

Major depressive disorder

Obsessive-compulsive disorder

1.4.1.C.1.a Major depressive disorder
1) The recommended initial dose of fluoxetine for the treatment of major depressive disorder in adolescents and children, 8 years and older, is 10 or 20 milligrams (mg) orally once daily. If starting at 10 mg daily, the dose should be increased to 20 mg daily after 1 week. For lower weight children, the starting and target dose may be 10 mg daily due to higher plasma levels. If sufficient clinical improvement is not observed after several weeks, a dose increase to 20 mg daily may be considered. The full effect may be delayed until 4 weeks of treatment or longer. Due to the long elimination half lives of both parent drug and metabolites, the full effect of a dosage change may not be observed for several weeks (Prod Info PROZAC(R) oral pulvule, oral solution, oral tablet, oral delayed-release capsule, 2005).

1.4.1.C.1.b Obsessive-compulsive disorder
1) The recommended initial dose of fluoxetine for the treatment of obsessive-compulsive disorder in adolescents and higher weight children (7 years and older) is 10 milligrams (mg) orally once daily. The dose should be increased to 20 mg daily after 2 weeks. If sufficient clinical response is not observed after several weeks, the dose may be increased further. Due to the long elimination half lives of both parent drug and metabolites, the full effect of a dosage change may not be observed for several weeks. The recommended dose range is 20 mg to 60 mg daily (Prod Info PROZAC(R) oral pulvule, oral solution, oral tablet, oral delayed-release capsule, 2005).
2) For lower weight children (7 years and older), the recommended starting dose of fluoxetine in the treatment of obsessive-compulsive disorder is 10 milligrams (mg) orally once daily. If sufficient clinical response is not observed after several weeks, the dose may be increased further. Due to the long elimination half lives of both parent drug and metabolites, the full effect of a dosage change may not be observed for several weeks. The recommended dose range is 20 mg to 30 mg daily (Prod Info PROZAC(R) oral pulvule, oral solution, oral tablet, oral delayed-release capsule, 2005).

1.4.2 Dosage in Renal Failure
A) Fluoxetine Hydrochloride
1) Dosage adjustments for renal impairment are not routinely necessary (Prod Info PROZAC(R) oral pulvule, oral solution, oral tablet, oral delayed-release capsule, 2005).

1.4.3 Dosage in Hepatic Insufficiency
A) Fluoxetine Hydrochloride
1) A lower dose or less frequent dosage schedule is recommended with fluoxetine in patients with hepatic insufficiency (Prod Info PROZAC(R) oral pulvule, oral solution, oral tablet, oral delayed-release capsule, 2005).

1.4.4 Dosage Adjustment During Dialysis
A) Fluoxetine Hydrochloride
1) Fluoxetine 20 milligrams once daily for 2 months, administered to patients with depression and on dialysis (n=12), produced steady-state fluoxetine and norfluoxetine plasma concentrations that were comparable to those found in patients with normal renal function. While it is possible that renally excreted metabolites may accumulate in patients with severe renal dysfunction, dose reduction is usually not necessary in patients with renal impairment (Prod Info PROZAC(R) oral pulvule, oral solution, oral tablet, oral delayed-release capsule, 2005).

2.0 Pharmacokinetics

Onset and Duration

Drug Concentration Levels

ADME

2.1 Onset and Duration

A) Onset

1) Initial Response

a) Depression, regular release: 1 to 2 weeks (Chouinard, 1985; Cohn & Wilcox, 1985c; Bremner, 1984).

2) Peak Response

a) Depression, regular release: 4 weeks (Prod Info Prozac(R), 2003b).

b) Obsessive compulsive disorder, regular release: 5 weeks or longer (Prod Info Prozac(R), 2003b).

2.2 Drug Concentration Levels

A) Time to Peak Concentration

1) Oral, regular release: 6 to 8 hours (Saletu & Grunberger, 1985; Lemberger et al, 1985a; Aronoff et al, 1984a; Lemberger et al, 1978).

a) Mean plasma concentrations were 477 ng/mL for fluoxetine and 393 ng/mL for the active metabolite, norfluoxetine, after fluoxetine 60 mg was taken for 5 weeks. These concentrations were associated with therapeutic benefit in depressed patients (Chouinard, 1985). Corresponding plasma concentrations in patients receiving fluoxetine 80 mg daily were 698 ng/mL and 421 ng/mL (norfluoxetine), respectively (Feighner & Cohn, 1985b).

B) PEAK AND TROUGH FLUCTUATIONS

1) Increased fluctuation of peak and trough concentrations resulted from 90 milligrams weekly dosing when compared to 20 mg daily dosing. Peak concentrations from the weekly dosing are within the average concentration range for the 20 mg dosing. Trough concentrations of fluoxetine and norfluoxetine are lower by 76% and 47%, respectively. Average steady state concentrations are 50% lower with weekly dosing than with daily dosing (Prod Info Prozac(R), 2003b).

2.3 ADME

Absorption

Distribution

Metabolism

Excretion

Elimination Half-life

Extracorporeal Elimination

2.3.1 Absorption

A) Bioavailability

1) Oral, regular release: 100% (Lemberger et al, 1985a).

2) The enteric-coated weekly formulation, pulvules, tablets, and oral solution are bioequivalent (Prod Info Prozac(R), 2003b).

3) The weekly formulation resists dissolution until the pH is greater than 5.5. Therefore, absorption is delayed 1-2 hours compared to immediate release formulations (Prod Info Prozac(R), 2003b).

B) Effects of Food

1) clinically insignificant (Lemberger et al, 1985a).

a) The absorption of fluoxetine is delayed but not decreased in the presence of food (Lemberger et al, 1985a).

2.3.2 Distribution

A) Distribution Sites

1) Protein Binding

a) 94.5% (Prod Info Prozac(R), 2003b; Lemberger et al, 1985a; Aronoff et al, 1984a).

1) Fluoxetine is bound to albumin and alpha-1-glycoprotein; protein binding is NOT altered in patients with renal failure (Prod Info Prozac(R), 2003b; Lemberger et al, 1985a; Aronoff et al, 1984a).

B) Distribution Kinetics

1) Volume of Distribution
a) 1000 to 7200 L (Aronoff et al, 1984a).
1) The corresponding volume of distribution for norfluoxetine ranged from 700 to 5,700 L. No relationship between the volume of distribution of fluoxetine or its metabolite and renal function has been observed (Aronoff et al, 1984a).

2.3.3 Metabolism

A) Metabolism Sites and Kinetics
1) Liver, extensive (Prod Info Prozac(R), 2003b; Aronoff et al, 1984a).
a) Fluoxetine is metabolized primarily via N-demethylation to the active metabolite, norfluoxetine (Lemberger et al, 1985a; Aronoff et al, 1984a). Glucuronide conjugates are also found but in small quantities (Lemberger et al, 1985a).
b) Extensive metabolizers with respect to cytochrome P450 2C19 (CYP2C19) showed lower maximum levels of fluoxetine (p less than 0.001) and higher levels of norfluoxetine (p less than 0.001) after a 40 milligram dose of fluoxetine than did poor metabolizers with the CYP2C19*2 or CYP2C19*3 mutation. Oral clearance by poor metabolizers was 55% lower than oral clearance by extensive metabolizers (p less than 0.001) (Liu et al, 2001).
B) Metabolites
1) Norfluoxetine, active (Aronoff et al, 1984a; Fuller et al, 1977).
a) Norfluoxetine has similar pharmacologic activity to the parent compound (Lemberger et al, 1985a).
2) Glucuronide metabolites (Lemberger et al, 1985a).

2.3.4 Excretion

A) Kidney
1) Renal Excretion (%)
a) 60% (Lemberger et al, 1985a).
2) Only 2.5 to 5.0% of an oral dose is recovered as unchanged drug; 10% is excreted as free norfluoxetine (Lemberger et al, 1985a; Aronoff et al, 1984a). Conjugated metabolites, fluoxetine glucuronide and norfluoxetine glucuronide, represent 5.2% and 9.5% of a dose, respectively (Lemberger et al, 1985a).
B) Other
1) OTHER EXCRETION
a) Feces, 12% (Lemberger et al, 1985a).

2.3.5 Elimination Half-life

A) Parent Compound
1) ELIMINATION HALF-LIFE
a) 4 to 6 days, chronic administration (Prod Info Sarafem(TM), 2002a; Prod Info Prozac(R), 2003b; Lemberger et al, 1985a).
1) Following acute administration, the elimination half-life of fluoxetine is 1 to 3 days (Prod Info Prozac(R), 2003b; Prod Info Sarafem(TM), 2002a).
2) The mean half-life of fluoxetine among extensive metabolizers with respect to cytochrome P450 2C19 (CYP2C19) was about 28 hours, whereas, among poor metabolizers with the CYP2C19*2 or CYP2C19*3 mutation, mean half-life was 62 hours (Liu et al, 2001).
3) A mean elimination half-life of 3.6 days was reported in normal subjects (range, 1 to 13 days) compared to 1.75 days in hemodialysis patients (Aronoff et al, 1984a).
B) Metabolites
1) Norfluoxetine, 4 to 16 days (Prod Info Prozac(R), 2003b; Lemberger et al, 1985a; Nash et al, 1982).

2.3.6 Extracorporeal Elimination

A) Hemodialysis
1) Dialyzable: No (Aronoff et al, 1984a).
a) Fluoxetine and norfluoxetine are not removed to a significant degree by hemodialysis (Aronoff et al, 1984a).

3.0 Cautions

Contraindications

Precautions

Adverse Reactions

Teratogenicity/Effects in Pregnancy/Breastfeeding

Drug Interactions

3.0.A Black Box WARNING

1) Fluoxetine Hydrochloride

a) Oral (Capsule; Capsule, Delayed Release; Solution)

1) 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 fluoxetine 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. Fluoxetine hydrochloride is approved for use in pediatric patients with MDD and obsessive compulsive disorder (OCD) (Prod Info PROZAC(R) delayed-release capsules, oral capsules, solution, 2009).

b) Oral (Tablet)

1) 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 fluoxetine hydrochloride or any other antidepressant in a child, adolescent, or young adult must balance this risk with the clinical need. Patients who are started on antidepressant therapy should be 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. SARAFEM(R) is not approved for use in pediatric patients.

2) Pooled analyses of short-term (4 to 16 weeks) placebo-contolled trials of 9 antidepressant drugs (SSRIs and others) in children and adolescents with major depressive disorder (MDD), obsessive compulsive disorder (OCD), or other psychiatric disorders (a total of 24 trials involving over 4400 patients) have revealed a greater risk of adverse events representing suicidal thinking or behavior (suicidality) during the first few months of treatment in those receiving antidepressants. The average risk of such events in patients receiving antidepressants was 4%, twice the placebo risk of 2%. No suicides occurred in these trials (Prod Info SARAFEM(R) oral tablets, 2007).

3.1 Contraindications

A) Fluoxetine Hydrochloride

1) concomitant use of monoamine oxidase inhibitors (MAOIs), pimozide, or thioridazine (Prod Info PROZAC(R) delayed-release capsules, oral capsules, solution, 2009)

2) hypersensitivity to fluoxetine or any components of the product (Prod Info PROZAC(R) delayed-release capsules, oral capsules, solution, 2009)

3) use of MAOIs within 5 weeks after fluoxetine discontinuation (Prod Info PROZAC(R) delayed-release capsules, oral capsules, solution, 2009)

4) use of fluoxetine within 14 days of MAOI discontinuation (Prod Info PROZAC(R) delayed-release capsules, oral capsules, solution, 2009)

3.2 Precautions

A) Fluoxetine 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 PROZAC(R) delayed-release capsules, oral capsules, solution, 2009)

2) abrupt withdrawal; serious discontinuation symptoms have been reported (Prod Info PROZAC(R) delayed-release capsules, oral capsules, solution, 2009)

3) allergic reactions, including anaphylaxis, angioedema, and erythema multiforme have been reported; in the case of rash, or other possibly allergic symptoms for which an alternative etiology cannot be identified, discontinue therapy (Prod Info PROZAC(R) delayed-release capsules, oral capsules, solution, 2009)

4) bipolar disorder; increased risk of precipitation of a mixed/manic episode with antidepressant treatment only (Prod Info PROZAC(R) delayed-release capsules, oral capsules, solution, 2009)

5) concomitant use of NSAIDs, aspirin, or other drugs that affect coagulation; abnormal bleeding, particularly the gastrointestinal tract, may occur (Prod Info PROZAC(R) delayed-release capsules, oral capsules, solution, 2009)

6) concomitant serotonergic drug use (serotonin precursors (tryptophan), SSRIs, serotonin-norepinephrine reuptake inhibitors); risk of serotonin syndrome, use is not recommended(Prod Info PROZAC(R) delayed-release capsules, oral capsules, solution, 2009)

7) concomitant use of thioridazine; risk of serious ventricular arrhythmias and sudden death (Prod Info PROZAC (R) delayed-release capsules, oral capsules, solution, 2009)

8) diabetes, history of; increased risk of hypoglycemia (Prod Info PROZAC(R) delayed-release capsules, oral capsules, solution, 2009)

9) cirrhosis of the liver; risk of drug toxicity (Prod Info PROZAC(R) delayed-release capsules, oral capsules, solution, 2009)

10) seizures, history of (Prod Info PROZAC(R) delayed-release capsules, oral capsules, solution, 2009)

11) serotonin syndrome and neuroleptic malignant syndrome-like reactions (serotonin syndrome in its most severe form), have been reported with fluoxetine therapy alone (Prod Info PROZAC(R) delayed-release capsules, oral capsules, solution, 2009)
12) volume-depleted, elderly, or concurrent diuretic therapy; hyponatremia, syndrome of inappropriate antidiuretic hormone secretion (SIADH) has occurred with fluoxetine (Prod Info PROZAC(R) delayed-release capsules, oral capsules, solution, 2009)

3.3 Adverse Reactions

Cardiovascular Effects

Dermatologic Effects

Endocrine/Metabolic Effects

Gastrointestinal Effects

Hematologic Effects

Hepatic 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 Fluoxetine Hydrochloride

Abnormal ECG

Bradyarrhythmia

Heart failure

Hypertension

Prolonged QT interval

Tachyarrhythmia

Vasculitis

3.3.1.A.1 Abnormal ECG

a) Cardiovascular side effects reported during treatment with fluoxetine included QT prolongation (Prod Info Prozac(R), 2003c);(Prod Info Sarafem(R), 2001)(Varriale, 2001b; Feighner, 1985a; Wernicke, 1985). ECGs of patients taking fluoxetine showed none of the prolongation of PR and QRS intervals seen with the tricyclics. Fluoxetine in therapeutic doses had no significant clinical effect on the ECG (Fisch, 1985).
b) One group of authors reported that 3 elderly female patients, with underlying life-threatening pulmonary and cardiac disorders, died of cardiac dysrhythmias within 10 days of beginning fluoxetine treatment. A clear relationship between the death of these patients and the start of fluoxetine therapy was not established (Spier & Frontera, 1991).
c) Fluoxetine 40 to 80 mg daily produced reductions in mean heart rate, as compared to significant increases in heart rate with imipramine and amitriptyline in doses of 150 to 300 mg daily. In this study, doxepin produced increases in heart rate which were not considered significant. No other significant clinical effects on the EKG were observed in this series of 312 fluoxetine-treated patients; however, significant increases in the QT and QRS interval were observed with other antidepressants. Intraventricular conduction delays were observed in 5 patients receiving imipramine and in one patient receiving amitriptyline, with 4 of these patients developing left bundle branch block. No Intraventricular conduction defects were observed in fluoxetine-treated patients (Fisch, 1985).

3.3.1.A.2 Bradyarrhythmia

a) One paper reported a case of bradycardia in an elderly woman treated with 20 mg fluoxetine per day (Buff et al, 1991). One report suggested that these effects are dose-related and therefore the fluoxetine dosage should be reduced in the elderly or patients with a history of cardiac problems (Friedman, 1991).

3.3.1.A.3 Heart failure

a) In a large cohort study including 481,744 persons and 1487 cases of sudden cardiac death occurring in a community setting, the use of SSRIs 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 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).

3.3.1.A.4 Hypertension

a) Of 796 patients treated with fluoxetine 20 mg daily in an open trial, 1.7% developed sustained hypertension, and 2.2% developed treatment-emergent hypertension. Patients with controlled hypertension were included if the sitting diastolic blood pressure (BP) was less than or equal to 95 mmHg. At week 12, the change in mean sitting and standing systolic BP was -2.9 and -2.6 mmHg, respectively. Changes in mean diastolic BP were similar with a 2.3 mmHg (sitting) and 1.5 mmHg (standing) decrease at 12 weeks (Amsterdam et al, 1999).
b) In a 7-week, open study, patients treated with fluoxetine who had preexisting cardiovascular disease had fewer cardiovascular side effects than patients treated with nortriptyline. Twenty-seven (8 left the study) received fluoxetine 20 to 60 mg daily. Seven patients were treated with nortriptyline but the majority of data was retrieved from historical controls. Fluoxetine decreased heart rate by 6% and increased supine blood pressure by 2%. Patients with a baseline ejection fraction less than 50% showed a 7% increase during treatment with fluoxetine. Patients with a prolonged QRS interval or ventricular premature depolarizations were not adversely effected by fluoxetine treatment. Conversely, nortriptyline increased diastolic supine blood pressure by 4%, decreased standing systolic blood pressure by 5%, increased the orthostatic blood pressure drop by 3-fold, increased heart rate by 9%, decreased ejection fraction by 7%, and decreased the frequency of ventricular premature depolarization by 47%. Since conclusions are limited by the small sample, open design, and use of historical controls, treatment of depression in this group of patients must be undertaken with careful monitoring and slow dose titration until more data are available (Roose et al, 1998).

3.3.1.A.5 Prolonged QT interval

a) QT prolongation was observed on the electrocardiogram (ECG) of a 52-year-old man who had been taking fluoxetine (20 mg/day for 2 weeks, followed by 40 mg/day thereafter) for depression for 3 months. An ECG just before the start of fluoxetine treatment showed a normal QT interval. The QT interval returned to normal within 10 days of discontinuing fluoxetine treatment (Varriale, 2001c).
b) A 74-year-old woman developed syncope and torsade de pointes requiring cardioversion 3 weeks after being switched from amitriptyline to fluoxetine. ECG revealed QTc prolongation. Symptoms stopped when fluoxetine was discontinued but the ECG was not repeated (Appleby et al, 1995).
c) Cardiovascular side effects reported during treatment with fluoxetine included QT prolongation (Prod Info Prozac(R), 2003c);(Prod Info Sarafem(R), 2001)(Varriale, 2001b; Feighner, 1985a; Wernicke, 1985)

3.3.1.A.6 Tachyarrhythmia

a) A 55-year-old woman developed supraventricular tachycardia on her fifty-second day of taking fluoxetine 20 mg/day. She was concomitantly taking trimethoprim and sulfamethoxazole. She had a history of supraventricular tachycardia, but this episode was more pronounced and of longer duration

than previous ones. Sinus rhythm was restored with verapamil. Treatment for depression was changed to moclobemide, after which she had only one other episode of tachycardia. The authors concluded that a causal relationship could not be established; however, fluoxetine treatment seemed to exacerbate the underlying condition (Allhoff et al, 2001).
b) Supraventricular tachycardia and hypotension were associated with maintenance therapy with fluoxetine 20 mg daily in a 54-year-old woman. Cardiac symptoms and palpitations have not recurred in 25 months of follow-up. The patient received verapamil initially, which was discontinued 6 weeks later (Gardner et al, 1991).

3.3.1.A.7 Vasculitis

a) An 83-year-old woman developed pain, swelling and tenderness of her arms with malaise, lethargy, nausea, and vomiting 3 days after beginning fluoxetine therapy. Muscle biopsy showed acute myositis and extensive muscle infarction. Fluoxetine was discontinued and the patient died suddenly on the seventh hospital day of a ruptured abdominal aortic aneurysm. Postmortem muscle biopsy showed muscle necrosis and necrotizing vasculitis of the small and medium sized arteries (Fisher et al, 1999).

3.3.2 Dermatologic Effects

3.3.2.A Fluoxetine Hydrochloride

Bullous pemphigoid

Diaphoresis

Rash

3.3.2.A.1 Bullous pemphigoid

a) Bullous pemphigoid developed approximately 2 months after fluoxetine was started in a 75-year-old woman. This woman was admitted to the hospital for treatment of tense blisters located on the abdomen, thighs, and arms. The blisters were accompanied by red skin and intense pruritus. Skin biopsy confirmed the diagnosis of bullous pemphigoid. Fluoxetine was stopped, and the lesions cleared over 3 weeks without any topical or systemic corticosteroid treatment. From the case report, the patient was receiving several other medications, and it was unclear as to whether these medications were also continued (Rault et al, 1999).

3.3.2.A.2 Diaphoresis

a) Excessive sweating has been reported in association with fluoxetine in up to 30% of patients (Cohn & Wilcox, 1985a; Wernicke, 1985; Feighner & Cohn, 1985a; Rickels et al, 1985). Sweating appeared in fewer patients treated with fluoxetine than imipramine; however, fluoxetine was associated with a higher incidence of sweating than placebo (Cohn & Wilcox, 1985a; Wernicke, 1985; Stark & Hardison, 1985a).

3.3.2.A.3 Rash

a) Incidence: 7% (Prod Info Prozac(R), 2003c)
b) During clinical trials in the United States, 7% of patients developed rash and/or urticaria. Other clinical findings reported with the rash included fever, leukocytosis, arthralgias, edema, carpal tunnel syndrome, respiratory distress, lymphadenopathy, proteinuria, and mild elevations in transaminases. In about a third of the patients, fluoxetine was stopped. Most patients improved quickly although some were treated with antihistamines or steroids (Prod Info Prozac(R), 2003c; Wernicke, 1985). One case of erythema multiforme was also reported (Prod Info Prozac(R), 2003c).

3.3.3 Endocrine/Metabolic Effects

3.3.3.A Fluoxetine Hydrochloride

Galactorrhea

Hypertriglyceridemia

Hypoglycemia

Hyponatremia

Syndrome of inappropriate antidiuretic hormone secretion

Syndrome of inappropriate antidiuretic hormone secretion, and concurrent serotonin syndrome

Weight change finding

3.3.3.A.1 Galactorrhea

a) Summary

1) Before fluoxetine was commercially available, galactorrhea occurred in 4 of 5920 patients (0.07%); during postmarketing surveillance, 204 cases of galactorrhea were reported in an estimated 3.4 million patients treated with fluoxetine. The probable mechanism for SSRI-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).

b) Over a 10-year period, the Netherlands Pharmacovigilance Foundation received 38 reports of nonpuerperal lactation related to medications of which 15 cases were attributed to antidepressants primarily the SSRIs. The odds ratio for the risk of galactorrhea due to all antidepressants versus other medications was 8.3 (95% 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 attributed to antidepressants, 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 (Bronzo & Stahl, 1993).

c) A case of galactorrhea with hyperprolactinemia was reported in a 17-year-old girl treated with fluoxetine. The dosage of fluoxetine was titrated to 60 mg daily. Two weeks after treatment began, she developed galactorrhea. The serum prolactin level was 50 mcg/L was noted. When the dose of fluoxetine was decreased to 40 mg daily, galactorrhea resolved and prolactin levels returned to normal. Fluoxetine was continued without further adverse events (Iancu et al, 1992).

3.3.3.A.2 Hypertriglyceridemia

a) A 42-year-old man with social phobia associated with panic attacks, agoraphobia, and depressive disorder developed hypertriglyceridemia when treated separately with fluoxetine and extended-release venlafaxine. He was given alprazolam 0.25 mg up to 3 times daily and fluoxetine, increasing over one week to 20 mg/day. Alprazolam was tapered thereafter. Five months later, he reported 80% to 90% benefit in symptoms. A nonfasting lipid panel before initiation of treatment had shown slightly elevated triglycerides (261 mg/dL), cholesterol, and cholesterol-to-HDL ratio. Therefore his lipid profile was reexamined 7 months later. At that time, triglycerides were highly elevated (over 600 mg/dL). Fluoxetine was discontinued and venlafaxine extended-release was begun 2 weeks later. One month later, the man reported symptom remission to be 85% of that with fluoxetine. The lipid profile was again measured, showing a further increase in triglycerides to more than 1000 mg/dL. Venlafaxine was discontinued over 10 days and replaced by alprazolam only. Two weeks later, his triglyceride level was reduced to 154 mg/dL; cholesterol and cholesterol-to-HDL ratio remained somewhat elevated as they had been initially. The author suggested that lipid profiles should be monitored during treatment with venlafaxine or SSRIs (Teitelbaum, 2001).

3.3.3.A.3 Hypoglycemia

a) Hypoglycemia has infrequently been associated with fluoxetine use (Prod Info Prozac(R), 2003c).

b) A 17-year-old male with a 2-year history of type 1 diabetes mellitus experienced unawareness of hypoglycemic episodes after receiving fluoxetine 40 mg/day for 1 month for treatment of depression. Prior to fluoxetine therapy, the subject experienced typical adrenergic symptoms with low blood glucose values of 70 mg/dL about once a week. The subject experienced depression and was treated with fluoxetine 20 mg/day for 2 weeks. Fluoxetine was increased to 40 mg/day with mood improvement. After 1 month of fluoxetine therapy, the subject reported hypoglycemic episodes (blood glucose less than 70 mg/dL) about 3 times a week with no change in insulin use; however, a strict diet log was not maintained. Episodes of hypoglycemia were associated with confusion rather than the usual symptoms for this subject. The subject experienced 3 grand mal seizures in 1 month with blood sugars ranging from 35 to 41 mg/dL. Glycosylated hemoglobin was not changed from baseline and the subject lost 1.4 kg during fluoxetine therapy. Hypoglycemic awareness returned when fluoxetine was decreased over 12 days to a dose of 10 mg every other day; however, hypoglycemic episodes still occurred about 3 times a week. Fluoxetine was discontinued and within weeks blood glucose levels rose and hypoglycemia did not occur. Depressive symptoms recurred and subsequent treatment with mirtazapine and bupropion did not cause hypoglycemia or weight loss (Sawka et al, 2000).

3.3.3.A.4 Hyponatremia

a) Hyponatremia may occur with the use of serotonin norepinephrine reuptake inhibitors (SNRIs) or SSRIs, including fluoxetine. Symptoms include headache, difficulty concentrating, memory impairment, confusion, weakness, and unsteadiness. More severe or acute cases may lead to hallucination, syncope, seizure, coma, respiratory arrest, and death. The hyponatremia may be the result of the SIADH. Reported cases in which the serum sodium was lower than 110 mmol/L appeared to be reversible when fluoxetine was discontinued. Patients who are older, who are taking a diuretic, or who are volume depleted may be at greater risk. If signs and symptoms of hyponatremia occur, fluoxetine should be discontinued (Prod Info PROZAC(R) oral capsules, delayed-release capsules, solution, 2008).

3.3.3.A.5 Syndrome of inappropriate antidiuretic hormone secretion

a) Summary

1) Of the 63 case reports of fluoxetine-induced SIADH reported to the United States Food and Drug Administration, the majority occurred in patients over 70 years of age. Based on published reports, the onset of the SIADH was between 3 days and 4 months after starting fluoxetine therapy. Symptoms included confusion, lethargy, dizziness, fatigue, anorexia, delirium, and abdominal pain. Abnormal laboratory findings consisted of a decreased serum osmolality (median 251 milliosmoles/liter (mOsm/L); range 214 to 272 mOsm/L), decreased serum sodium concentration (median 118 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 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).

b) Hyponatremia secondary to SIADH has been reported in patients taking therapeutic doses of fluoxetine (Jackson et al, 1995; Flint et al, 1996; Girault et al, 1997; Anon, 1994).

c) Hyponatremia occurred in 2 elderly patients also taking thiazide diuretics. The mechanism of this adverse effect is thought to be due to inappropriate secretion of antidiuretic hormone. The authors advise careful monitoring of serum sodium in this patient population (ten Holt et al, 1996).

d) Seven cases of hyponatremia associated with fluoxetine use were identified over a 4-year period of time in the New Zealand Intensive Monitoring Program. All of the patients were women who were taking fluoxetine 20 mg/day; normalization of serum sodium occurred after fluoxetine therapy was withdrawn (Pillans & Coulter, 1994).

e) Hyponatremia consistent with SIADH associated with fluoxetine has been reported. A 75-year-old woman was switched from dothiepin 75 mg daily of fluoxetine 20 mg daily because of urinary retention. Her only other medication was ranitidine. The patient was noted to be drowsy and confused 12 days after starting fluoxetine. Serum sodium had declined from 140 mmol/L to 116 mmol/L; serum and urine osmolality were 242 milliosmoles/liter (mOsmol/L) and 337 mOsmol/L, respectively; urine sodium was 91 mmol/L. Fluid restriction and discontinuation of fluoxetine resulted in a serum sodium of 130 mmol/L in 2 days; in another 4 days, this value had risen to 138 mmol/L, and serum osmolality had risen to 283 mOsmol/L. The patient experienced an acute myocardial infarction complicated by left ventricular failure and died 5 days later. The authors state that the patient had recovered from the metabolic derangement before her heart attack. The authors note that the manufacturer informed them that several cases of hyponatremia, with the possibility of SIADH for some, had occurred in their studies (Gommans & Edwards, 1990).

f) Prolonged hyponatremia was observed in a 75-year-old male with depression after receiving fluoxetine 20 mg orally each day for 15 days. Serum sodium and chloride were observed to decrease progressively over the first 14 days of fluoxetine therapy, reaching a nadir of 126 and 89 mmol/L, respectively, on day 14. On the fifteenth day of treatment, serum and urine osmolality were lower than normal (264 milliosmoles/liter (mOsmol/L) and 416 mOsmol/kg, respectively), consistent with the SIADH. After withdrawal of fluoxetine, electrolyte levels returned to normal within 10 days. The patient was not rechallenged with fluoxetine. Additional investigations are required to determine whether there is a true cause-effect relationship between fluoxetine and SIADH (Hwang & Magraw, 1989).

3.3.3.A.6 Syndrome of inappropriate antidiuretic hormone secretion, and concurrent serotonin syndrome

a) A 56-year-old man, with a history of intracerebral hemorrhagic stroke and depression, developed SIADH and serotonin syndrome concurrently following the addition of fluoxetine to his existing antidepressant regimen (olanzapine 2.5 mg/day and buspirone 10 mg twice daily). Four weeks following the initiation of fluoxetine 40 mg/day and one week following an increase in the dosage to 60 mg/day, the man presented with symptoms of SIADH (ie, serum osmolality of 240 mOsm/kg, low BUN, low sodium, normal serum glucose) and serotonin syndrome (ie, dilated pupils, restlessness, change in mental status, facial flushing, myoclonus, hyperreflexia, increased blood pressure, tachycardia). Following water restriction (1000 mL/day), an infusion of lorazepam (0.07 mg/kg/hr for 24 hours then tapered over 48 hours) and discontinuation of buspirone, olanzapine, and fluoxetine, the man's symptoms resolved over several days. Buspirone and olanzapine were reinitiated at the previous doses

with no recurrence of adverse effects and fluoxetine was eliminated from his therapeutic drug regimen. A probable relationship between the use of fluoxetine and the development of the concurrent syndromes was indicated through the use of the Naranjo probability scale. The authors speculate that patients with a history of stroke may be more susceptible to severe adverse effects that may result from combination antidepressant therapy; however, additional studies are required to clarify any association between this patient group an increased incidence or severity of antidepressant-related adverse events (Bogdanovic et al, 2005).

3.3.3.A.7 Weight change finding

a) Weight gain has not occurred with fluoxetine therapy; stabilization of weight or weight loss has occurred in most controlled studies (Stark & Hardison, 1985a; Cohn & Wilcox, 1985a; Feighner, 1985a; Young et al, 1987a; Levine et al, 1987).

3.3.4 Gastrointestinal Effects

3.3.4.A Fluoxetine Hydrochloride

Gastrointestinal hemorrhage

Gastrointestinal tract finding

Grinding teeth

Loss of appetite

Nausea and vomiting

Stomatitis

Upper gastrointestinal hemorrhage

3.3.4.A.1 Gastrointestinal hemorrhage

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

3.3.4.A.2 Gastrointestinal tract finding

a) Gastrointestinal side effects of fluoxetine have included dry mouth and diarrhea, occurring in 14% and 10% of patients, respectively (Wernicke, 1985). Diarrhea developed in 38% of patients receiving therapeutic doses of fluoxetine for panic attacks (Gorman et al, 1987). Dryness of the mouth generally occurs to a lesser degree with fluoxetine than with imipramine (Stark & Hardison, 1985a; Cohn & Wilcox, 1985a), doxepin (Feighner & Cohn, 1985a) and amitriptyline (Feighner, 1985a; Chouinard, 1985b). constipation, dyspepsia, abdominal pain and taste changes have also occurred less frequently with fluoxetine (Bremner, 1984b; Stark & Hardison, 1985a; Wernicke, 1985).

3.3.4.A.3 Grinding teeth

a) Onset of symptoms of nocturnal bruxism within 2 weeks after beginning fluoxetine 15 to 20 mg daily for unipolar depressive episodes or mood instability was reported in 3 women aged 28 to 43 years. Teeth clenching during sleep caused nighttime awakening with headaches, earaches, and aching jaws. Buspirone doses ranging from 5 mg at bedtime to 10 mg 3 times daily were effective in 2 (Ellison & Stanziani, 1993). One 28-year-old woman developed symptoms of both diurnal and nocturnal bruxism, with tender, bleeding gums and jaw clenching. The patient stopped taking fluoxetine abruptly, with improvement, then restarted fluoxetine therapy when symptoms of depression returned, which aggravated her bruxism. Alternative SSRI therapy with paroxetine 20 mg/day, sertraline 50 mg/day, and fluvoxamine 100 mg/day in succession failed to alleviate the bruxism. She discontinued all SSRI treatment when she became pregnant. After pregnancy she started taking oral fluoxetine again which exacerbated her tooth grinding. Oral buspirone 5 mg/day was added, temporarily alleviating her bruxism, but was eventually discontinued because of intolerable sedative effects (Fitzgerald & Healy, 1995).

3.3.4.A.4 Loss of appetite

a) Anorexia has also occurred during fluoxetine therapy, and is most likely associated with the weight loss observed in several studies. Anorexia has occurred in 9% to 15% of patients treated, and occurs more frequently with fluoxetine than with other antidepressants; however, it is rarely a cause for drug

discontinuation (Feighner & Cohn, 1985a; Wernicke, 1985; Prod Info Prozac(R), 2003c). Fluoxetine has been shown to cause anorexia with resultant weight loss in overweight, non-depressed individuals at fluoxetine dosages of 20 to 80 mg/day (Ferguson & Feighner, 1987).

b) In a double-blind, placebo-controlled study of 35 patients, improvement in depression and reduction in BMI (calculated as weight in kg divided by the square of height in meters) were not significantly correlated, suggesting different mechanisms for these effects. The reduction in patient's BMI bore a curvilinear relationship to fluoxetine dose (in mg per square meter of body surface area), with daily doses of 20 mg and 40 mg leading to greater decreases of BMI than 5 mg doses (Harto et al, 1988).

3.3.4.A.5 Nausea and vomiting

a) Summary

1) The most common side effect of fluoxetine therapy is nausea, which may occur in 25% to 30% of patients (Wernicke, 1985; Cohn & Wilcox, 1985a; Stark & Hardison, 1985a; Feighner & Cohn, 1985a; Chouinard, 1985b). Clinical trials, however, have reported that only 4% of patients discontinue treatment due to this side effect (Ayd, 1988). Vomiting occurs less frequently with fluoxetine (Bremner, 1984b; Stark & Hardison, 1985a; Wernicke, 1985).

b) The 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. 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).

3.3.4.A.6 Stomatitis

a) Two women developed stomatitis during treatment with fluoxetine. A 24-year-old woman with anorexia nervosa had received fluoxetine 20 mg daily for 6 months. During the course of treatment, she experienced 6 episodes of stomatitis which showed a partial response to metronidazole 750 mg daily and spiramycin 4,500,000 International Units (IU) daily for 7 days. When she presented to the emergency department due to aphthae and inflammation of the oral cavity, fluoxetine was stopped, and complete healing was noted in 7 days. This patient was rechallenged with fluoxetine and developed stomatitis again. The second patient, a 41-year-old woman with depression, received fluoxetine 20 mg daily and a benzodiazepine. Since beginning treatment, the patient complained of dysgeusia, a dry mouth, and inflammation of the mouth which prevented swallowing. Both drugs were stopped but alprazolam was restarted. Her symptoms improved within 2 days but she refused rechallenge. The authors attribute the stomatitis to a hypersensitivity reaction (Palop et al, 1997).

3.3.4.A.7 Upper gastrointestinal hemorrhage

a) Upper gastrointestinal bleeding has been reported in association with psychotropic drugs that interfere with serotonin uptake such as fluoxetine. Epidemiological studies have suggested that concurrent use of an NSAID increases the risk of bleeding episodes (Prod Info Sarafem (R) pulvules, 2004).

3.3.5 Hematologic Effects

3.3.5.A Fluoxetine Hydrochloride

Aplastic anemia

Bleeding

Neutropenia

3.3.5.A.1 Aplastic anemia

a) Aplastic anemia developed in a 28-year-old man taking fluoxetine 40 mg/day for 6 weeks. He presented with a high fever, painful oral ulcers, and pleuritic chest pain. Pancytopenia was noted on the peripheral blood smear (ie, absolute granulocyte count 480 x 10(6) cells/L, platelets 34 x 10(9)/L, and mild macrocytic anemia). A bone marrow biopsy showed severe depression of megakaryocytes and myeloid cells with moderate depression of the erythroid cell line. Fluoxetine was stopped, and imipenem plus cilastatin was started. Complete recovery of the blood count was reported at 19 days. Rechallenge with fluoxetine resulted in reduction of the leukocyte and platelet count within 5 days; 12 days after stopping fluoxetine, the blood count returned to normal (Bosch & Vera, 1998).

3.3.5.A.2 Bleeding

a) Summary

1) Case reports, case-control, and cohort studies have shown an association between the use of drugs that interfere with serotonin reuptake and gastrointestinal bleeding. Bleeding events associated with SSRI and serotonin norepinephrine reuptake inhibitor (SNRI) use include ecchymoses, hematomas, epistaxis, petechiae, and life-threatening hemorrhages. There have also been postmarketing reports of vaginal bleeding after fluoxetine discontinuation. Risk of bleeding events may be increased by concomitant use of NSAIDs, aspirin, warfarin, and other anticoagulants; patients should be cautioned of this increased risk (Prod Info PROZAC(R) oral capsules, delayed-release capsules, solution, 2008).

b) Incidence: up to 1% (Berk & Jacobson, 1998)

c) Increased bleeding (eg, bruising, ecchymoses, epistaxis, prolonged bleeding time, and rectal bleeding) has been reported with the use of SSRIs. SSRIs reduce uptake of serotonin by platelets; therefore, reduction in granular storage of serotonin is observed. Serotonin-mediated platelet aggregation may be decreased. The majority of cases have been reported in patients taking fluoxetine, but case reports are also available for paroxetine, sertraline, and fluvoxamine. Risk is increased with higher doses and in patients with underlying diseases; one case occurred in a patient with HIV. 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).

d) A 31-year-old woman developed bruising 4 weeks after she began taking fluoxetine 20 mg daily for depression; the bruising worsened over the 5 days preceding her clinic visit. Examination revealed multiple bruises which were disproportionally large for the trauma incurred. The complete blood count, prothrombin time, and partial thromboplastin time were within normal limits. Although bruising continued, the patient did not want to stop fluoxetine since her depression was improving. During pre-marketing clinical trials, bruising was reported in 1% of fluoxetine-treated patients compared to 0.6% for placebo. Fluoxetine disrupts normal platelet aggregation by blocking uptake of serotonin into platelets; the end result is bruising or bleeding (Pai & Kelly, 1996).

e) Fluoxetine blocks 5-hydroxytryptamine reuptake in platelets and may lead to platelet dysfunction. One case described a patient with a minor history of bleeding disorder (occasional epistaxis and bruising) who developed a prolonged bleeding time and petechiae while taking fluoxetine 20 mg every other day for 2 years. Her platelet count, prothrombin time, and von Willebrand factors were normal, and she was on no medication. The patient was taken off fluoxetine, and bleeding time returned to normal. After a return to fluoxetine therapy at the same dose, prolonged bleeding time and petechiae again returned (Humphries et al, 1990).

3.3.5.A.3 Neutropenia

a) A 79-year-old man developed neutropenia associated with fluoxetine. Presenting symptoms included fatigue and weakness; a hemogram detected a leukocyte count of 2800 cells/mm(3) with granulocytopenia (0% segmented cells, 11% band cells). All drug therapies (ie, fluoxetine, warfarin, glipizide, diphenhydramine, and tobramycin/dexamethasone ophthalmic drops) were stopped after granulocytopenia was identified; the absolute neutrophil count returned to normal. First, fluoxetine 20 mg daily was restarted, and 3 days later, severe neutropenia recurred. After stopping fluoxetine, neutropenia resolved rapidly. Reinstitution of glipizide and warfarin had no effect on the neutrophil count. Serum drug-dependent neutrophil antibodies did not react with fluoxetine; however, the rapid response to rechallenge with fluoxetine suggests a drug-related antineutrophil antibody reaction (Vilinsky & Lubin, 1997).

3.3.6 Hepatic Effects

3.3.6.A Fluoxetine Hydrochloride

3.3.6.A.1 Hepatotoxicity

a) Asymptomatic increased liver enzymes have been reported in 0.5% of patients; however, only a few cases of hepatitis have been reported (Cai et al, 1999a; Friedenberg & Rothstein, 1996; Wernicke, 1985; Anon, 1996).

b) Elevations in total bilirubin, direct bilirubin, AST/SGOT, ALT/SGPT, total alkaline phosphatase, and gamma-glutamyltransferase were documented (Cai et al, 1999a).

c) A 35-year-old man developed chronic hepatitis in association with intermittent use of fluoxetine for depression. Liver enzymes increased shortly after fluoxetine was restarted at a daily dose of 40 mg. At the initial evaluation, fatigue resulting in an inability to work for 10 months and elevated liver enzymes (ie, gamma-glutamyl transferase) with a positive antibody against hepatitis C were present. He received prednisone 30 mg daily for 1 month followed by azathioprine 50 mg daily for 1 month which resulted in slight decreases in ALT. However, the ALT fell after stopping fluoxetine and was normal within 6 months. A liver biopsy supported a diagnosis of autoimmune hepatitis. Although hepatotoxicity occurred during fluoxetine use, this patient had a history IV drug abuse about 15 years earlier and admitted to binge drinking, marijuana and amphetamine abuse about 2 years ago (Johnston & Wheeler, 1997).

3.3.8 Musculoskeletal Effects

3.3.8.A Fluoxetine Hydrochloride

Fracture of bone

Fracture of bone, Nonvertebral

3.3.8.A.1 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 fluoxetine (adjusted odds ratio (OR), 1.2; 95% CI, 1.09 to 1.32) compared to those who were not exposed to fluoxetine. Fluoxetine use was associated with an increased risk of hip fracture (adjusted OR, 1.33; 95% CI, 1.02 to 1.73) and forearm fracture (adjusted OR, 1.32; 95% CI, 1.04 to 1.68), but not spine fracture (adjusted OR, 0.7; CI, 0.4 to 1.22) (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 fluoxetine, 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% 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). 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.2 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, and 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% 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).

3.3.9 Neurologic Effects

Fluoxetine

Fluoxetine Hydrochloride

3.3.9.A Fluoxetine

3.3.9.A.1 Seizure

See Drug Consult reference: COMPARATIVE INCIDENCE OF SEIZURES FROM ANTIDEPRESSANTS

3.3.9.B Fluoxetine Hydrochloride

Asthenia

Extrapyramidal disease

Impaired cognition

Impaired psychomotor performance

Myoclonus

Neurological finding

Paresthesia

Restless legs syndrome

Seizure

3.3.9.B.1 Asthenia

a) Incidence: 9% to 21% (Prod Info Prozac(R), 2003c)

b) Asthenia has occurred in 9% to 21% of patients treated with fluoxetine. This side effect is dose-related with higher incidences reported in patients being treated with a dosage of 60 mg/day for bulimia nervosa (Prod Info Prozac(R), 2003c). Asthenia has occurred to a greater degree with imipramine than with fluoxetine (Cohn & Wilcox, 1985a).

3.3.9.B.2 Extrapyramidal disease

a) The majority of extrapyramidal reactions (EPRs) occur within the first few days to the first month of starting treatment or increasing the dose. Therefore, careful monitoring for EPRs is recommended weekly during the first 4 weeks of fluoxetine therapy In all cases, symptoms disappeared after reducing the dose or stopping the SSRI. 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 mg daily, and the dose of clonazepam was 1.5 mg daily. Dystonic reactions were treated with an unspecified dose of intramuscular trihexyphenidyl or diphenhydramine 50 mg (Caley, 1997);(Gill et al, 1997).

b) Two women with dopa-responsive dystonia (DRD) noted worsening of the dystonia after starting venlafaxine or fluoxetine. The first patient had onset of DRD during childhood; DRD had been well controlled with Sinemet(R) plus which was continued during fluoxetine treatment. Five days after starting fluoxetine 20 mg/day, she developed torticollis, and 2 days later, she noted inversion of the left ankle. She described the changes as exactly the same as they were as a child. She stopped fluoxetine, and within 2 days, the dystonia improved and completely resolved at 1 week. The second patient developed dystonia 4 days after starting venlafaxine although she continued Sinemet(R) LS at the same dose. Without seeing a physician, she stopped venlafaxine, and the dystonia completely resolved after approximately 1 week (Mathen et al, 1999).

c) Choreiform movements were observed in an otherwise healthy 74-year-old woman treated with fluoxetine 20 mg/day. After taking fluoxetine for 7 months for major depression, the patient developed unsteadiness, with a tendency to fall backward, abnormal involuntary choreiform movements involving the tongue, lips, lower face, and buccal and masticatory muscles. The patient was hospitalized, fluoxetine was stopped, and clothiapine 20 mg/day was substituted. She improved rapidly over the next 3 weeks and was discharged from the hospital (Marchioni et al, 1996).

d) In a series of 5555 patients taking fluoxetine therapeutically 15 developed extrapyramidal effects. Eight of these were taking other drugs which may have contributed to these effects (Coulter & Pillans, 1995).

e) Tics developed in a 12-year-old boy after 8 months of therapy with fluoxetine 20 mg daily. This suggests the modulating effect that serotonin may have on dopaminergic neurons (Eisenhauer & Jermain, 1993).

f) Akathisia occurred within 7 days of initiation of fluoxetine therapy in 5 patients being treated for obsessive-compulsive disorder. Three of the patients, who had previously experienced neuroleptic-induced akathisia, described the effect of fluoxetine as identical, but milder. In all 5 cases, akathisia resolved with propranolol therapy and/or reduction of the fluoxetine dose. This side effect appears to be common, as it occurred in 5 patients among a study group of 51 (20 of whom were evaluated for akathisia from the start of therapy). They propose that the same pathophysiologic mechanism accounts for fluoxetine-induced "jitteriness," namely inhibition of dopamine transmission via increased serotonergic activity (Lipinski et al, 1989).

g) In an open trial of fluoxetine in patients with obsessive-compulsive disorder, 8 of 50 patients reported tremors and 2 of 50 reported involuntary movements. The mean daily dose of fluoxetine for the study group was 78 mg/day (undivided) (Fontaine & Chouinard, 1989).

3.3.9.B.3 Impaired cognition

a) Summary

1) In one study, the use of fluoxetine or paroxetine was not associated with degradation of cognitive function in depressed non-demented elderly patients, however, there have been case reports of memory loss associated with the use of fluoxetine (Joss et al, 2003; Cassano et al, 2002).

b) Severe memory loss resulting in hospitalization developed in an 87-year-old Caucasian woman following the administration of fluoxetine for the treatment of depression. Approximately 2 weeks after beginning fluoxetine therapy (initial, 10 mg/day for 2 weeks, then 20 mg/day) the woman's memory began to decline. Fluoxetine was discontinued after approximately 2 months of therapy and symptoms of memory loss peaked 5 days later. Symptoms improved within 2 weeks of fluoxetine cessation and continued to get better over the following 2 months. Fluoxetine therapy was cited as the probable cause of memory loss in this patient because the timeline correlates well with the half-life of fluoxetine and other possible causes of memory loss were ruled out (Joss et al, 2003).
c) 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 posttreatment. 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.4 Impaired psychomotor performance

a) Summary

1) Fluoxetine therapy may have an effect on psychomotor function (Thapa et al, 1998; Hindmarch, 1988). Nursing home patients treated with fluoxetine and other SSRIs including paroxetine and sertraline have an increased risk of falls compared to patients who are not on antidepressants (Thapa et al, 1998).

b) Nursing home patients treated with fluoxetine and other SSRIs including paroxetine and sertraline have an increased risk of falls compared to patients who are not on antidepressants. 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), 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% 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 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).
c) The effects of amitriptyline 50 mg, dothiepin 50 mg, fluoxetine 40 mg, and placebo were assessed with and without alcohol 0.5 g/kg body weight, on a battery of 7 tests of psychomotor and cognitive functions relevant to automobile driving. Eight female volunteers were studied, each acting as her own control. Subjects were trained on each test to a plateau of performance before the study in order to eliminate confounding effects of learning. Results indicated that, compared to placebo, single doses of fluoxetine 40 mg (with or without alcohol) did not result in any significant effect on performance for any of the tests. However, amitriptyline (with or without alcohol) and dothiepin (with or without alcohol) caused significantly impaired performance on several of the tests when compared to placebo. This difference may be important for outpatients who must be able to maintain skilled performance of various tasks, as well as for depressed patients for whom a decrease in psychomotor and cognitive function would be counter-therapeutic (Hindmarch, 1988).

3.3.9.B.5 Myoclonus

a) One month after starting treatment with fluoxetine 40 mg daily for depression following alcohol withdrawal, a 35-year-old woman developed spontaneous, non-rhythmical, involuntary jerks of the head, arm, or legs. Other medications included triazolam and vitamin B complex. Upon examination, proprioceptive, luminous, and auditory stimulation produced spontaneous, reflex, and induced myoclonic jerks. Other neurological and neuropsychological evaluations were normal; the electroencephalogram and laboratory tests were also normal. All symptoms resolved 2 days after fluoxetine was stopped. This case differs from others because the patient had no underlying cerebral disease (Ghika-Schmid et al, 1997).

3.3.9.B.6 Neurological finding

a) Summary

1) The most common side effects of fluoxetine therapy (excluding nausea) involve the CNS, including nervousness, insomnia, headache, tremor and drowsiness (Wernicke, 1985; Fabre & Crismon, 1985; Stark & Hardison, 1985a; Cohn & Wilcox, 1985a; Chouinard, 1985b; Rickels et al, 1985). Nervousness and insomnia occur in approximately 10% to 20% of patients, and have occurred more frequently than in patients receiving amitriptyline or imipramine (Cohn & Wilcox,

1985a; Wernicke, 1985; Prod Info Prozac(R), 2003c). Headache (20.3%), somnolence (13%), and tremor (10%) are also frequently reported (Prod Info Prozac(R), 2003c). Other rare CNS side effects with fluoxetine have included ataxia, dizziness, sensation disturbances, and a "high" feeling (Cohn & Wilcox, 1985a; Bremner, 1984b; Stark & Hardison, 1985a; Feighner, 1985a; Wernicke, 1985; Borys et al, 1990; Gorman et al, 1987). The incidence of dizziness, lightheadedness, and sensation disturbances has been greater with imipramine than with fluoxetine (Cohn & Wilcox, 1985a). Exacerbation of multiple sclerosis symptoms may occur with fluoxetine therapy (Browning, 1990).

b) Exacerbation of symptoms of multiple sclerosis (arm numbness and grogginess) developed in a 41-year-old woman 10 hours after beginning fluoxetine and progressed over the next 4 days of therapy. Symptoms returned to baseline after discontinuing fluoxetine therapy (Browning, 1990).

3.3.9.B.7 Paresthesia

a) Paresthesia is a rare side effect reported with SSRI therapy. In a case report, tingling in the lower extremities occurred with initiation of fluoxetine that worsened with an increase in dose and continued therapy. Following discontinuation of the drug, resolution of paresthesia was noted after 2 weeks. The patient was then started on sertraline with no further recurrence of symptoms (Bhatara et al, 1996).

3.3.9.B.8 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).

3.3.9.B.9 Seizure

a) Summary

1) In United States placebo-controlled studies the reported seizure incidence of 0.2% with fluoxetine is no greater than that observed with other antidepressants (Prod Info Prozac(R), 2003c). Several isolated reports of seizure activity have been reported in patients given therapeutic doses of fluoxetine; however, it is difficult to implicate the drug as the sole cause in some cases (Wernicke, 1985).

b) A 53-year-old woman with no prior history of seizures experienced an episode of generalized tonic-clonic convulsions 6 days after her daily dose of fluoxetine was raised from 40 to 60 mg. The patient had been receiving fluoxetine for 5 months for the treatment of depression. No causative factor was identified in laboratory or hematological tests, lumbar puncture, or brain MRI. Fluoxetine was initially discontinued and later restarted at 20 mg/day. At 3-month follow-up, she had experienced no other seizures (Oke et al, 2001).

c) Seizures were described in an 84-year-old woman after receiving fluoxetine 20 mg orally daily for approximately 5 days. The patient had no prior history of seizure activity and was on concurrent therapy with diltiazem and docusate. No factors were identified in the patient's history, laboratory data, or neurological examinations that would affect seizure threshold. This case report suggests a possible epileptogenic potential of fluoxetine; however, it does not establish a definite cause/effect relationship (Weber, 1989). Previously, seizures have been observed in 12 of 6000 patients receiving fluoxetine during premarketing trials (Prod Info Prozac(R), 2003c).

d) Two patients currently taking lithium and fluoxetine in therapeutic doses for depression and suicidal ideation experienced seizures following ingestion of LSD (Jackson & Hornfeldt, 1991).

e) Seizure activity was described in a 35-year-old woman with bipolar affective disorder after receiving fluoxetine 20 mg orally daily for approximately 3 days. The patient had no history of seizure activity and was not receiving other medications at the time. On the third day of treatment, the patient's roommate reported that the patient was flailing her arms; the patient was subsequently found in bed, unresponsive, and had a tongue laceration. It was felt that the patient had a major motor seizure. Following the withdrawal of fluoxetine, no recurrent seizure activity was observed. It is unclear whether seizure activity would have occurred in this patient in the absence of fluoxetine therapy (Ware & Stewart, 1989).

3.3.10 Ophthalmic Effects

3.3.10.A Fluoxetine Hydrochloride

Eye / vision finding

Raised intraocular pressure

Visual disturbance

3.3.10.A.1 Eye / vision finding

a) Blurred vision and other visual disturbances, cataracts, conjunctivitis, dry eyes, mydriasis, optic neuritis, photophobia and increased intraocular pressure have been reported with fluoxetine administration (Prod Info Prozac(R), 2003c; Prod Info Sarafem(TM), 2002).

3.3.10.A.2 Raised intraocular pressure

a) Increased intraocular pressure has been described following fluoxetine administration. In a series of depressed patients (n=20) in whom baseline intraocular pressures (IOP) were normal, oral fluoxetine 20 mg resulted in a significant increase (p less than 0.05) in IOP 2 hours after drug administration that persisted for up to 8 hours (Costagliola et al, 1996).

3.3.10.A.3 Visual disturbance

a) Visual disturbances, primarily blurred vision, have been described in patients receiving fluoxetine and have necessitated withdrawal of therapy (Wernicke, 1985; Prod Info Prozac(R), 2003c; Borys et al, 1990; Gorman et al, 1987). These disturbances tend to occur early in treatment. Approximately 3% of patients in clinical trials have noted changes in vision (Prod Info Prozac(R), 2003c).

3.3.12 Psychiatric Effects

3.3.12.A Fluoxetine Hydrochloride

Anxiety

Depression, worsening

Feeling nervous

Hallucinations

Hypomania

Mania

Nightmares

Psychotic disorder

Suicidal thoughts

3.3.12.A.1 Anxiety

a) Anxiety has been reported with fluoxetine therapy (Wernicke, 1985; Fabre & Crismon, 1985; Stark & Hardison, 1985a; Cohn & Wilcox, 1985a; Chouinard, 1985b; Rickels et al, 1985).

3.3.12.A.2 Depression, worsening

a) Incidence: rare (Anon, 2004)

b) 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 Feeling nervous

a) Incidence: 13% (Prod Info PROZAC(R) oral capsules, oral solution, delayed-release oral capsules, 2006)

b) In pooled analysis controlled clinical trials (US major depressive disorder, obsessive compulsive disorders, bulimia) (n=4542), the incidence of nervousness is 13% in patients on fluoxetine vs 8% in patients on placebo (Prod Info PROZAC(R) oral capsules, oral solution, delayed-release oral capsules, 2006).

3.3.12.A.4 Hallucinations

a) In a case report, a 16-year-old boy developed auditory hallucinations following the administration of fluoxetine for the treatment of major depressive disorder without psychotic symptoms. Three days after beginning fluoxetine therapy at a 20-mg dose, the patient presented with auditory hallucinations telling him to kill his father, mother, sister, and himself. Fluoxetine was discontinued and the hallucinations stopped 3 days later (Webb & Cranswick, 2003).

b) A 38-year-old man developed a complex visual hallucination with both sertraline and fluoxetine therapy. The hallucination was described as a blue-green central disc that nearly filled the visual fields, with a dynamic yellow central portion and peripheral yellow regions and a red vertical bar in the left visual field of both eyes. The visual pattern was present daily on awakening and would last 30 to 40 seconds. The pattern occurred initially with sertraline therapy and recurred when fluoxetine was substituted. It gradually disappeared when both were discontinued and nefazodone was substituted (Bourgeois et al, 1998).

3.3.12.A.5 Hypomania

a) Incidence: rare (Prod Info Prozac(R), 2003c)

b) In United States placebo-controlled trials, 0.7% of 10,872 fluoxetine-treated patients reported mania or hypomania (Prod Info Prozac(R), 2003c).

c) Hypomania was described in 2 patients who ingested 120 mg/day for 7 days and 140 mg/day for 16 days, respectively (Tech Info, 1987), and in another patient who took 140 mg for 36 hours (Chouinard & Steiner, 1986).

d) A 28-year-old woman with depression developed hypomanic symptoms after receiving fluoxetine 80 mg daily for approximately 7 weeks. Reduction in the dose of fluoxetine resulted in frank mania, with symptoms including racing thoughts, markedly decreased sleep without fatigue, and distractibility. Withdrawal of fluoxetine and initiation of therapy with thiothixene was undertaken, but the mania continued for several more days. Lithium therapy was initiated 5 days after withdrawal of fluoxetine and thiothixene was discontinued, and mania resolved over a period of 2 weeks. The patient had never suffered a hypomanic or manic swing prior to fluoxetine therapy (Settle & Settle, 1984).

3.3.12.A.6 Mania

a) Summary

1) Several reports of manic episodes have occurred in fluoxetine-treated patients who received the drug for several months (Settle & Settle, 1984; Rickels et al, 1985). In United States placebo-controlled trials, 0.7% of 10,872 fluoxetine-treated patients reported mania or hypomania (Prod Info Prozac(R), 2003c).

b) Incidence: rare (Prod Info Prozac(R), 2003c)

c) In United States placebo-controlled trials, 0.7% of 10,872 fluoxetine-treated patients reported mania or hypomania (Prod Info Prozac(R), 2003c).

d) Hypomania was described in 2 patients who ingested 120 mg/day for 7 days and 140 mg/day for 16 days, respectively (Tech Info, 1987), and in another patient who took 140 mg for 36 hours (Chouinard & Steiner, 1986).

e) A 28-year-old woman with depression developed hypomanic symptoms after receiving fluoxetine 80 mg daily for approximately 7 weeks. Reduction in the dose of fluoxetine resulted in frank mania, with symptoms including racing thoughts, markedly decreased sleep without fatigue, and distractibility. Withdrawal of fluoxetine and initiation of therapy with thiothixene was undertaken, but the mania continued for several more days. Lithium therapy was initiated 5 days after withdrawal of fluoxetine and thiothixene was discontinued, and mania resolved over a period of 2 weeks. The patient had never suffered a hypomanic or manic swing prior to fluoxetine therapy (Settle & Settle, 1984).

3.3.12.A.7 Nightmares

a) Four cases of vivid nightmares (and night terrors) were reported in patients on fluoxetine monotherapy. The nightmares generally disappeared after several days of continued therapy; 2 of the patients required the addition of a sedative at bedtime (Lepkifker et al, 1995).

3.3.12.A.8 Psychotic disorder

a) One paper reported a case of psychosis in an 11-year-old girl who was given fluoxetine 20 mg for 35 days. The patient had no history of delusional psychosis, but had sustained head trauma 5 years before and had an abnormal electroencephalogram (EEG). The patient was normal 3 weeks after cessation of fluoxetine therapy (Hersh et al, 1991).

b) A 58-year-old man exhibited dose-related paranoid symptoms during treatment of depression with fluoxetine. The patient previously showed no psychotic symptoms. Initial treatment with 20 mg/day of fluoxetine yielded no improvement after 3 weeks and the dose was subsequently increased to 40 mg/day. The paranoia became evident 2 weeks after dissipation of the depressive symptoms. The dose was lowered back to 20 mg/day and the paranoia subsided within a week of the decrease. The patient was controlled on this dose with no further evidence of depression or paranoia. The delayed length of time to see the symptoms may be due to the long half-life of fluoxetine. Other pertinent factors include concurrent therapy with diltiazem, which may have led to higher than expected plasma fluoxetine levels

and discontinuation of triazolam, and possible withdrawal, prior to fluoxetine initiation (Mandalos & Szarek, 1990).

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 are 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).

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 9 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).

3) Considerable controversy exists regarding the association of fluoxetine with suicidal ideation. Controlled and prospective trials and combined meta-analysis have both failed and supported an increased emergence or worsening of suicidal thoughts or actions with fluoxetine therapy and several case reports have been noted where there may be an association. Various theories have been proposed to explain these anecdotal reports, including development of akathisia which may represent toxicity; excessive doses; recent withdrawal from MAOI therapy; concomitant treatment with other neuroleptic agents that might potentiate the effects of fluoxetine or cause extrapyramidal effects such as akathisia; patients with a history of panic attacks; or possibly underlying worsening of depression (Perlis et al, 2007; Warshaw & Keller, 1996; Beasley et al, 1992a; Beasley et al, 1991).

b) In a 12-week, open multicenter trial of adults (18 to 65 yr) with nonpsychotic major depressive episodes (n=414), 14.3% of patients experienced treatment-emergent or worsening of suicidal ideation, usually early in therapy, during treatment with fluoxetine. Patients were given a modified 17-item Hamilton Depression (mHAMD) assessment at screening, baseline, and at each visit (weekly for 4 weeks, biweekly for 6 weeks and again weekly for up to 12 weeks). Suicidal ideation was defined as a score of at least 2 on item 3 of the mHAMD scale (HAMD-3); treatment-emergent suicidal ideation was defined only if the HAMD-3 score was less than 2 at both screening and baseline. A 10-week analysis reported that 14.3% (59 of 414) of subjects had treatment-emergent or worsening of suicidality; 79.7% (47 of 59) reported so by the fourth week. Patients experiencing treatment-emergent suicidality were also less likely to respond or remit to treatment than those who didn't (responders: 56% (33 of 59) vs. 75% (266 of 355) (p less than 0.004) and remitters: 41% (24 of 59) vs. 63% (225 of 355) (p=0.001), respectively). Female gender was more prevalent among the emergent group (80% vs. 65%, emergent vs. non-emergent, p=0.04) as was younger patient age (p=0.04). Emergence of suicidality was also associated with the emergence of activation (adjusted hazard ratio of 2.31 (95% CI, 1.21 to 4.43, p=0.011)) and worsening of mood (adjusted hazard ratio was 1.54 (95% CI, 1.37 to 1.72, p less than 0.001)) (Perlis et al, 2007).

c) A retrospective review of 6 cases of patients with refractory or chronic depression reported the development of intense, violent suicidal preoccupation after 2 to 7 weeks of therapy with fluoxetine. Four of the 6 patients had complicated psychiatric histories and were receiving multiple psychotropic medications at the time symptoms were experienced (Teicher et al, 1990). A review of these reports suggests that these patients were previously at risk for suicide and that none of these patients was demonstrating a therapeutic antidepressant response to fluoxetine.

d) Fluoxetine use was not found to increase the risk of suicidal behavior in patients with anxiety disorders. In a longitudinal study of 654 patients, there was a lower probability of suicidal gestures in patients with both anxiety and depressive disorders who received fluoxetine than those patients who did not receive the drug. This study further supports the concept that preexisting risk factors for suicidal behavior are the strongest determinant of suicidal acts, rather than use of a particular medication (Warshaw & Keller, 1996).

e) In a review of pooled data from clinical trials, fluoxetine was not associated with an increased risk of suicidal acts or emergence of suicidal thoughts in patients who were depressed or suffered from obsessive-compulsive disorder (Beasley et al, 1992a; Beasley et al, 1991). The incidence of suicidal

acts and suicidal ideation in fluoxetine-treated patients were compared to those patients treated with either tricyclic antidepressant agents or placebo. Suicidal ideation occurred marginally significantly less often with fluoxetine than with placebo and numerically less often than with tricyclic antidepressants (Beasley et al, 1991).
f) One trial studied 1017 patients receiving treatment for depression. Two hundred and thirty-one of those were treated with fluoxetine alone, and when compared with patients treated with other regimens, no significant increase in suicidal episodes was found. Association between fluoxetine and suicide is disputed (Hoover, 1991; Fava & Rosenbaum, 1991).
g) One paper reported 2 patients without previous history of suicidal ideation, gestures, mania, or hypomania who developed suicidal ideations beginning 3 days to 2 weeks following initiation of fluoxetine therapy for depression. Suicidal ideations disappeared within a week of discontinuing treatment in both patients (Masand et al, 1991).
h) One paper reported 3 cases in which the patient's suicidal thoughts while on fluoxetine seemed to stem directly from problems with akathisia. Cessation of fluoxetine treatment was associated with elimination of both akathisia and suicidal thoughts (Rothschild & Locke, 1991).

3.3.13 Renal Effects

3.3.13.A Fluoxetine Hydrochloride

3.3.13.A.1 Urogenital finding
a) Sexual dysfunction, abortion, albuminuria, amenorrhea, cystitis, dysuria, impotence, leukorrhea, menorrhagia, nocturia, ovarian disorder, priapism, impaired urination, polyuria, urethritis, urinary incontinence, urinary urgency, and vaginitis have been reported with fluoxetine therapy (Prod Info Prozac(R), 2003c).

3.3.14 Reproductive Effects

Fluoxetine

Fluoxetine Hydrochloride

3.3.14.A Fluoxetine

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 Fluoxetine Hydrochloride

Fibrocystic disease of breast

Sexual dysfunction

3.3.14.B.1 Fibrocystic disease of breast
a) Exacerbation of fibrocystic breast disease occurred in a woman following 6 months of therapy with fluoxetine 20 mg/day. The patient experienced increased breast pain, discomfort, and enlargement of palpable cysts; her symptoms stabilized after fluoxetine was discontinued (McKenzie & Risch, 1995).

3.3.14.B.2 Sexual dysfunction
a) Summary
1) Both anorgasmia and delayed orgasm have been reported in both males and females receiving fluoxetine (Prod Info Prozac(R), 2003c; Herman et al, 1990; Kline, 1989; Fontaine & Chouinard, 1989). Paradoxically, there is at least one case report of a woman experiencing multiple orgasms and repeated yawning (Modell, 1989), as well as improvement of sexual response in a few cases of elderly men (Power-Smith, 1994; Smith & Levitte, 1993). Administration of oral cyproheptadine 4 mg or granisetron 1 mg about 1 hour before sexual intercourse increased sexual interest and increased the ability to achieve orgasm in 2 women (Nelson et al, 1997; Ellison, 1996). Sexual dysfunction may be more common with fluoxetine than with other antidepressants. In one small open study, 36% of patients reported some sexual dysfunction, which disappeared when the dose of fluoxetine was lowered (Benazzi & Mazzoli, 1994). Other accounts range from 7.8% to 75% (Balon, 1995; Silverglat, 1995; Hopkins, 1995; Hollander, 1995). It is not clear whether or not this

sexual dysfunction is reversible; in one study, fluoxetine was the only SSRI for which improvement of sexual functioning did not result after brief cessation of administration (Rothschild, 1995).

b) Induction of sexual dysfunction may be a positive effect in some persons, such as men with premature ejaculation. One open clinical trial found significant improvement of premature ejaculation with fluoxetine doses up to 60 mg/day (Lee et al, 1996). Positive results were also obtained in a double-blind placebo controlled study on 17 patients (Kara et al, 1996).

c) A 50-year-old woman reported difficulty achieving orgasm during sexual intercourse and unintended exercise-induced orgasms after her fluoxetine dosage was increased to 20 mg daily. Oral cyproheptadine 4 mg before sexual intercourse partially alleviated anorgasmia. Treatment with fluoxetine for several months resolved depressive symptoms; fluoxetine was tapered and stopped. Her sexual function returned to baseline. The exact mechanism by which fluoxetine causes sexual dysfunction is unknown (Ellison, 1996).

d) In 3 case reports of elderly men (Smith & Levitte, 1993) return of normal erections and sexual potency occurred with fluoxetine therapy. Improvement in sexual functioning was reported in 2 elderly men that ceased after drug discontinuance, but returned in both cases after reinstitution of therapy (Power-Smith, 1994).

e) Sexual dysfunction was reported in 5 of 60 patients treated on an outpatient basis with fluoxetine. Three of the patients (all male) experienced delayed orgasm while taking 20 mg/day of fluoxetine; 2 of the patients (both female) suffered anorgasmia. One of the women experienced anorgasmia on the initial regimen of 20 mg/day; the other woman experienced anorgasmia after the dosage had been titrated to 80 mg/day over 3 weeks. Interestingly, all of the men, but neither of the women, had a history of sexual dysfunction associated with previous antidepressant therapy. One patient (male) found the dysfunction to resolve despite continued fluoxetine therapy. The authors state that the 8% rate of sexual dysfunction associated with fluoxetine in this series of observations is similar to the 5% rate reported by others (Stark & Hardison, 1985a). The authors note that sexual dysfunction is likely to be more common than reported, due to embarrassment on the part of patients and lack of active questioning by clinicians. Proposed treatment strategies include lowering the fluoxetine dose, if possible, or adding the serotonin antagonist cyproheptadine, although these have not been tested (Herman et al, 1990).

f) The repeated occurrence of yawning (without drowsiness) and multiple orgasms (associated with clitoral engorgement) were reported in a 30-year-old woman with depression treated with fluoxetine. The patient was given doses of 20 mg orally once daily in the morning for 7 days, followed by an increase in dose to 40 mg every morning. Symptoms developed within 2 days following the dosage increase and subsided following dose reductions to 20 mg daily. The patient was rechallenged with successively increasing doses of fluoxetine, resulting in recurrence of symptoms on several occasions and abatement of symptoms after withdrawal of the drug. It is suggested that acute increases in serotonergic neuronal activity may have caused the adverse effects observed in this patient (Modell, 1989).

g) In an open trial of fluoxetine in patients with obsessive-compulsive disorder, 2 of 28 male patients reported inhibited ejaculation. The doses of fluoxetine taken by the subjects were not reported; for the study sample, the mean daily dose was 78 mg (undivided) (Fontaine & Chouinard, 1989).

3.3.15 Respiratory Effects

3.3.15.A Fluoxetine Hydrochloride

3.3.15.A.1 Respiratory finding

a) Both rhinitis (23%) and pharyngitis (10%) have been reported to occur at a greater rate with fluoxetine therapy than placebo (17% and 6%, respectively). A 62-year-old woman developed cough and dyspnea 4 months after beginning fluoxetine. Symptoms resolved when fluoxetine was discontinued and recurred within 5 days when it was restarted. She developed interstitial infiltrates and restrictive lung disease and bronchioalveolar lavage was suggestive of hypersensitivity pneumonitis (Gonzalez-Rothi et al, 1995).

3.3.16 Other

Fluoxetine

Fluoxetine Hydrochloride

3.3.16.A Fluoxetine

3.3.16.A.1 Drug withdrawal

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

3.3.16.B Fluoxetine Hydrochloride

Drug withdrawal

Fever

Serotonin syndrome

Serotonin syndrome, and concurrent syndrome of inappropriate vasopressin secretion

3.3.16.B.1 Drug withdrawal

a) A discontinuation syndrome of dizziness, light-headedness, insomnia, fatigue, anxiety, agitation, nausea, headache, and sensory disturbances has been described after abrupt discontinuation of fluoxetine therapy (Zajecka et al, 1997).

b) In 395 subjects completing 12 weeks of maintenance treatment of depression with fluoxetine 20 mg/day, abrupt discontinuation of fluoxetine was not associated with symptoms of a discontinuation syndrome over 6 weeks of follow-up. Subjects with depression and a Hamilton Rating Scale for Depression (HAM-D) score of greater than or equal to 16 (mean, 20.9 +/- 3.6) received fluoxetine 20 mg/day for 12 weeks. After acute treatment with fluoxetine, responding subjects were abruptly randomized to placebo (n=96) or fluoxetine 20 mg/day (n=299) and were followed for adverse events for 6 weeks. One week prior to randomization to placebo or fluoxetine, reports of new or worsened adverse events were similar in both groups. No significant difference between treatment groups in the number of patients reporting adverse events at baseline, at any reporting interval after randomization, or over the 6-week observation period was observed. With the exceptions of dizziness, somnolence, rhinitis, and dysmenorrhea, which occurred significantly more often in placebo patients at different time points during the follow-up period, the profile of new adverse events reported was similar for both treatment groups (Zajecka et al, 1998).

3.3.16.B.2 Fever

a) Pyrexia has infrequently been associated with fluoxetine use (Prod Info Prozac(R), 2003c).

3.3.16.B.3 Serotonin syndrome

a) Serotonin syndrome, including life-threatening cases, or neuroleptic malignant syndrome (NMS)-like reactions have been reported with the use of fluoxetine 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 PROZAC(R) delayed-release capsules, oral capsules, solution, 2009).

b) A 36-year-old woman developed serotonin syndrome on 4 separate occasions; 2 were attributable to fluoxetine treatment and 2 to citalopram treatment. Fluoxetine was first prescribed when she reported anxiety and insomnia precipitated by a stalker. She routinely took guaifenesin/pseudoephedrine for nasal allergies. Approximately 1 month after starting fluoxetine 20 mg/day, she collapsed. She had earlier had a few mixed drinks. She became flaccid in all extremities and unresponsive to verbal commands and painful stimuli. This was followed by apnea, requiring ventilation for 1 hour before recovery of spontaneous respiration. She recovered from coma in another hour and was immediately alert and could move all muscles normally. She had diffuse muscle aches afterward. A week later, she resumed fluoxetine treatment, while avoiding alcohol. About 2 weeks later, she was found unresponsive and became apneic, again requiring ventilation, this time for about 2 hours. No diagnostic tests showed any abnormalities. She was diagnosed with serotonin syndrome. She recovered completely the next day. Afterward, she had severe diffuse muscle pain, weakness, and tremors, which were alleviated by magnesium and vitamin B6 supplements over a 2-month period. Nearly 2 years later, after reporting trembling, a shaky feeling, easy fatigability, palpitations, sweating, exaggerated startle response, and insomnia, she was given alprazolam 0.25 mg if needed in the morning and zaleplon 10 mg if needed for sleep at night. Citalopram 10 mg/day was later added, with no change in the alprazolam and zaleplon dosages. Three days after starting citalopram, she had another attack of serotonin syndrome, which she anticipated when she developed tremulousness and palpitations. Her neurologic response was the same as it had been previously, except that she did not develop apnea. The coma lasted 3 hours. The psychiatrist chose not to discontinue citalopram but reduced the dose to 5 mg/day. Three days later, she had another episode. The coma lasted for 1.5 hours. Citalopram was discontinued and she had no recurrence of symptoms of serotonin syndrome (Chechani, 2002).

c) A 37-year-old male taking fluoxetine 20 mg/day developed confusion, diaphoresis, incoordination, diarrhea, and myoclonus after buspirone was added to his drug regimen (Manos, 2000).
d) A 50-year-old man developed serotonin syndrome several days after beginning nefazodone treatment for major depression. Rather than first tapering his standing treatment of fluoxetine over 4 days before starting nefazodone, he reduced the fluoxetine dose from 60 to 40 mg/day for 2 days and thereafter concurrently took fluoxetine and nefazodone 200 mg/day. He was hospitalized on day 6 with symptoms of serotonin syndrome. Although his condition worsened immediately after the discontinuation of the 2 antidepressants, he recovered completely by day 4 (Smith & Wenegrat, 2000).
e) The serotonin syndrome manifested by mental status changes, sweating, diarrhea, and slurred speech developed in a 39-year-old woman and was possibly attributed to use of several drugs (ie, fluoxetine, venlafaxine, clonazepam, trazodone, cimetidine) concurrently or in close proximity. This patient initially received fluoxetine, trazodone, clonazepam, and cimetidine; her psychiatric diagnoses included major depression and panic attacks. Due to continued symptoms, fluoxetine and clonazepam were abruptly stopped, and venlafaxine and lorazepam were started. Within 1 day, symptoms consistent with the serotonin syndrome developed but she delayed contacting her physician for 4 days. All medications except cimetidine were stopped with worsening symptoms over 2 days. On day 3, she restarted fluoxetine, trazodone, and clorazepate with resolution of symptoms over the next 3 days. This case is complicated by use of several drugs in close proximity with the potential for numerous drug interactions, pharmacodynamic interactions, and disease interference. Cimetidine and fluoxetine inhibit several cytochrome P450 enzymes which may have resulted in elevated concentrations of venlafaxine and the metabolite of trazodone. Noradrenergic effects of venlafaxine may have exacerbated panic disorder. Additionally, several drugs increased serotonergic activity. This case illustrates the importance of recognizing additive pharmacodynamic effects of drugs and potential drugs when prescribing several different drugs (Bhatara et al, 1998).

3.3.16.B.4 Serotonin syndrome, and concurrent syndrome of inappropriate vasopressin secretion
a) A 56-year-old man, with a history of intracerebral hemorrhagic stroke and depression, developed SIADH and serotonin syndrome concurrently following the addition of fluoxetine to his existing antidepressant regimen (olanzapine 2.5 mg/day and buspirone 10 mg twice daily). Four weeks following the initiation of fluoxetine 40 mg/day and one week following an increase in the dosage to 60 mg/day, the man presented with symptoms of SIADH (ie, serum osmolality of 240 milliosmoles (mOsm)/kg, low BUN, low sodium, normal serum glucose) and serotonin syndrome (ie, dilated pupils, restlessness, change in mental status, facial flushing, myoclonus, hyperreflexia, increased blood pressure, tachycardia). Following water restriction (1000 mL/day), an infusion of lorazepam (0.07 mg/kg/hr for 24 hours then tapered over 48 hours) and discontinuation of buspirone, olanzapine, and fluoxetine, the man's symptoms resolved over several days. Buspirone and olanzapine were reinitiated at the previous doses with no recurrence of adverse effects and fluoxetine was eliminated from his therapeutic drug regimen. A probable relationship between the use of fluoxetine and the development of the concurrent syndromes was indicated through the use of the Naranjo probability scale. The authors speculate that patients with a history of stroke may be more susceptible to severe adverse effects that may result from combination antidepressant therapy; however, additional studies are required to clarify any association between this patient group an increased incidence or severity of antidepressant-related adverse events (Bogdanovic et al, 2005).

3.4 Teratogenicity/Effects in Pregnancy/Breastfeeding
A) Teratogenicity/Effects in Pregnancy
1) U.S. Food and Drug Administration's Pregnancy Category: Category C (Prod Info PROZAC(R) oral capsules, delayed-release capsules, solution, 2008) (All Trimesters)
a) Either studies in animals have revealed adverse effects on the fetus (teratogenic or embryocidal or other) and there are no controlled studies in women or studies in women and animals are not available. Drugs should be given only if the potential benefit justifies the potential risk to the fetus.
2) Australian Drug Evaluation Committee's (ADEC) Category: C(Batagol, 1999)
a) Drugs which, owing to their pharmacological effects, have caused or may be suspected of causing harmful effects on the human fetus or neonate without causing malformations. These effects may be reversible. Accompanying texts should be consulted for further details.
See Drug Consult reference: PREGNANCY RISK CATEGORIES
3) Crosses Placenta: Yes
4) Clinical Management
a) A large, population-based study found no increased risk of malformations in infants exposed to selective serotonin reuptake inhibitors (SSRI) , but the exposed infants were more likely to require treatment in a special or intensive care unit (Malm et al, 2005). The use of an SSRI, including fluoxetine, 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). 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). Neonates exposed to fluoxetine and other SSRI and selective serotonin and norepinephrine reuptake inhibitors (SNRI), late in the third trimester have developed signs and

symptoms of SSRI and SNRI toxicity or withdrawal syndrome (Prod Info PROZAC(R) oral capsules, delayed-release capsules, solution, 2008). However, the dangers of failing to treat major depression are obvious, and in each case, these dangers must be weighed against the potential for teratogenic effects (Nulman et al, 1997; Lamberg, 1999). In pregnant patients diagnosed with obsessive compulsive disorder, fluoxetine is recommended when behavioral therapy has proven inadequate (Anon, 2000; Altshuler et al, 1996).

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) In a prospective longitudinal study (n=201), discontinuation of antidepressant medication in women with a history of major depression and who were euthymic at the start of pregnancy increased the chance for relapse of major depression compared to women who continued antidepressant medication. However, neonatal exposure, particularly in the third trimester, to fluoxetine and other selective serotonin reuptake inhibitors (SSRIs) or serotonin and norepinephrine reuptake inhibitors (SNRIs) has led to complications requiring prolonged hospitalization, respiratory support, and tube feeding. Clinical findings have included cyanosis, apnea, seizures, tremor, and constant crying, and the clinical scenario is reflective of serotonin syndrome. Therefore, a careful assessments of potential risks and benefits of treatment must be conducted prior to using fluoxetine during pregnancy, particularly in the third trimester (Prod Info PROZAC(R) oral capsules, delayed-release capsules, solution, 2008).

d) A case-control study found that the use of selective serotonin reuptake inhibitors (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 2.2-16.8; 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).

e) A population-based study of 1782 pregnant women exposed to selective serotonin reuptake inhibitors (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 six 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 525 women purchasing fluoxetine during the first trimester, 232 during the second trimester, 239 during the third, and 65 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).

f) In a prospective clinical trial designed to evaluate the pharmacokinetics of fluoxetine and norfluoxetine during pregnancy, delivery, and lactation, pregnancy outcomes were found to be similar in both the control

and treated groups. The study compared results from 11 women taking fluoxetine 20 to 50 mg per day during pregnancy and lactation to 10 women in the control group who were not exposed to psychotropic medications. Due to increased hepatic blood flow, increased volume of distribution and decreased binding to plasma proteins, trough plasma concentrations of fluoxetine and norfluoxetine were low. At delivery, umbilical vein concentrations were 65% and 72% of the maternal concentrations, respectively. During the early postnatal period, plasma concentrations of fluoxetine and norfluoxetine were still elevated, likely due to the slow development of infant glucuronidation capacity and CYP2D6 enzyme activity. There were no fetal malformations or difference in birth weights between the two groups. However, Apgar scores at fifteen minutes were lower in the fluoxetine group (Heikkinen et al, 2003).

g) In one study assessing the direct effects of fluoxetine on infant outcome at birth (Chambers et al, 1996), the authors concluded that neonates exposed to fluoxetine in the third trimester may be at an increased risk for perinatal complications such as respiratory difficulty, cyanosis on feeding, and jitteriness. These neonates may have had difficulty clearing the drug due to its long half-life. Depending on the woman's clinical situation, the practitioner and patient may consider tapering the dose of fluoxetine to discontinue 10 to 14 days prior to delivery to minimize the fetal load at birth (Wisner et al, 1999).

h) Based on analyses of independently collected data and that obtained through the Motherisk Program, there appear to be no differences in cognitive function, temperament and general behavior in children exposed prenatally to fluoxetine as compared to controls (Nulman et al, 2002; Wisner et al, 1999; Nulman & Koren, 1996; Nulman et al, 1997). However, among infants who were exposed to either fluoxetine or tricyclic antidepressants throughout gestation, those born to mothers with uncontrolled depressive symptoms showed lower cognitive and language achievements than those born to mothers who were well-controlled (Nulman et al, 2002).

i) An increased risk for central nervous system serotonergic symptoms was observed during the first four days of life in infants of mothers taking selective serotonin reuptake inhibitors (SSRI) during the third trimester of pregnancy. In a controlled, prospective study, women taking 20 to 40 milligrams/day of either citalopram (n=10) or fluoxetine (n=10) while pregnant were compared to a control group (n=20). Exposure to SSRI therapy ranged from 7 to 41 weeks. Newborns in the SSRI group had a lower Apgar score at 15 minutes as compared with the control group (8.8 vs 9.4; p=0.02). The only significant difference observed in the vital signs of the newborns was a higher heart rate in the SSRI group at two weeks as compared with the controls (mean, 153 vs 141 beats per minute; p=0.049). Serotonergic symptom scores in the first 4 days after birth were significantly higher in the SSRI group than in the control group (total score, 121 vs 30, respectively; p=0.008). Tremor, restlessness, and rigidity were the most prominent symptoms. Myoclonus was reported in one infant exposed to fluoxetine. Significantly lower cord blood 5-hydroxyindoleacetic acid (5-HIAA) concentrations were seen in the SSRI-exposed infants as compared with the control group (mean, 63 mmol/L vs 77 mmol/L; p=0.02). Additionally, a significant inverse correlation was observed between the serotonergic symptom score and the umbilical vein 5-HIAA concentrations in the SSRI-exposed newborns, but not in the control group (p=0.007). Although not statistically significant, mean umbilical cord serum prolactin concentrations were 29% lower in SSRI- exposed infants than in control infants at the time of birth (Laine et al, 2003).

B) Breastfeeding

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

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

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

3) Clinical Management

a) Fluoxetine and its active metabolite, norfluoxetine, appear in breast milk and the oral dose available to the infant has been estimated at 15 to 20 mcg/kg/day for fluoxetine (Burch & Wells, 1992), and 40 mcg/kg/day for fluoxetine plus norfluoxetine (Taddio et al, 1996). Despite the manufacturer's recommendation that fluoxetine not be used by women while breastfeeding (Prod Info PROZAC(R) oral capsules, delayed-release capsules, solution, 2008), many women choose to do so. The American Academy of Pediatrics considers antidepressants to be drugs worthy of concern in the nursing infant (Anon, 2001). There is insufficient data available to safely recommend use of fluoxetine by nursing mothers. If the decision is made to use fluoxetine, the infant should be monitored for anorexia, weight loss, irritability, and insomnia. The long-term effects of exposure to selective serotonin reuptake inhibitors (SSRIs) via breast milk on the cognitive development of the infant have not been determined.

4) Literature Reports

a) A number of cases have been reported in which fluoxetine was used to treat postpartum depression in nursing mothers. No effect on milk production or composition was observed. While increased infant irritability during maternal fluoxetine treatment has been described, all infants developed normally after exposure to fluoxetine during nursing (Epperson et al, 2003; Burch & Wells, 1992; Isenberg, 1990).

b) In a study of 14 mother-infant pairs, the mean total infant exposure was estimated as 6.81% (3.36% for fluoxetine and 3.45% for norfluoxetine). Of the 9 infants with blood samples, 5 and 7 had detectable concentrations of fluoxetine and norfluoxetine, respectively. Two infants had colic, while 2 others had withdrawal symptoms described as uncontrollable crying, irritability, and poor feeding. Symptoms in the latter infants were consistent with high plasma concentrations of fluoxetine and/or norfluoxetine. One mother also used methadone, and 4 infants were exposed to fluoxetine in utero. The authors recommend caution

especially during the early neonatal period and in infants exposed in utero to fluoxetine (Kristensen et al, 1999).
c) A 1996 cohort study involved 11 infants nursed by 10 mothers. Although limited by maternal perception, no adverse effects in the breastfeeding infants were reported by the mothers (Taddio et al, 1996).
d) One study described 4 nursing mothers, taking 20 to 40 mg of fluoxetine per day, in which the Bayley Scales were used to assess the neurological development of the infants. None of the infants exhibited any neurological abnormality (Taddio et al, 1996).
e) The manufacturer reports a maternal plasma concentration of 295 nanograms/mL for fluoxetine plus norfluoxetine, with a corresponding breast milk concentration of 70.4 nanograms/mL. No adverse effects in the nursing infant were reported. In another case, a nursing infant's plasma drug levels were 340 nanograms/mL of fluoxetine and 208 nanograms/mL of norfluoxetine on the second day of breastfeeding. The mother's daily dose of fluoxetine was not reported. The infant developed crying, sleep disturbance, vomiting, and watery stools (Prod Info PROZAC(R) oral capsules, delayed-release capsules, solution, 2008).
f) No clinically significant changes in platelet 5-hydroxytryptamine (5-HT) transport were reported in 11 infants (mean age of 16.8 weeks at the start of the study) exposed to fluoxetine through maternal breast milk. Determinations of whole-blood 5-HT, fluoxetine, and norfluoxetine levels were made in both infants and mothers prior to initiating fluoxetine doses of 20 mg to 40 mg per day. Post-exposure levels were measured at 4 to 12 weeks later. Mean maternal plasma concentrations of fluoxetine were 125 nanograms/mL, and norfluoxetine were 142 nanograms/mL. All but one infant had plasma fluoxetine levels below 1 nanograms/mL, and the mean infant plasma concentration of norfluoxetine was 3.2 nanograms/mL. Mean maternal pre- and post-fluoxetine 5-HT levels were 157 nanograms/mL and 23 nanograms/mL, respectively. The mean infant pre- and postexposure 5-HT concentrations were 217 nanograms/mL and 230 nanograms/mL, respectively. Baley Scale scores were determined for 7 of the infants (age range 24 to 56 weeks), revealing that 6 infants were within one standard deviation of the mean on mental and motor developmental indices. The investigators concluded that most exclusively breastfed infants will not likely experience changes in platelet 5-HT levels upon maternal fluoxetine use (Epperson et al, 2003).

5) Drug Levels in Breastmilk
- **a)** Parent Drug
  - **1)** Milk to Maternal Plasma Ratio
    - **a)** 0.21-1.51 (Isenberg, 1990; Taddio & Ito, 1996)
- **b)** Active Metabolites
  - **1)** NORFLUOXETINE (Pons & Rey, 1994)

3.5 Drug Interactions

3.5.1 Drug-Drug Combinations

Abciximab

Acecainide

Aceclofenac

Acemetacin

Acenocoumarol

Ajmaline

Alclofenac

Almotriptan

Alprazolam

Amiodarone

Amisulpride

Amitriptyline

Amoxapine

Anagrelide

Ancrod

Anisindione

Antithrombin III Human

Aprindine

Ardeparin

Aripiprazole

Arsenic Trioxide

Aspirin

Astemizole

Atomoxetine

Azimilide

Benoxaprofen

Bepridil

Bivalirudin

Bretylium

Bromfenac

Bufexamac

Bupropion

Buspirone

Cannabis

Carbamazepine

Carprofen

Celecoxib

Certoparin

Chloral Hydrate

Chloroquine

Chlorpromazine

Cilostazol

Clarithromycin

Clonixin

Clopidogrel

Clopidogrel

Clorgyline

Clozapine

Cyclobenzaprine

Cyproheptadine

Dalteparin

Danaparoid

Defibrotide

Dehydroepiandrosterone

Delavirdine

Dermatan Sulfate

Desipramine

Desirudin

Desvenlafaxine

Dexfenfluramine

Dexketoprofen

Dextromethorphan

Diazepam

Dibenzepin

Diclofenac

Dicumarol

Diflunisal

Digitoxin

Digoxin

Dihydroergotamine

Dipyridamole

Dipyrone

Disopyramide

Dofetilide

Dolasetron

Doxepin

Droperidol

Droxicam

Duloxetine

Eletriptan

Enflurane

Enoxaparin

Epoprostenol

Eptifibatide

Ergoloid Mesylates

Ergonovine

Ergotamine

Erythromycin

Etodolac

Etofenamate

Etoricoxib

Felbinac

Fenbufen

Fenfluramine

Fenoprofen

Fentiazac

Flecainide

Floctafenine

Fluconazole

Flufenamic Acid

Fluphenazine

Flurbiprofen

Fondaparinux

Foscarnet

Fosphenytoin

Frovatriptan

Furazolidone

Galantamine

Gemifloxacin

Ginkgo

Halofantrine

Haloperidol

Halothane

Heparin

Hydroquinidine

Hydroxytryptophan

Ibuprofen

Ibutilide

Iloperidone

Iloprost

Imipramine

Indomethacin

Indoprofen

Insulin Aspart, Recombinant

Insulin Detemir

Insulin Glargine, Recombinant

Insulin Glulisine

Insulin Human Inhaled

Iproniazid

Isocarboxazid

Isoflurane

Isoxicam

Isradipine

Ketoprofen

Ketorolac

Lamifiban

Levomethadyl

Lexipafant

Lidoflazine

Linezolid

Lithium

Lorcainide

Lornoxicam

Meclofenamate

Mefenamic Acid

Mefloquine

Meloxicam

Meperidine

Mesoridazine

Methylergonovine

Methylphenidate

Methysergide

Metoprolol

Milnacipran

Mirtazapine

Moclobemide

Morniflumate

Nabumetone

Nadroparin

Naproxen

Naratriptan

Nebivolol

Nialamide

Niflumic Acid

Nimesulide

Nortriptyline

Octreotide

Oxaprozin

Parecoxib

Pargyline

Parnaparin

Paroxetine

Pentamidine

Pentazocine

Pentosan Polysulfate Sodium

Phenelzine

Phenindione

Phenprocoumon

Phenylbutazone

Phenytoin

Pimozide

Pirazolac

Pirmenol

Piroxicam

Pirprofen

Prajmaline

Probucol

Procainamide

Procarbazine

Prochlorperazine

Propafenone

Propranolol

Propyphenazone

Proquazone

Quetiapine

Quinidine

Rasagiline

Reviparin

Risperidone

Ritonavir

Rizatriptan

Rofecoxib

Selegiline

Sematilide

Sertindole

Sibrafiban

Sibutramine

Sotalol

Spiramycin

St John's Wort

Sulfamethoxazole

Sulfinpyrazone

Sulindac

Sulodexide

Sultopride

Sumatriptan

Suprofen

Tamoxifen

Tamsulosin

Tapentadol

Tedisamil

Telithromycin

Tenidap

Tenoxicam

Terfenadine

Tetrabenazine

Thioridazine

Tiaprofenic Acid

Ticlopidine

Tinzaparin

Tipranavir

Tirofiban

Tolmetin

Toloxatone

Tramadol

Tranylcypromine

Trazodone

Trifluoperazine

Trimethoprim

Trimipramine

Tryptophan

Valdecoxib

Vasopressin

Venlafaxine

Warfarin

Xemilofiban

Ziprasidone

Zolmitriptan

Zolpidem

Zomepirac

Zotepine

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 Acecainide

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Even though no formal drug interaction studies have been done, the coadministration of Class III antiarrhythmics and other drugs known to prolong the QTc interval is not recommended (Allen et al, 2002; Prod Info Tikosyn(TM) dofetilide capsules, 1999; Prod Info Corvert(R), 1998). Fluoxetine has been shown to prolong the QTc interval at the recommended therapeutic dose (Prod Info Prozac(R), 2001a).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of class III antiarrhythmic agents and agents that prolong the QT interval, such as fluoxetine, is not recommended.
7) Probable Mechanism: additive effects on QT prolongation

3.5.1.C 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.D 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.E 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 PROZAC(R) oral capsules, delayed-release capsules, solution, 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 (Prod Info PROZAC(R) oral capsules, delayed-release capsules, solution, 2008).
3) Severity: major
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: When fluoxetine and an anticoagulant are given concurrently, monitor patient for signs of increased bleeding. Patients who are taking warfarin should be monitored closely for altered anticoagulant effects, including increased bleeding, when fluoxetine therapy is initiated or discontinued (Prod Info PROZAC(R) oral capsules, delayed-release capsules, solution, 2008).
7) Probable Mechanism: unknown

8) Literature Reports

a) Fluoxetine is thought to inhibit the cytochrome P450 2C9 isoenzyme (CYP2C9). This is the enzyme by which the more potent warfarin isomer, S-warfarin, is metabolized (Riesenman, 1995). In addition, both fluoxetine and warfarin are tightly bound to albumin. In combination, the possibility for protein-binding displacement of either drug is present (Prod Info Coumadin(R), 1999).

b) 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).

c) 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).

d) In 6 reported cases, INR increased during combined fluoxetine and warfarin therapy. In a seventh case, severe bruising of the lower legs occurred in a woman initially treated with fluoxetine and, secondarily, started on warfarin (Woolfrey et al, 1993; Claire et al, 1991).

e) An 83-year-old man died from cerebral hemorrhage secondary to increased warfarin concentrations. The patient had been taking warfarin 30 mg per week for atrial fibrillation with a target INR between 2 and 3. The patient's other drugs included lisinopril, furosemide, potassium, digoxin, and acetaminophen. After being seen for symptoms of depression, anxiety, and insomnia, the patient was given fluoxetine 20 mg per day and diazepam 2.5 mg 3 to 4 times per day. Eight days later, the patient's INR increased to 4.8, and the dose of warfarin was decreased to 27.5 mg per week. The patient was later seen for symptoms of drug delirium, including confusion, incoherence, and speaking irrationally. At this point, the INR was 3.64 and fluoxetine was discontinued. The next day the patient presented to the hospital with left-sided weakness and later died from complications of a large interparenchymal hemorrhage. The authors proposed that the addition of fluoxetine to the patient's regimen resulted in increased serum levels of both warfarin and diazepam, resulting in delirium and loss of anticoagulant control (Dent & Orrock, 1997).

3.5.1.F Ajmaline

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)

2) Summary: Even though no formal drug interaction studies have been done, the coadministration of Class Ia antiarrhythmics and other drugs known to prolong the QTc interval is not recommended (Prod Info Quinaglute Dura-tabs(R), 1999). Fluoxetine has demonstrated QT prolongation at therapeutic doses (Prod Info Prozac(R), 2001z).

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: The concurrent administration of class Ia antiarrhythmic agents and agents that prolong the QT interval, such as fluoxetine, is not recommended.

7) Probable Mechanism: additive effects on QT prolongation

3.5.1.G 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.H 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.I Alprazolam

1) Interaction Effect: an increased risk of alprazolam toxicity (somnolence, dizziness, ataxia, slurred speech, hypotension, psychomotor impairment)
2) Summary: Coadministered fluoxetine increases alprazolam serum concentrations (Greenblatt et al, 1992a; Lasher et al, 1991a). The mechanism of this interaction is thought to be inhibition by fluoxetine of the cytochrome P453A4 isoenzyme (CYP3A4), which is principally responsible for alprazolam metabolism. Some benzodiazepines (lorazepam, oxazepam) are metabolized by glucuronidation rather than by the P450 system and may be the better choice for fluoxetine and benzodiazepine cotherapy.
3) Severity: moderate
4) Onset: rapid
5) Substantiation: probable
6) Clinical Management: Monitor patients for signs and symptoms of alprazolam intoxication (somnolence, dizziness, ataxia, slurred speech, hypotension, psychomotor impairment). Alprazolam doses may need to be reduced. Alternatively, consider substituting a benzodiazepine (such as lorazepam or oxazepam) that has

less potential for interacting with fluoxetine.
7) Probable Mechanism: inhibition of cytochrome P450 3A-mediated alprazolam metabolism
8) Literature Reports
a) Alprazolam serum concentrations were analyzed in a double-blind, placebo-controlled study involving 80 healthy male volunteers (Lasher et al, 1991). Concurrent administration of alprazolam 1 mg four times a day and fluoxetine 60 mg each morning for four days resulted in a 30% increase in plasma alprazolam levels and a 21% decrease in the alprazolam elimination rate. The elevated alprazolam concentrations caused increased psychomotor impairment, but did not affect mood status or sedation.
b) The effect of fluoxetine on the pharmacokinetics of alprazolam was analyzed in a 31-day, double-blind, crossover, placebo-controlled study, which included a 10-day washout period (Greenblatt et al, 1992). Twelve healthy male volunteers were given fluoxetine 20 mg twice a day or placebo and a single dose of alprazolam 1 mg on days 3 and 24. Fluoxetine significantly increased the half-life of alprazolam from 17 hours to 20 hours and significantly decreased its clearance from 61 mL/min to 48 mL/min.
c) Inhibition of alprazolam metabolism by fluoxetine occurs via cytochrome P450 3A4. A randomized, double-blind, placebo-controlled with-in subject design was used to assess this potential interaction. Twenty healthy volunteers attended four study sessions: alprazolam/placebo was given in the absence of an SSRI in the first two study sessions; alprazolam/placebo while at steady-state with either citalopram 20 mg/day or fluoxetine 20 mg/day was given in the last two study sessions. At each session they received alprazolam 1 mg orally or placebo. Fluoxetine significantly prolonged the half-life of alprazolam by 16% and increased the area under the concentration-time curve by 32%. Citalopram did not affect these parameters. The effects of alprazolam were not altered by either SSRI. These findings suggest that citalopram and fluoxetine differentially alter alprazolam concentrations (Hall et al, 2002).

3.5.1.J Amiodarone
1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Even though no formal drug interaction studies have been done, the coadministration of Class III antiarrhythmics and other drugs known to prolong the QTc interval is not recommended (Allen et al, 2002; Prod Info Tikosyn(TM) dofetilide capsules, 1999; Prod Info Corvert(R), 1998). Fluoxetine has been shown to prolong the QTc interval at the recommended therapeutic dose (Prod Info Prozac(R), 2001a).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of class III antiarrhythmic agents and agents that prolong the QT interval, such as fluoxetine, is not recommended.
7) Probable Mechanism: additive effects on QT prolongation

3.5.1.K Amisulpride
1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Fluoxetine has been shown to prolong the QTc interval at the recommended therapeutic dose (Prod Info Prozac(R), 2001l). Even though no formal drug interaction studies have been done, the coadministration of antipsychotics and other drugs known to prolong the QTc interval, including fluoxetine, is not recommended. Several antipsychotic agents have demonstrated QT prolongation including amisulpride (Prod Info Solian(R), 1999), quetiapine (Owens, 2001b), sertindole (Agelink et al, 2001), sultopride (Lande et al, 1992), and zotepine (Sweetman, 2003).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of fluoxetine and antipsychotics is not recommended.
7) Probable Mechanism: additive effects on QT prolongation

3.5.1.L Amitriptyline
1) Interaction Effect: tricyclic antidepressant toxicity (dry mouth, urinary retention, sedation) and an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Tricyclic antidepressants (TCAs) and fluoxetine have been shown to prolong the QTc interval at the recommended therapeutic dose (Prod Info Prozac(R), 2001h; Marshall & Forker, 1982). Even though no formal drug interaction studies have been done which demonstrate QT prolongation, the coadministration of tricyclic antidepressants and other drugs known to prolong the QTc interval, such as fluoxetine, is not recommended (Prod Info Elavil(R), 1999). In addition, concurrent use of fluoxetine and TCAs such as desipramine, nortriptyline, and imipramine has resulted in significant increases in TCA concentrations (Preskorn et al, 1994a; Preskorn et al, 1994a; Aranow et al, 1989a; Downs et al, 1989a; Goodnick, 1989a; Bell & Cole, 1988a).
3) Severity: major
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: The concurrent administration of fluoxetine and a tricyclic antidepressant is not

recommended.
7) Probable Mechanism: decreased tricyclic antidepressant metabolism; additive effects on QT prolongation
8) Literature Reports
a) Fluoxetine increased the level of tricyclic antidepressants (nortriptyline, imipramine, desipramine) in 4 patients. After the addition of fluoxetine, the ratio of antidepressant level to dose increased by 109% to 486% in the patients. Three patients developed clinical symptoms (anticholinergic effects, constipation, urinary hesitancy, sedation, unstable gait) as a result of the increased levels (Aranow et al, 1989).
b) Fluoxetine statistically and clinically significantly increased desipramine concentrations in 18 healthy subjects. When fluoxetine (20 mg daily) was added to desipramine (50 mg daily), the mean maximum concentration of desipramine increased by 278% and the area under the concentration-time curve increased by 342%. Desipramine trough concentrations continued to be 198% above baseline three weeks after fluoxetine was discontinued. The same study compared pharmacokinetics of desipramine when combined with sertraline. The impact of sertraline was modest, resulting in small and short-term increases in desipramine plasma concentrations (Preskorn et al, 1994).
c) A 75-year-old female experienced symptomatic increases in her desipramine serum concentrations when fluoxetine was added. Desipramine serum levels ranged from 109 to 150 ng/mL with oral doses of 300 mg at bedtime prior to fluoxetine therapy. Following the addition of oral fluoxetine 20 mg daily to the regimen, the desipramine serum level increased to 212 ng/mL within five days. The fluoxetine dose was increased to 40 mg/day three days later, and the desipramine serum level was 419 ng/mL after four days. A worsening of depression and severe fatigue coincided with the increases in desipramine serum levels. Withdrawal of fluoxetine and reduction in the desipramine dose to 200 mg daily reduced the desipramine serum level to 231 ng/mL within two weeks (Bell & Cole, 1988).
d) A 33-year-old depressed male developed adverse effects of dry mouth, tinnitus, and difficulties with alertness and memory while receiving fluoxetine 40 mg daily and desipramine 150 mg daily for five weeks; fluoxetine was discontinued and the blood levels of desipramine decreased from 938 to 48 ng/mL with resolution of clinical symptoms (Goodnick, 1989).
e) A 39-year-old female experienced symptomatic increases in her desipramine levels with concomitant fluoxetine therapy. Prior to fluoxetine therapy, the patient's measured levels of desipramine had ranged from 148 to 160 ng/mL on a regimen of 300 mg daily. Five weeks after the addition of fluoxetine 20 mg daily, she reported anticholinergic symptoms, sedation, and confusion with a desipramine level of 527 ng/mL. The desipramine dose was lowered to 200 mg/day; eleven days later, the level was 244 ng/mL; the patient reported decreased energy, impaired short-term memory, and some "garbled" speech, as well as an episode of nausea, dizziness, and syncope. The desipramine dose was reduced to 50 mg/day; the adverse effects resolved in six days. Eight days later, the desipramine level was 122 ng/mL (Downs et al, 1989).
f) Concomitant administration of fluoxetine and desipramine was reported to result in an increased desipramine level and new onset of delirium in a 69-year-old male within 10 days of the addition of fluoxetine to the patient's regimen (Preskorn et al, 1990).

3.5.1.M Amoxapine
1) Interaction Effect: tricyclic antidepressant toxicity (dry mouth, urinary retention, sedation) and an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Tricyclic antidepressants (TCAs) and fluoxetine have been shown to prolong the QTc interval at the recommended therapeutic dose (Prod Info Prozac(R), 2001h; Marshall & Forker, 1982). Even though no formal drug interaction studies have been done which demonstrate QT prolongation, the coadministration of tricyclic antidepressants and other drugs known to prolong the QTc interval, such as fluoxetine, is not recommended (Prod Info Elavil(R), 1999). In addition, concurrent use of fluoxetine and TCAs such as desipramine, nortriptyline, and imipramine has resulted in significant increases in TCA concentrations (Preskorn et al, 1994a; Preskorn et al, 1994a; Aranow et al, 1989a; Downs et al, 1989a; Goodnick, 1989a; Bell & Cole, 1988a).
3) Severity: major
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: The concurrent administration of fluoxetine and a tricyclic antidepressant is not recommended.
7) Probable Mechanism: decreased tricyclic antidepressant metabolism; additive effects on QT prolongation
8) Literature Reports
a) Fluoxetine increased the level of tricyclic antidepressants (nortriptyline, imipramine, desipramine) in 4 patients. After the addition of fluoxetine, the ratio of antidepressant level to dose increased by 109% to 486% in the patients. Three patients developed clinical symptoms (anticholinergic effects, constipation, urinary hesitancy, sedation, unstable gait) as a result of the increased levels (Aranow et al, 1989).
b) Fluoxetine statistically and clinically significantly increased desipramine concentrations in 18 healthy subjects. When fluoxetine (20 mg daily) was added to desipramine (50 mg daily), the mean maximum concentration of desipramine increased by 278% and the area under the concentration-time curve increased by 342%. Desipramine trough concentrations continued to be 198% above baseline three weeks after fluoxetine was discontinued. The same study compared pharmacokinetics of desipramine

when combined with sertraline. The impact of sertraline was modest, resulting in small and short-term increases in desipramine plasma concentrations (Preskorn et al, 1994).
c) A 75-year-old female experienced symptomatic increases in her desipramine serum concentrations when fluoxetine was added. Desipramine serum levels ranged from 109 to 150 ng/mL with oral doses of 300 mg at bedtime prior to fluoxetine therapy. Following the addition of oral fluoxetine 20 mg daily to the regimen, the desipramine serum level increased to 212 ng/mL within five days. The fluoxetine dose was increased to 40 mg/day three days later, and the desipramine serum level was 419 ng/mL after four days. A worsening of depression and severe fatigue coincided with the increases in desipramine serum levels. Withdrawal of fluoxetine and reduction in the desipramine dose to 200 mg daily reduced the desipramine serum level to 231 ng/mL within two weeks (Bell & Cole, 1988).
d) A 33-year-old depressed male developed adverse effects of dry mouth, tinnitus, and difficulties with alertness and memory while receiving fluoxetine 40 mg daily and desipramine 150 mg daily for five weeks; fluoxetine was discontinued and the blood levels of desipramine decreased from 938 to 48 ng/mL with resolution of clinical symptoms (Goodnick, 1989).
e) A 39-year-old female experienced symptomatic increases in her desipramine levels with concomitant fluoxetine therapy. Prior to fluoxetine therapy, the patient's measured levels of desipramine had ranged from 148 to 160 ng/mL on a regimen of 300 mg daily. Five weeks after the addition of fluoxetine 20 mg daily, she reported anticholinergic symptoms, sedation, and confusion with a desipramine level of 527 ng/mL. The desipramine dose was lowered to 200 mg/day; eleven days later, the level was 244 ng/mL; the patient reported decreased energy, impaired short-term memory, and some "garbled" speech, as well as an episode of nausea, dizziness, and syncope. The desipramine dose was reduced to 50 mg/day; the adverse effects resolved in six days. Eight days later, the desipramine level was 122 ng/mL (Downs et al, 1989).
f) Concomitant administration of fluoxetine and desipramine was reported to result in an increased desipramine level and new onset of delirium in a 69-year-old male within 10 days of the addition of fluoxetine to the patient's regimen (Preskorn et al, 1990).

3.5.1.N 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.O 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 PROZAC(R) oral capsules, delayed-release capsules, solution, 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 (Prod Info PROZAC(R) oral capsules, delayed-release capsules, solution, 2008).
3) Severity: major
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: When fluoxetine and an anticoagulant are given concurrently, monitor patient for signs of increased bleeding. Patients who are taking warfarin should be monitored closely for altered anticoagulant effects, including increased bleeding, when fluoxetine therapy is initiated or discontinued (Prod Info PROZAC(R) oral capsules, delayed-release capsules, solution, 2008).
7) Probable Mechanism: unknown
8) Literature Reports
a) Fluoxetine is thought to inhibit the cytochrome P450 2C9 isoenzyme (CYP2C9). This is the enzyme by which the more potent warfarin isomer, S-warfarin, is metabolized (Riesenman, 1995). In addition, both fluoxetine and warfarin are tightly bound to albumin. In combination, the possibility for protein-binding displacement of either drug is present (Prod Info Coumadin(R), 1999).
b) 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).

c) 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).

d) In 6 reported cases, INR increased during combined fluoxetine and warfarin therapy. In a seventh case, severe bruising of the lower legs occurred in a woman initially treated with fluoxetine and, secondarily, started on warfarin (Woolfrey et al, 1993; Claire et al, 1991).

e) An 83-year-old man died from cerebral hemorrhage secondary to increased warfarin concentrations. The patient had been taking warfarin 30 mg per week for atrial fibrillation with a target INR between 2 and 3. The patient's other drugs included lisinopril, furosemide, potassium, digoxin, and acetaminophen. After being seen for symptoms of depression, anxiety, and insomnia, the patient was given fluoxetine 20 mg per day and diazepam 2.5 mg 3 to 4 times per day. Eight days later, the patient's INR increased to 4.8, and the dose of warfarin was decreased to 27.5 mg per week. The patient was later seen for symptoms of drug delirium, including confusion, incoherence, and speaking irrationally. At this point, the INR was 3.64 and fluoxetine was discontinued. The next day the patient presented to the hospital with left-sided weakness and later died from complications of a large interparenchymal hemorrhage. The authors proposed that the addition of fluoxetine to the patient's regimen resulted in increased serum levels of both warfarin and diazepam, resulting in delirium and loss of anticoagulant control (Dent & Orrock, 1997).

3.5.1.P 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 PROZAC(R) oral capsules, delayed-release capsules, solution, 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 (Prod Info PROZAC(R) oral capsules, delayed-release capsules, solution, 2008).

3) Severity: major

4) Onset: delayed

5) Substantiation: probable

6) Clinical Management: When fluoxetine and an anticoagulant are given concurrently, monitor patient for signs of increased bleeding. Patients who are taking warfarin should be monitored closely for altered anticoagulant effects, including increased bleeding, when fluoxetine therapy is initiated or discontinued (Prod Info PROZAC(R) oral capsules, delayed-release capsules, solution, 2008).

7) Probable Mechanism: unknown

8) Literature Reports

a) Fluoxetine is thought to inhibit the cytochrome P450 2C9 isoenzyme (CYP2C9). This is the enzyme by which the more potent warfarin isomer, S-warfarin, is metabolized (Riesenman, 1995). In addition, both fluoxetine and warfarin are tightly bound to albumin. In combination, the possibility for protein-binding displacement of either drug is present (Prod Info Coumadin(R), 1999).

b) 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).

c) 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).

d) In 6 reported cases, INR increased during combined fluoxetine and warfarin therapy. In a seventh case, severe bruising of the lower legs occurred in a woman initially treated with fluoxetine and, secondarily, started on warfarin (Woolfrey et al, 1993; Claire et al, 1991).

e) An 83-year-old man died from cerebral hemorrhage secondary to increased warfarin concentrations. The patient had been taking warfarin 30 mg per week for atrial fibrillation with a target INR between 2 and 3. The patient's other drugs included lisinopril, furosemide, potassium, digoxin, and acetaminophen. After being seen for symptoms of depression, anxiety, and insomnia, the patient was given fluoxetine 20 mg per day and diazepam 2.5 mg 3 to 4 times per day. Eight days later, the patient's INR increased to 4.8, and the dose of warfarin was decreased to 27.5 mg per week. The patient was later seen for symptoms of drug delirium, including confusion, incoherence, and speaking irrationally. At this point, the INR was 3.64 and fluoxetine was discontinued. The next day the patient presented to the hospital with left-sided weakness and later died from complications of a large interparenchymal hemorrhage. The authors proposed that the addition of fluoxetine to the patient's regimen resulted in increased serum levels of both warfarin and diazepam, resulting in delirium and loss of anticoagulant control (Dent & Orrock, 1997).

3.5.1.Q 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 PROZAC(R) oral capsules, delayed-release capsules, solution, 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 (Prod Info PROZAC(R) oral capsules, delayed-release capsules, solution, 2008).

3) Severity: major

4) Onset: delayed

5) Substantiation: probable

6) Clinical Management: When fluoxetine and an anticoagulant are given concurrently, monitor patient for signs of increased bleeding. Patients who are taking warfarin should be monitored closely for altered anticoagulant effects, including increased bleeding, when fluoxetine therapy is initiated or discontinued (Prod Info PROZAC(R) oral capsules, delayed-release capsules, solution, 2008).

7) Probable Mechanism: unknown

8) Literature Reports

a) Fluoxetine is thought to inhibit the cytochrome P450 2C9 isoenzyme (CYP2C9). This is the enzyme by which the more potent warfarin isomer, S-warfarin, is metabolized (Riesenman, 1995). In addition, both fluoxetine and warfarin are tightly bound to albumin. In combination, the possibility for protein-binding displacement of either drug is present (Prod Info Coumadin(R), 1999).

b) 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).

c) 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).

d) In 6 reported cases, INR increased during combined fluoxetine and warfarin therapy. In a seventh case, severe bruising of the lower legs occurred in a woman initially treated with fluoxetine and, secondarily, started on warfarin (Woolfrey et al, 1993; Claire et al, 1991).

e) An 83-year-old man died from cerebral hemorrhage secondary to increased warfarin concentrations. The patient had been taking warfarin 30 mg per week for atrial fibrillation with a target INR between 2 and 3. The patient's other drugs included lisinopril, furosemide, potassium, digoxin, and acetaminophen. After being seen for symptoms of depression, anxiety, and insomnia, the patient was given fluoxetine 20 mg per day and diazepam 2.5 mg 3 to 4 times per day. Eight days later, the patient's INR increased to 4.8, and the dose of warfarin was decreased to 27.5 mg per week. The patient was later seen for symptoms of drug delirium, including confusion, incoherence, and speaking irrationally. At this point, the INR was 3.64 and fluoxetine was discontinued. The next day the patient presented to the hospital with left-sided weakness and later died from complications of a large interparenchymal hemorrhage. The authors proposed that the addition of fluoxetine to the patient's regimen resulted in increased serum levels of both warfarin and diazepam, resulting in delirium and loss of anticoagulant control (Dent & Orrock, 1997).

3.5.1.R Aprindine

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)

2) Summary: Even though no formal drug interaction studies have been done, the coadministration of Class I antiarrhythmics and other drugs known to prolong the QTc interval is not recommended (Prod Info Tambocor(R) flecainide acetate, 1998). Fluoxetine has been shown to prolong the QTc interval at the recommended therapeutic dose (Prod Info Prozac(R), 2001w).

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: The concurrent administration of class I antiarrhythmic agents and agents that prolong the QT interval, such as fluoxetine, is not recommended.

7) Probable Mechanism: additive effects on QT prolongation

3.5.1.S 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 PROZAC(R) oral capsules, delayed-release capsules, solution, 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 (Prod Info PROZAC(R) oral capsules, delayed-release capsules, solution, 2008).

3) Severity: major

4) Onset: delayed

5) Substantiation: probable

6) Clinical Management: When fluoxetine and an anticoagulant are given concurrently, monitor patient for signs of increased bleeding. Patients who are taking warfarin should be monitored closely for altered anticoagulant effects, including increased bleeding, when fluoxetine therapy is initiated or discontinued (Prod Info PROZAC(R) oral capsules, delayed-release capsules, solution, 2008).

7) Probable Mechanism: unknown

8) Literature Reports

a) Fluoxetine is thought to inhibit the cytochrome P450 2C9 isoenzyme (CYP2C9). This is the enzyme by which the more potent warfarin isomer, S-warfarin, is metabolized (Riesenman, 1995). In addition, both fluoxetine and warfarin are tightly bound to albumin. In combination, the possibility for protein-binding displacement of either drug is present (Prod Info Coumadin(R), 1999).

b) 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).

c) 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).

d) In 6 reported cases, INR increased during combined fluoxetine and warfarin therapy. In a seventh case, severe bruising of the lower legs occurred in a woman initially treated with fluoxetine and, secondarily, started on warfarin (Woolfrey et al, 1993; Claire et al, 1991).

e) An 83-year-old man died from cerebral hemorrhage secondary to increased warfarin concentrations. The patient had been taking warfarin 30 mg per week for atrial fibrillation with a target INR between 2 and 3. The patient's other drugs included lisinopril, furosemide, potassium, digoxin, and acetaminophen. After being seen for symptoms of depression, anxiety, and insomnia, the patient was given fluoxetine 20 mg per day and diazepam 2.5 mg 3 to 4 times per day. Eight days later, the patient's INR increased to 4.8, and the dose of warfarin was decreased to 27.5 mg per week. The patient was later seen for symptoms of drug delirium, including confusion, incoherence, and speaking irrationally. At this point, the INR was 3.64 and fluoxetine was discontinued. The next day the patient presented to the hospital with left-sided weakness and later died from complications of a large interparenchymal hemorrhage. The authors proposed that the addition of fluoxetine to the patient's regimen resulted in increased serum levels of both warfarin and diazepam, resulting in delirium and loss of anticoagulant control (Dent & Orrock, 1997).

3.5.1.T 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 fluoxetine, may inhibit aripiprazole elimination causing increased blood concentrations. Consider a dosage reduction for aripiprazole when these agents are coadministered. If therapy with fluoxetine 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 fluoxetine. Consider a dosage reduction for aripiprazole when these agents are coadministered. If therapy with fluoxetine 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.U Arsenic Trioxide

1) Interaction Effect: cardiotoxicity (QT interval prolongation, torsades de pointes, cardiac arrest)

2) Summary: Arsenic trioxide and fluoxetine have been shown to prolong the QTc interval at the recommended therapeutic dose (Prod Info Trisenox(R), 2001a; Prod Info Prozac(R), 2001u). Even though no formal drug interaction studies have been done, arsenic trioxide should not be administered with other drugs which are also known or have the potential to prolong the QTc interval, including fluoxetine (Prod Info Trisenox(R), 2001a).

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: The concurrent administration of arsenic trioxide and fluoxetine is not recommended.

7) Probable Mechanism: additive effects on QT prolongation

8) Literature Reports

a) QT/QTc prolongation should be expected during treatment with arsenic trioxide and torsade de pointes as well as complete heart block has been reported. Over 460 ECG tracings from 40 patients with refractory or relapsed APL treated with arsenic trioxide were evaluated for QTc prolongation. Sixteen of 40 patients (40%) had at least one ECG tracing with a QTc interval greater than 500 msec. Prolongation of the QTc was observed between 1 and 5 weeks after arsenic trioxide infusion, and then returned towards baseline by the end of 8 weeks after arsenic trioxide infusion. In these ECG evaluations, women did not experience more pronounced QT prolongation than men, and there was no

correlation with age (Prod Info Trisenox(R), 2001).
b) QT Prolongation was observed on the electrocardiogram (ECG) of a 52- year-old man who had been taking fluoxetine (20 milligrams/day for 2 weeks, followed by 40 milligrams/day thereafter) for depression for 3 months. An ECG just before the start of fluoxetine treatment showed a normal QT interval. The QT interval returned to normal within 10 days of discontinuing fluoxetine treatment (Varriale, 2001).

3.5.1.V 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.W Astemizole
1) Interaction Effect: cardiotoxicity (QT interval prolongation, torsades de pointes, cardiac arrest)
2) Summary: It is theoretically possible that an interaction might occur between astemizole and fluoxetine because both drugs are metabolized by the cytochrome P450 system. Astemizole is metabolized by CYP3A4. Fluoxetine is known to be a potent inhibitor of CYP2D6 and is suspected of inhibiting other P450 enzymes, including CYP3A4 (Riesenman, 1995a). Coadministered fluoxetine may inhibit astemizole clearance, thereby leading to increased astemizole serum concentrations and potential astemizole toxicity. The manufacturer of astemizole recommends avoiding coadministration with fluoxetine (Prod Info Hismanal (R), 1998). In addition, fluoxetine has been shown to prolong the QTc interval at the recommended therapeutic dose (Prod Info Prozac(R), 2001c).
3) Severity: major
4) Onset: rapid
5) Substantiation: theoretical
6) Clinical Management: Concomitant use of astemizole and fluoxetine is not recommended.
7) Probable Mechanism: possible inhibition of astemizole P450 metabolism by fluoxetine and/or additive effects on QT prolongation
8) Literature Reports
a) Astemizole has been shown to prolong the QTc interval at the recommended therapeutic dose (Prod Info Hismanal(R), 1996). Even though no formal drug interaction studies have been done, the coadministration of astemizole and other drugs known to prolong the QTc interval, including fluoxetine, is not recommended.

3.5.1.X 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 fluoxetine. The exposure is similar to that observed in poor metabolizers. In extensive metabolizers treated with fluoxetine, 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 fluoxetine.
7) Probable Mechanism: inhibition of cytochrome P450 2D6-mediated metabolism of atomoxetine by fluoxetine

3.5.1.Y Azimilide
1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Even though no formal drug interaction studies have been done, the coadministration of Class III antiarrhythmics and other drugs known to prolong the QTc interval is not recommended (Allen et al, 2002; Prod Info Tikosyn(TM) dofetilide capsules, 1999; Prod Info Corvert(R), 1998). Fluoxetine has been shown to prolong the QTc interval at the recommended therapeutic dose (Prod Info Prozac(R), 2001a).
3) Severity: major

4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of class III antiarrhythmic agents and agents that prolong the QT interval, such as fluoxetine, is not recommended.
7) Probable Mechanism: additive effects on QT prolongation

3.5.1.Z 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.AA Bepridil

1) Interaction Effect: cardiotoxicity (QT interval prolongation, torsades de pointes, cardiac arrest)
2) Summary: Both bepridil and fluoxetine have been shown to prolong the QTc interval at therapeutic doses (Prod Info Prozac(R), 2001aa; Prod Info Vascor(R), 2000). Even though no formal drug interaction studies have been done, the coadministration of bepridil and fluoxetine is contraindicated (Prod Info Vascor(R), 2000).
3) Severity: contraindicated
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of bepridil and fluoxetine is contraindicated.
7) Probable Mechanism: additive effects on QT prolongation

3.5.1.AB 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 PROZAC(R) oral capsules, delayed-release capsules, solution, 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 (Prod Info PROZAC(R) oral capsules, delayed-release capsules, solution, 2008).
3) Severity: major
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: When fluoxetine and an anticoagulant are given concurrently, monitor patient for signs of increased bleeding. Patients who are taking warfarin should be monitored closely for altered anticoagulant effects, including increased bleeding, when fluoxetine therapy is initiated or discontinued (Prod Info PROZAC(R) oral capsules, delayed-release capsules, solution, 2008).
7) Probable Mechanism: unknown
8) Literature Reports
a) Fluoxetine is thought to inhibit the cytochrome P450 2C9 isoenzyme (CYP2C9). This is the enzyme by which the more potent warfarin isomer, S-warfarin, is metabolized (Riesenman, 1995). In addition, both fluoxetine and warfarin are tightly bound to albumin. In combination, the possibility for protein-binding displacement of either drug is present (Prod Info Coumadin(R), 1999).
b) 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).

c) 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).

d) In 6 reported cases, INR increased during combined fluoxetine and warfarin therapy. In a seventh case, severe bruising of the lower legs occurred in a woman initially treated with fluoxetine and, secondarily, started on warfarin (Woolfrey et al, 1993; Claire et al, 1991).

e) An 83-year-old man died from cerebral hemorrhage secondary to increased warfarin concentrations. The patient had been taking warfarin 30 mg per week for atrial fibrillation with a target INR between 2 and 3. The patient's other drugs included lisinopril, furosemide, potassium, digoxin, and acetaminophen. After being seen for symptoms of depression, anxiety, and insomnia, the patient was given fluoxetine 20 mg per day and diazepam 2.5 mg 3 to 4 times per day. Eight days later, the patient's INR increased to 4.8, and the dose of warfarin was decreased to 27.5 mg per week. The patient was later seen for symptoms of drug delirium, including confusion, incoherence, and speaking irrationally. At this point, the INR was 3.64 and fluoxetine was discontinued. The next day the patient presented to the hospital with left-sided weakness and later died from complications of a large interparenchymal hemorrhage. The authors proposed that the addition of fluoxetine to the patient's regimen resulted in increased serum levels of both warfarin and diazepam, resulting in delirium and loss of anticoagulant control (Dent & Orrock, 1997).

3.5.1.AC Bretylium

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)

2) Summary: Even though no formal drug interaction studies have been done, the coadministration of Class III antiarrhythmics and other drugs known to prolong the QTc interval is not recommended (Allen et al, 2002; Prod Info Tikosyn(TM) dofetilide capsules, 1999; Prod Info Corvert(R), 1998). Fluoxetine has been shown to prolong the QTc interval at the recommended therapeutic dose (Prod Info Prozac(R), 2001a).

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: The concurrent administration of class III antiarrhythmic agents and agents that prolong the QT interval, such as fluoxetine, is not recommended.

7) Probable Mechanism: additive effects on QT prolongation

3.5.1.AD 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.AE 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.AF Bupropion

1) Interaction Effect: increased plasma levels of fluoxetine

2) Summary: Because bupropion inhibits CYP2D6-mediated metabolism it is recommended that fluoxetine, 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 Wellbutrin XL(TM), 2003; Prod Info Zyban(R), 2000). Increased plasma concentrations of fluoxetine may result in increased adverse effects.

3) Severity: moderate

4) Onset: delayed

5) Substantiation: probable

6) Clinical Management: Coadministration of bupropion and fluoxetine should be approached with caution and should be initiated at the lower end of the dose range of fluoxetine. If bupropion is added to the treatment regimen of a patient already receiving fluoxetine, consider decreasing the dose of fluoxetine. Monitor for increased adverse effects including weight gain or loss, anxiety, weakness, or sleeping disturbances.

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

8) Literature Reports

a) The concomitant administration of fluoxetine and bupropion was associated with a hyperactive libido in a patient receiving treatment for major depression. The patient, a 35-year-old woman, initially received treatment with fluoxetine 40 milligrams (mg) daily after converting from clomipramine therapy due to suboptimal therapeutic effect. She experienced a diminished libido from the onset of clomipramine therapy which did not resolve after conversion to fluoxetine. Three months after the conversion to fluoxetine, bupropion 100 mg/day was added to her treatment regimen as a potential antidote for the sexual dysfunction. Sexual function appeared to normalize 1 month after the start of bupropion therapy. Approximately 5 months after beginning bupropion, the patient complained of having an exaggerated increase in libido, causing her to discontinue all medications. Her libido returned to normal within 2 months of stopping all medication, accompanied by a recurrence of depressive symptoms. Fluoxetine was reintroduced within the same time period, producing another reduction in libido yet accompanied by a full remission from depressive symptoms (Chollet & Andreatini, 2003).

3.5.1.AG Buspirone

1) Interaction Effect: worsening of psychiatric symptoms

2) Summary: In a number of case reports, the concomitant use of buspirone and fluoxetine has been

reported to result in a worsening of the patient's underlying anxiety/or obsessive-compulsive disorder (Bodkin & Teicher, 1989; Tanquary & Masand, 1990; Markovitz et al, 1990). One case report describes a patient maintained on fluoxetine who presented with symptoms of serotonin syndrome, including confusion, diaphoresis, incoordination, diarrhea, and myoclonus after buspirone was added to his drug regimen (Manos, 2000a).

3) Severity: moderate

4) Onset: delayed

5) Substantiation: probable

6) Clinical Management: If possible, the combination of fluoxetine and buspirone should be avoided; however, if deemed clinically appropriate, monitor for worsening of psychiatric symptoms.

7) Probable Mechanism: possible inhibition of buspirone serotonergic effects

8) Literature Reports

a) One of 10 patients with obsessive-compulsive disorder experienced anorgasmia after buspirone (mean maximum dose, 54 mg daily) was added to fluoxetine therapy (mean maximum dose, 78 mg daily). The anorgasmia could not be definitely attributed to the buspirone or to an interaction between the two agents. Both fluoxetine and buspirone have reported a low incidence of sexual dysfunction when taken as monotherapy (Prod Info Prozac(R), 1999d; Prod Info Buspar(R), 1994; Jenike et al, 1991).

b) Three cases of potentiation of the antidepressant effects of fluoxetine by buspirone have been reported (Bakish, 1991). All three patients had treatment-resistant symptoms of depression, obsessional traits, anxiety, and a history of eating disorder prior to adding buspirone to the treatment regimen.

c) A case report describes a 37-year-old male patient maintained on fluoxetine 20mg per day who began combination treatment with buspirone to augment the actions of fluoxetine. The starting dose of buspirone was gradually increased from 5mg twice a day to 30mg twice a day over approximately five weeks. After five days at this dose, the patient complained of confusion, diaphoresis, incoordination, diarrhea, and myoclonus, which was thought to be serotonin syndrome. The patients symptoms resolved shortly after discontinuation of buspirone (Manos, 2000).

3.5.1.AH 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.AI Carbamazepine

1) Interaction Effect: carbamazepine toxicity (ataxia, nystagmus, diplopia, headache, vomiting, apnea, seizures, coma)

2) Summary: The addition of fluoxetine to carbamazepine therapy has increased carbamazepine concentrations and side effects, including diplopia, blurred vision, dizziness, and tremors in some reports (Grimsley et al, 1991a; Gernaat et al, 1991a; Pearson, 1990a). Conversely, no changes in steady state carbamazepine levels have been reported with the addition of fluoxetine (Spina et al, 1993a). Symptoms of serotonin syndrome (hypertension, hyperthermia, myoclonus, mental status changes) have also been reported with this combination (Dursun et al, 1993a).

3) Severity: moderate

4) Onset: delayed

5) Substantiation: probable

6) Clinical Management: Due to the potential to increase carbamazepine levels, patients should be monitored for evidence of carbamazepine toxicity when fluoxetine is added to therapy. Carbamazepine levels should be considered within two to three weeks of adding or discontinuing fluoxetine, with dosage adjustments made as indicated.

7) Probable Mechanism: decreased carbamazepine metabolism
8) Literature Reports
a) An interaction between fluoxetine and carbamazepine was reported in six normal volunteers (Grimsley et al, 1991). Carbamazepine was given for 28 days, and fluoxetine was added to the regimen on day 7. The addition of fluoxetine 20 mg daily to carbamazepine 400 mg daily resulted in an increase in the area under the concentration-time curve for both carbamazepine and carbamazepine-epoxide and a decrease in clearance of carbamazepine. No significant changes were observed in absorption, volume of distribution or elimination rate constant, indicating that fluoxetine inhibits the metabolism of carbamazepine.
b) The effect of fluoxetine 20 mg daily was studied for three weeks in eight epileptic patients who were stabilized on carbamazepine therapy (Spina et al, 1993). Steady-state plasma levels of carbamazepine and its epoxide metabolite were not significantly changed with concurrent use of fluoxetine. These results differ from previous reports. The authors speculate that chronic carbamazepine administration may have resulted in enzyme induction that caused decreased levels of fluoxetine, thereby lowering the chances of a metabolic interaction. Unfortunately fluoxetine levels were not measured.
c) An interaction between fluoxetine and carbamazepine was reported in two patients receiving chronic carbamazepine dosages of 600 mg and 1000 mg daily respectively. Within 7 to 10 days of initiation of fluoxetine 20 mg daily, both patients developed symptoms of carbamazepine toxicity. Symptoms disappeared within two weeks in one patient following carbamazepine dosage reduction by 200 mg daily; in the other patient, fluoxetine was discontinued with symptom resolution within two weeks (Pearson, 1990).
d) Two cases of parkinsonism were reported after fluoxetine was added to an existing carbamazepine regimen. One patient, a 74-year old man, developed symptoms three days after fluoxetine 20 mg per day was added to an existing 12-month regimen of carbamazepine 200 mg twice daily. The patient developed cogwheel rigidity, a mask-like face, and a parkinsonian gait. After discontinuation of fluoxetine and treatment with dexetimide, the patient showed only a slight hypertonia of the arms 17 days later. The other patient, a 53-year old woman, developed parkinsonian symptoms after fluoxetine 20 mg per day was added to an existing regimen of carbamazepine 200 mg twice daily. The patient had also been taking thioridazine 275 mg per day which was stopped when fluoxetine was added. The patient developed cogwheel rigidity and a mask-like face nine days after initiation of fluoxetine therapy (Gernaat et al, 1991).
e) A female patient experienced a drug interaction 14 days after she had fluoxetine 20 mg added to a regimen of carbamazepine 200 mg daily. The patient presented with symptoms of serotonin syndrome, such as uncontrollable shivering, agitation, incoordination, myoclonus, hyperreflexia, and diaphoresis. The patient also had leukopenia and thrombocytopenia. After discontinuation of fluoxetine, all symptoms of serotonin syndrome and hematological abnormalities resolved over the next 72 hours (Dursun et al, 1993).

3.5.1.AJ 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.AK 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.AL 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 PROZAC(R) oral capsules, delayed-release capsules, solution, 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 (Prod Info PROZAC(R) oral capsules, delayed-release capsules, solution, 2008).

3) Severity: major

4) Onset: delayed

5) Substantiation: probable

6) Clinical Management: When fluoxetine and an anticoagulant are given concurrently, monitor patient for signs of increased bleeding. Patients who are taking warfarin should be monitored closely for altered anticoagulant effects, including increased bleeding, when fluoxetine therapy is initiated or discontinued (Prod Info PROZAC(R) oral capsules, delayed-release capsules, solution, 2008).

7) Probable Mechanism: unknown

8) Literature Reports

a) Fluoxetine is thought to inhibit the cytochrome P450 2C9 isoenzyme (CYP2C9). This is the enzyme by which the more potent warfarin isomer, S-warfarin, is metabolized (Riesenman, 1995). In addition, both fluoxetine and warfarin are tightly bound to albumin. In combination, the possibility for protein-binding displacement of either drug is present (Prod Info Coumadin(R), 1999).

b) 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).

c) 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).

d) In 6 reported cases, INR increased during combined fluoxetine and warfarin therapy. In a seventh case, severe bruising of the lower legs occurred in a woman initially treated with fluoxetine and, secondarily, started on warfarin (Woolfrey et al, 1993; Claire et al, 1991).
e) An 83-year-old man died from cerebral hemorrhage secondary to increased warfarin concentrations. The patient had been taking warfarin 30 mg per week for atrial fibrillation with a target INR between 2 and 3. The patient's other drugs included lisinopril, furosemide, potassium, digoxin, and acetaminophen. After being seen for symptoms of depression, anxiety, and insomnia, the patient was given fluoxetine 20 mg per day and diazepam 2.5 mg 3 to 4 times per day. Eight days later, the patient's INR increased to 4.8, and the dose of warfarin was decreased to 27.5 mg per week. The patient was later seen for symptoms of drug delirium, including confusion, incoherence, and speaking irrationally. At this point, the INR was 3.64 and fluoxetine was discontinued. The next day the patient presented to the hospital with left-sided weakness and later died from complications of a large interparenchymal hemorrhage. The authors proposed that the addition of fluoxetine to the patient's regimen resulted in increased serum levels of both warfarin and diazepam, resulting in delirium and loss of anticoagulant control (Dent & Orrock, 1997).

3.5.1.AM Chloral Hydrate

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Chloral hydrate and fluoxetine have been shown to prolong the QTc interval at the recommended therapeutic dose (Prod Info Prozac(R), 2001ac; Young et al, 1986). Even though no formal drug interaction studies have been done, the coadministration of drugs known to prolong the QTc interval is not recommended.
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Concomitant use of chloral hydrate and fluoxetine is not recommended.
7) Probable Mechanism: additive effects on QT prolongation
8) Literature Reports
a) QT Prolongation was observed on the electrocardiogram (ECG) of a 52- year-old man who had been taking fluoxetine (20 milligrams/day for 2 weeks, followed by 40 milligrams/day thereafter) for depression for 3 months. An ECG just before the start of fluoxetine treatment showed a normal QT interval. The QT interval returned to normal within 10 days of discontinuing fluoxetine treatment (Varriale, 2001a).

3.5.1.AN Chloroquine

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Chloroquine and fluoxetine have been shown to prolong the QTc interval at the recommended therapeutic dose (Prod Info Prozac(R), 2001r; Prod Info Aralen(R), 2001). Even though no formal drug interaction studies have been done, the coadministration of drugs known to prolong the QTc interval is not recommended.
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of chloroquine and fluoxetine is not recommended.
7) Probable Mechanism: additive effects on QT prolongation

3.5.1.AO Chlorpromazine

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Although citing no data, the manufacturers of some phenothiazines state that concomitant use with other drugs which prolong the QT interval is not recommended. Q and T wave distortions have been observed in patients taking phenothiazines (Prod Info Compazine(R), 2002; Prod Info Stelazine(R), 2002; Prod Info Thorazine(R), 2002) . Other phenothiazines may have similar effects, though no reports are available. Fluoxetine has been shown to prolong the QTc interval at the recommended therapeutic dose (Prod Info Prozac(R), 2003).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of fluoxetine and a phenothiazine is not recommended.
7) Probable Mechanism: additive effects on QT prolongation

3.5.1.AP 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.AQ Clarithromycin
1) Interaction Effect: delirium and psychosis
2) Summary: Delirium and psychosis were reported in a 53-year-old male after clarithromycin was added to therapy of fluoxetine and nitrazepam. These effects are most likely due to accumulation of fluoxetine (Pollak et al, 1995a).
3) Severity: major
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: Clarithromycin should be avoided in patients treated with fluoxetine.
7) Probable Mechanism: fluoxetine toxicity due to decreased metabolism
8) Literature Reports
a) Delirium and psychosis were reported in a 53-year-old male after clarithromycin was added to therapy of fluoxetine and nitrazepam. These effects are most likely due to accumulation of fluoxetine, because these symptoms have been associated with fluoxetine and not with nitrazepam. In addition, the patient had previously tolerated an inadvertent overdose of nitrazepam without symptoms of delirium and psychosis (Pollak et al, 1995).

3.5.1.AR 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.AS 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.AT Clopidogrel

1) Interaction Effect: reduction in clinical efficacy of clopidogrel

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

3) Severity: moderate

4) Onset: unspecified

5) Substantiation: theoretical

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

7) Probable Mechanism: inhibition of CYP2C19- mediated clopidogrel metabolism by fluoxetine

3.5.1.AU Clorgyline

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

2) Summary: Concurrent administration or overlapping therapy with fluoxetine 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 (Prod Info Prozac(R), 1999l; Sternbach, 1991w; Coplan & Gorman, 1993t; Feighner et al, 1990t; Kline et al, 1989u; Suchowersky & de Vries, 1990u). Concomitant use is contraindicated.

3) Severity: contraindicated

4) Onset: rapid

5) Substantiation: theoretical

6) Clinical Management: Concurrent use of fluoxetine and a MAO inhibitor is contraindicated. Wait at least two weeks after discontinuing a MAO inhibitor before initiating fluoxetine therapy. In addition, wait at least five weeks after discontinuing fluoxetine before initiating therapy with a MAO inhibitor.

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

8) Literature Reports

a) Concomitant use of serotonin specific reuptake inhibitors and monoamine oxidase inhibitors can produce a toxic reaction known as serotonin syndrome (Sternbach, 1991v). Serotonin syndrome is a condition of serotonergic hyperstimulation and manifests as restlessness, myoclonus, changes in mental status, hyperreflexia, diaphoresis, shivering, and tremor (Sternbach, 1991v). If the syndrome is not recognized and correctly treated, death can result.

b) It has been suggested that fluoxetine therapy be discontinued for five weeks before beginning therapy with a monoamine oxidase inhibitor. However, one case report describes a 28-year old woman who had discontinued a 2-year fluoxetine regimen for six weeks before starting therapy with tranylcypromine. Over the next few days the patient developed fever, paresthesias, confusion, abdominal cramping, and various other CNS symptoms. Upon discontinuation of tranylcypromine, the patient's symptoms began to resolve. Blood samples taken three days after discontinuation of tranylcypromine revealed no presence of fluoxetine; however, the norfluoxetine level was 84 ng/mL (Coplan & Gorman, 1993s).

c) Adverse reactions reported when fluoxetine was given concomitantly with phenelzine (n=9) or tranylcypromine (n=4) include tremor (50%), agitation or restlessness (42%), mental status changes (42%), myoclonus (33%), diarrhea (33%), and blood pressure changes (25%) (Feighner et al, 1990s). All but one of the patients were taking other medications (ie, benzodiazepines, neuroleptics, anticonvulsants, antidepressants) that may have contributed to the adverse reactions.

d) Ten hours after her last dose of fluoxetine, a 45-year-old woman began tranylcypromine therapy (Kline et al, 1989t). Headache, muscle contractions, insomnia, and unsteady gait were reported on the second day. Thioridazine and tryptophan were added to her therapy. The patient experienced fever, rigidity of the arms and legs, and hyperreflexia. She died in the intensive care unit of a hospital 44 hours later.

e) Two cases suggestive of an interaction between fluoxetine and selegiline were reported (Suchowersky & de Vries, 1990t). One case involved a first episode of mania being observed approximately one month after adding selegiline to fluoxetine therapy. 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 and selegiline. Both drugs were discontinued, with relatively quick resolution of symptoms. Rechallenge with fluoxetine alone occurred without incident.

3.5.1.AV Clozapine

1) Interaction Effect: an increased risk of clozapine toxicity (sedation, seizures, hypotension)

2) Summary: With concurrent administration of fluoxetine, increased serum clozapine concentrations have been reported (Prod Info Clozaril(R), 2002; Centorrino et al, 1994a; Centorrino et al, 1996a; Spina et al, 1998a). Certain adverse effects associated with clozapine are dose-dependent, including sedation (Ayd, 1974) and seizures (Haller & Binder, 1990), and might be expected to occur with concurrent use of these

medications.
3) Severity: moderate
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: Monitor the therapeutic efficacy of clozapine and for any evidence of toxicity, particularly when the daily clozapine dose exceeds 300 mg or 3.5 mg/kg. Lower clozapine dosage may be required in some clinical situations.
7) Probable Mechanism: inhibition by fluoxetine of N-dealkylation and N-oxidation of clozapine via the cytochrome P450 2D6 enzymatic pathway
8) Literature Reports
a) Subjects receiving concurrent clozapine and fluoxetine had 76% higher serum clozapine concentrations and 61% higher metabolite concentrations on average compared with controls receiving only clozapine. The mean ratio of total drug level (clozapine plus metabolites) to dose was 60% higher and the mean ratio of concentrations to dose was 75% higher in patients receiving clozapine and fluoxetine compared with concentrations in patients receiving clozapine alone (Centorrino et al, 1994).
b) A study evaluated the serum concentrations of clozapine and norclozapine, the major metabolite, 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).
c) A 44-year-old male receiving fluoxetine and clozapine was found dead in his yard. The dates of the prescriptions and the number of tablets which remained indicated that he had been taking his medications as prescribed. Autopsy results showed a high therapeutic fluoxetine concentration (0.7 mcg/mL) and also a high therapeutic norfluoxetine concentration (0.6 mcg/mL). Fluoxetine found in his gastric contents also indicated that the medication was being taken as directed. The clozapine blood concentration was in the lethal concentration range (4.9 mcg/mL), but the clozapine in the gastric contents suggested that the clozapine was being taken as prescribed and that the patient had not consumed a large overdose amount prior to his death. Other pathological findings included pulmonary edema, visceral vascular congestion, paralytic ileus, gastroenteritis, and eosinophilia, which are all consistent with clozapine toxicity. The combined central nervous system, respiratory, and cardiovascular depression caused by these two drugs was sufficient to result in the death of this patient, and his death was ruled to be a clozapine overdose due to a fatal drug interaction (Ferslew et al, 1998).
d) Ten institutionalized schizophrenic patients stabilized on clozapine therapy for at least one month participated in a prospective study to evaluate the effect of fluoxetine on clozapine pharmacokinetics. Fluoxetine 20 mg once daily was administered for eight consecutive weeks. Mean plasma clozapine concentrations increased from 348 ng/mL to 550 ng/mL (58%) at week 8. Plasma levels of norclozapine were also increased by 36% (from 280 ng/mL to 381 ng/mL). Clozapine N-oxide levels rose from 89 ng/mL at baseline to 128 ng/mL, representing a 38% increase. However, these increases in clozapine and metabolite plasma concentrations were not associated with significant changes in efficacy or safety (Spina et al, 1998).

3.5.1.AW Cyclobenzaprine
1) Interaction Effect: an increased risk of QT prolongation
2) Summary: Fluoxetine and cyclobenzaprine caused asymptomatic QT prolongation in a female patient. However, the administration of droperidol preoperatively to this patient resulted in torsades de pointes and cardiac arrest. The authors of this case report postulated that the metabolism of cyclobenzaprine, which is structurally similar to the tricyclic antidepressants, was inhibited by fluoxetine. Cytochrome P450 2D6 hepatic enzymes are inhibited by fluoxetine, and cyclobenzaprine may also be metabolized via this pathway (Michalets et al, 1998a).
3) Severity: moderate
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: Clinicians should monitor patients receiving cyclobenzaprine and fluoxetine for cardiac arrhythmias and QT prolongation. Patients who receive these two agents concurrently should avoid other drugs which are also known to prolong the QT interval.
7) Probable Mechanism: inhibition of cyclobenzaprine metabolism by fluoxetine via the cytochrome P450 hepatic enzyme system
8) Literature Reports
a) A 59-year-old female patient was receiving fluoxetine 30 mg daily, cyclobenzaprine 10 mg daily, amlodipine 5 mg daily, diclofenac 100 mg daily, and triamterene 37.5 mg/hydrochlorothiazide 25 mg daily. Five days prior to elective Achilles tendon surgery, her QTc was prolonged at 497 msec. Despite this finding, she was premedicated for surgery with intravenous droperidol 0.625 mg and

metoclopramide 10 mg. Approximately 105 minutes into the surgery, the patient developed ventricular tachycardia consistent with torsades de pointes which progressed into ventricular fibrillation and cardiac arrest. Immediately following cardioversion, the patient's QTc was 500 msec. All preadmission medications were discontinued following surgery. On postoperative day 1, the QTc was 440 msec and an electrocardiogram showed normal sinus rhythm (Michalets et al, 1998).

3.5.1.AX Cyproheptadine

1) Interaction Effect: decreased fluoxetine efficacy

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

3) Severity: moderate

4) Onset: rapid

5) Substantiation: probable

6) Clinical Management: Monitor patients for a reduction in fluoxetine efficacy. When cyproheptadine is coadministered with fluoxetine, fluoxetine doses might need to be adjusted upward. In some cases, it may be necessary to withdraw cyproheptadine.

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

8) Literature Reports

a) Although not consistently reported, decreased antidepressant effects were found in some patients when cyproheptadine was added to fluoxetine therapy (Katz & Rosenthal, 1994; Feder, 1991; Goldbloom & Kennedy, 1991). A 42-year-old woman using fluoxetine 40 mg once a day for episodes of depression, subsequently started cyproheptadine (4 mg per dose) for its antihistaminic properties (Katz & Rosenthal, 1994). Approximately 36 hours later and after four doses of cyproheptadine, she experienced dysphoria, irritability, and suicidal ideation. She improved after withdrawal of cyproheptadine. On rechallenge, her feelings of dysphoria returned.

b) A 54-year-old woman was using paroxetine 20 mg per day for the treatment of nonpsychotic major depression (Christensen, 1995). 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.

3.5.1.AY 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 PROZAC(R) oral capsules, delayed-release capsules, solution, 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 (Prod Info PROZAC(R) oral capsules, delayed-release capsules, solution, 2008).

3) Severity: major

4) Onset: delayed

5) Substantiation: probable

6) Clinical Management: When fluoxetine and an anticoagulant are given concurrently, monitor patient for signs of increased bleeding. Patients who are taking warfarin should be monitored closely for altered anticoagulant effects, including increased bleeding, when fluoxetine therapy is initiated or discontinued (Prod Info PROZAC(R) oral capsules, delayed-release capsules, solution, 2008).

7) Probable Mechanism: unknown

8) Literature Reports

a) Fluoxetine is thought to inhibit the cytochrome P450 2C9 isoenzyme (CYP2C9). This is the enzyme by which the more potent warfarin isomer, S-warfarin, is metabolized (Riesenman, 1995). In addition, both fluoxetine and warfarin are tightly bound to albumin. In combination, the possibility for protein-binding displacement of either drug is present (Prod Info Coumadin(R), 1999).

b) 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).

c) 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).

d) In 6 reported cases, INR increased during combined fluoxetine and warfarin therapy. In a seventh case, severe bruising of the lower legs occurred in a woman initially treated with fluoxetine and, secondarily, started on warfarin (Woolfrey et al, 1993; Claire et al, 1991).

e) An 83-year-old man died from cerebral hemorrhage secondary to increased warfarin concentrations. The patient had been taking warfarin 30 mg per week for atrial fibrillation with a target INR between 2 and 3. The patient's other drugs included lisinopril, furosemide, potassium, digoxin, and acetaminophen. After being seen for symptoms of depression, anxiety, and insomnia, the patient was given fluoxetine 20 mg per day and diazepam 2.5 mg 3 to 4 times per day. Eight days later, the patient's INR increased to 4.8, and the dose of warfarin was decreased to 27.5 mg per week. The patient was later seen for symptoms of drug delirium, including confusion, incoherence, and speaking irrationally. At this point, the INR was 3.64 and fluoxetine was discontinued. The next day the patient presented to the hospital with left-sided weakness and later died from complications of a large interparenchymal hemorrhage. The authors proposed that the addition of fluoxetine to the patient's regimen resulted in increased serum levels of both warfarin and diazepam, resulting in delirium and loss of anticoagulant control (Dent & Orrock, 1997).

3.5.1.AZ 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 PROZAC(R) oral capsules, delayed-release capsules, solution, 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 (Prod Info PROZAC(R) oral capsules, delayed-release capsules, solution, 2008).

3) Severity: major

4) Onset: delayed

5) Substantiation: probable

6) Clinical Management: When fluoxetine and an anticoagulant are given concurrently, monitor patient for signs of increased bleeding. Patients who are taking warfarin should be monitored closely for altered anticoagulant effects, including increased bleeding, when fluoxetine therapy is initiated or discontinued (Prod Info PROZAC(R) oral capsules, delayed-release capsules, solution, 2008).

7) Probable Mechanism: unknown

8) Literature Reports

a) Fluoxetine is thought to inhibit the cytochrome P450 2C9 isoenzyme (CYP2C9). This is the enzyme by which the more potent warfarin isomer, S-warfarin, is metabolized (Riesenman, 1995). In addition, both fluoxetine and warfarin are tightly bound to albumin. In combination, the possibility for protein-binding displacement of either drug is present (Prod Info Coumadin(R), 1999).

b) 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).

c) 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).

d) In 6 reported cases, INR increased during combined fluoxetine and warfarin therapy. In a seventh case, severe bruising of the lower legs occurred in a woman initially treated with fluoxetine and, secondarily, started on warfarin (Woolfrey et al, 1993; Claire et al, 1991).

e) An 83-year-old man died from cerebral hemorrhage secondary to increased warfarin concentrations. The patient had been taking warfarin 30 mg per week for atrial fibrillation with a target INR between 2 and 3. The patient's other drugs included lisinopril, furosemide, potassium, digoxin, and acetaminophen. After being seen for symptoms of depression, anxiety, and insomnia, the patient was given fluoxetine 20 mg per day and diazepam 2.5 mg 3 to 4 times per day. Eight days later, the patient's INR increased to 4.8, and the dose of warfarin was decreased to 27.5 mg per week. The patient was later seen for symptoms of drug delirium, including confusion, incoherence, and speaking irrationally. At this point, the INR was 3.64 and fluoxetine was discontinued. The next day the patient presented to the hospital with left-sided weakness and later died from complications of a large interparenchymal hemorrhage. The authors proposed that the addition of fluoxetine to the patient's regimen resulted in increased serum levels of both warfarin and diazepam, resulting in delirium and loss of anticoagulant control (Dent & Orrock, 1997).

3.5.1.BA 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 PROZAC(R) oral capsules, delayed-release capsules, solution, 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 (Prod Info PROZAC(R) oral capsules, delayed-release capsules, solution, 2008).

3) Severity: major

4) Onset: delayed

5) Substantiation: probable

6) Clinical Management: When fluoxetine and an anticoagulant are given concurrently, monitor patient for signs of increased bleeding. Patients who are taking warfarin should be monitored closely for altered anticoagulant effects, including increased bleeding, when fluoxetine therapy is initiated or discontinued (Prod Info PROZAC(R) oral capsules, delayed-release capsules, solution, 2008).

7) Probable Mechanism: unknown

8) Literature Reports

a) Fluoxetine is thought to inhibit the cytochrome P450 2C9 isoenzyme (CYP2C9). This is the enzyme by which the more potent warfarin isomer, S-warfarin, is metabolized (Riesenman, 1995). In addition, both fluoxetine and warfarin are tightly bound to albumin. In combination, the possibility for protein-binding displacement of either drug is present (Prod Info Coumadin(R), 1999).

b) 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).

c) 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).
d) In 6 reported cases, INR increased during combined fluoxetine and warfarin therapy. In a seventh case, severe bruising of the lower legs occurred in a woman initially treated with fluoxetine and, secondarily, started on warfarin (Woolfrey et al, 1993; Claire et al, 1991).
e) An 83-year-old man died from cerebral hemorrhage secondary to increased warfarin concentrations. The patient had been taking warfarin 30 mg per week for atrial fibrillation with a target INR between 2 and 3. The patient's other drugs included lisinopril, furosemide, potassium, digoxin, and acetaminophen. After being seen for symptoms of depression, anxiety, and insomnia, the patient was given fluoxetine 20 mg per day and diazepam 2.5 mg 3 to 4 times per day. Eight days later, the patient's INR increased to 4.8, and the dose of warfarin was decreased to 27.5 mg per week. The patient was later seen for symptoms of drug delirium, including confusion, incoherence, and speaking irrationally. At this point, the INR was 3.64 and fluoxetine was discontinued. The next day the patient presented to the hospital with left-sided weakness and later died from complications of a large interparenchymal hemorrhage. The authors proposed that the addition of fluoxetine to the patient's regimen resulted in increased serum levels of both warfarin and diazepam, resulting in delirium and loss of anticoagulant control (Dent & Orrock, 1997).

3.5.1.BB 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.BC Delavirdine

1) Interaction Effect: increased trough delavirdine concentrations
2) Summary: Population pharmacokinetic data in 36 patients suggested that coadministration of delavirdine and fluoxetine resulted in an approximate 50% increase in trough delavirdine concentrations (Prod Info Rescriptor(R), 1999). The clinical significance of this interaction is not known.
3) Severity: moderate
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: Concurrent use of delavirdine with fluoxetine should be coadministered with caution. Monitor patients for an increased incidence of delavirdine adverse effects.
7) Probable Mechanism: unknown

3.5.1.BD 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 PROZAC(R) oral capsules, delayed-release capsules, solution, 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 (Prod Info PROZAC(R) oral capsules, delayed-release capsules, solution, 2008).
3) Severity: major
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: When fluoxetine and an anticoagulant are given concurrently, monitor patient for signs of increased bleeding. Patients who are taking warfarin should be monitored closely for altered anticoagulant effects, including increased bleeding, when fluoxetine therapy is initiated or discontinued (Prod Info PROZAC(R) oral capsules, delayed-release capsules, solution, 2008).
7) Probable Mechanism: unknown
8) Literature Reports
a) Fluoxetine is thought to inhibit the cytochrome P450 2C9 isoenzyme (CYP2C9). This is the enzyme by which the more potent warfarin isomer, S-warfarin, is metabolized (Riesenman, 1995). In addition, both fluoxetine and warfarin are tightly bound to albumin. In combination, the possibility for protein-binding displacement of either drug is present (Prod Info Coumadin(R), 1999).
b) 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).
c) 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).
d) In 6 reported cases, INR increased during combined fluoxetine and warfarin therapy. In a seventh case, severe bruising of the lower legs occurred in a woman initially treated with fluoxetine and, secondarily, started on warfarin (Woolfrey et al, 1993; Claire et al, 1991).
e) An 83-year-old man died from cerebral hemorrhage secondary to increased warfarin concentrations. The patient had been taking warfarin 30 mg per week for atrial fibrillation with a target INR between 2 and 3. The patient's other drugs included lisinopril, furosemide, potassium, digoxin, and acetaminophen. After being seen for symptoms of depression, anxiety, and insomnia, the patient was given fluoxetine 20 mg per day and diazepam 2.5 mg 3 to 4 times per day. Eight days later, the patient's INR increased to 4.8, and the dose of warfarin was decreased to 27.5 mg per week. The patient was later seen for symptoms of drug delirium, including confusion, incoherence, and speaking irrationally. At this point, the INR was 3.64 and fluoxetine was discontinued. The next day the patient presented to the hospital with left-sided weakness and later died from complications of a large interparenchymal hemorrhage. The authors proposed that the addition of fluoxetine to the patient's regimen resulted in increased serum levels of both warfarin and diazepam, resulting in delirium and loss of anticoagulant control (Dent & Orrock, 1997).

3.5.1.BE Desipramine

1) Interaction Effect: tricyclic antidepressant toxicity (dry mouth, urinary retention, sedation) and an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Tricyclic antidepressants (TCAs) and fluoxetine have been shown to prolong the QTc interval at the recommended therapeutic dose (Prod Info Prozac(R), 2001h; Marshall & Forker, 1982). Even though no formal drug interaction studies have been done which demonstrate QT prolongation, the coadministration of tricyclic antidepressants and other drugs known to prolong the QTc interval, such as fluoxetine, is not recommended (Prod Info Elavil(R), 1999). In addition, concurrent use of fluoxetine and TCAs such as desipramine, nortriptyline, and imipramine has resulted in significant increases in TCA concentrations (Preskorn et al, 1994a; Preskorn et al, 1994a; Aranow et al, 1989a; Downs et al, 1989a; Goodnick, 1989a; Bell & Cole, 1988a).
3) Severity: major

4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: The concurrent administration of fluoxetine and a tricyclic antidepressant is not recommended.
7) Probable Mechanism: decreased tricyclic antidepressant metabolism; additive effects on QT prolongation
8) Literature Reports
a) Fluoxetine increased the level of tricyclic antidepressants (nortriptyline, imipramine, desipramine) in 4 patients. After the addition of fluoxetine, the ratio of antidepressant level to dose increased by 109% to 486% in the patients. Three patients developed clinical symptoms (anticholinergic effects, constipation, urinary hesitancy, sedation, unstable gait) as a result of the increased levels (Aranow et al, 1989).
b) Fluoxetine statistically and clinically significantly increased desipramine concentrations in 18 healthy subjects. When fluoxetine (20 mg daily) was added to desipramine (50 mg daily), the mean maximum concentration of desipramine increased by 278% and the area under the concentration-time curve increased by 342%. Desipramine trough concentrations continued to be 198% above baseline three weeks after fluoxetine was discontinued. The same study compared pharmacokinetics of desipramine when combined with sertraline. The impact of sertraline was modest, resulting in small and short-term increases in desipramine plasma concentrations (Preskorn et al, 1994).
c) A 75-year-old female experienced symptomatic increases in her desipramine serum concentrations when fluoxetine was added. Desipramine serum levels ranged from 109 to 150 ng/mL with oral doses of 300 mg at bedtime prior to fluoxetine therapy. Following the addition of oral fluoxetine 20 mg daily to the regimen, the desipramine serum level increased to 212 ng/mL within five days. The fluoxetine dose was increased to 40 mg/day three days later, and the desipramine serum level was 419 ng/mL after four days. A worsening of depression and severe fatigue coincided with the increases in desipramine serum levels. Withdrawal of fluoxetine and reduction in the desipramine dose to 200 mg daily reduced the desipramine serum level to 231 ng/mL within two weeks (Bell & Cole, 1988).
d) A 33-year-old depressed male developed adverse effects of dry mouth, tinnitus, and difficulties with alertness and memory while receiving fluoxetine 40 mg daily and desipramine 150 mg daily for five weeks; fluoxetine was discontinued and the blood levels of desipramine decreased from 938 to 48 ng/mL with resolution of clinical symptoms (Goodnick, 1989).
e) A 39-year-old female experienced symptomatic increases in her desipramine levels with concomitant fluoxetine therapy. Prior to fluoxetine therapy, the patient's measured levels of desipramine had ranged from 148 to 160 ng/mL on a regimen of 300 mg daily. Five weeks after the addition of fluoxetine 20 mg daily, she reported anticholinergic symptoms, sedation, and confusion with a desipramine level of 527 ng/mL. The desipramine dose was lowered to 200 mg/day; eleven days later, the level was 244 ng/mL; the patient reported decreased energy, impaired short-term memory, and some "garbled" speech, as well as an episode of nausea, dizziness, and syncope. The desipramine dose was reduced to 50 mg/day; the adverse effects resolved in six days. Eight days later, the desipramine level was 122 ng/mL (Downs et al, 1989).
f) Concomitant administration of fluoxetine and desipramine was reported to result in an increased desipramine level and new onset of delirium in a 69-year-old male within 10 days of the addition of fluoxetine to the patient's regimen (Preskorn et al, 1990).

3.5.1.BF 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 PROZAC(R) oral capsules, delayed-release capsules, solution, 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 (Prod Info PROZAC(R) oral capsules, delayed-release capsules, solution, 2008).
3) Severity: major
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: When fluoxetine and an anticoagulant are given concurrently, monitor patient for signs of increased bleeding. Patients who are taking warfarin should be monitored closely for altered anticoagulant effects, including increased bleeding, when fluoxetine therapy is initiated or discontinued (Prod Info PROZAC(R) oral capsules, delayed-release capsules, solution, 2008).
7) Probable Mechanism: unknown
8) Literature Reports
a) Fluoxetine is thought to inhibit the cytochrome P450 2C9 isoenzyme (CYP2C9). This is the enzyme by which the more potent warfarin isomer, S-warfarin, is metabolized (Riesenman, 1995). In addition, both fluoxetine and warfarin are tightly bound to albumin. In combination, the possibility for protein-binding displacement of either drug is present (Prod Info Coumadin(R), 1999).
b) 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).

c) 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).

d) In 6 reported cases, INR increased during combined fluoxetine and warfarin therapy. In a seventh case, severe bruising of the lower legs occurred in a woman initially treated with fluoxetine and, secondarily, started on warfarin (Woolfrey et al, 1993; Claire et al, 1991).

e) An 83-year-old man died from cerebral hemorrhage secondary to increased warfarin concentrations. The patient had been taking warfarin 30 mg per week for atrial fibrillation with a target INR between 2 and 3. The patient's other drugs included lisinopril, furosemide, potassium, digoxin, and acetaminophen. After being seen for symptoms of depression, anxiety, and insomnia, the patient was given fluoxetine 20 mg per day and diazepam 2.5 mg 3 to 4 times per day. Eight days later, the patient's INR increased to 4.8, and the dose of warfarin was decreased to 27.5 mg per week. The patient was later seen for symptoms of drug delirium, including confusion, incoherence, and speaking irrationally. At this point, the INR was 3.64 and fluoxetine was discontinued. The next day the patient presented to the hospital with left-sided weakness and later died from complications of a large interparenchymal hemorrhage. The authors proposed that the addition of fluoxetine to the patient's regimen resulted in increased serum levels of both warfarin and diazepam, resulting in delirium and loss of anticoagulant control (Dent & Orrock, 1997).

3.5.1.BG 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.BH 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 fluoxetine, 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, 1991x). Dexfenfluramine should not be used in combination with fluoxetine (Prod Info Redux(R), 1997).

3) Severity: major

4) Onset: rapid

5) Substantiation: theoretical

6) Clinical Management: Concurrent use of dexfenfluramine and fluoxetine 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 fluoxetine or other serotonin specific reuptake inhibitors.
7) Probable Mechanism: additive serotonergic effects

3.5.1.BI 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.BJ Dextromethorphan
1) Interaction Effect: possible dextromethorphan toxicity (nausea, vomiting, blurred vision, hallucinations) or serotonin syndrome (hypertension, hyperthermia, myoclonus, mental status changes)
2) Summary: Fluoxetine strongly inhibits hepatic cytochrome P450IID6 (CYP2D6), the isoenzyme known to catalyze dextromethorphan metabolism (Stevens & Wrighton, 1993). Fluoxetine inhibits dextromethorphan metabolism (Otton et al, 1993a). With concomitant administration, it is possible that both agents may competitively inhibit each others metabolism, increasing serum levels of both drugs. Serotonin syndrome, characterized by restlessness, myoclonus, and changes in mental status (Sternbach, 1991e), is a possibility with the combined use of dextromethorphan and serotonergic agents. There have been two case reports of serotonin syndrome associated with concurrent paroxetine and dextromethorphan therapy (Skop et al, 1994a; Skop et al, 1995).
3) Severity: major
4) Onset: rapid
5) Substantiation: theoretical
6) Clinical Management: Caution patients taking fluoxetine 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) Therapeutic doses of fluoxetine were found to potently inhibit the metabolism of dextromethorphan, a marker of cytochrome P450 2D6 (CYP2D6) function (Otton et al, 1993). A 30 mg dose of dextromethorphan hydrobromide was given to 19 patients taking fluoxetine for clinical depression. In addition, dextromethorphan was given to 208 known extensive metabolizers and to 15 known poor metabolizers (those lacking CYP2D6 function). While dextromethorphan metabolism was reduced in the fluoxetine-treated patients, it was more significantly affected in the poor metabolizer controls. This indicates that patients who are slow metabolizers may be at greater risk for experiencing dextromethorphan toxicity when used in combination with fluoxetine.
b) A 32-year-old woman experienced visual hallucinations after concomitant use of fluoxetine and dextromethorphan (Achamallah, 1992). She had taken fluoxetine 20 mg daily for 18 days prior to taking two doses of dextromethorphan. After each dose of dextromethorphan she experienced distorted vision and saw bright colors. These effects continued for six to eight hours. Fluoxetine was withdrawn and she had no more hallucinations.
c) A 51-year old male patient with vascular disease following concurrent use of dextromethorphan and paroxetine developed serotonin syndrome. 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.BK Diazepam

1) Interaction Effect: higher serum concentrations of diazepam

2) Summary: During coadministration of fluoxetine with diazepam, the fluoxetine area under the concentration-time curve (AUC) was increased, but this was not associated with increased impairment (Lemberger et al, 1988a). Conversely, a controlled study observed significant decreases in psychomotor performance when diazepam was added to fluoxetine (Moskowitz & Burns, 1988a). The metabolism of diazepam is mediated by several P450 enzymes which may be inhibited by fluoxetine (Riesenman, 1995c; Shen, 1995a; Nemeroff et al, 1996b). Further case reports or controlled studies are necessary to appropriately define the pharmacokinetic effects as well as the degree of psychomotor impairment resulting from coadministration of these two agents.

3) Severity: minor

4) Onset: delayed

5) Substantiation: probable

6) Clinical Management: Although dose adjustments are thought not to be necessary when fluoxetine and diazepam are given concomitantly, monitor patients for signs and symptoms of excessive diazepam concentrations (sedation, dizziness, ataxia, decreased cognition or motor performance). In some patients, such as the elderly, it may be safer to give a lower dose of diazepam during combination therapy.

7) Probable Mechanism: inhibition of the hepatic P450 metabolism of diazepam

8) Literature Reports

a) Coadministration of fluoxetine and diazepam resulted in prolonged half-life, reduced plasma clearance, and increased AUC for diazepam. Oral diazepam 10 mg was given alone, after a single dose of oral fluoxetine 60 mg, and after 8 daily doses of fluoxetine 60 mg. Psychometric data demonstrated no effect of fluoxetine on the psychomotor response to diazepam. Thus, although fluoxetine decreases the clearance of diazepam, this does not appear to be of clinical relevance and dosing adjustments are not required during combined therapy (Lemberger et al, 1988).

b) Combined therapy with diazepam and fluoxetine caused an increase in the half-life of the metabolite desmethyldiazepam, but this did not appear to be clinically significant. Diazepam had no effect on the disposition of fluoxetine or norfluoxetine (Lemberger et al, 1985).

c) To date, in-vitro studies have found that diazepam demethylation occurs via P450 1A2, 3A4, 2C9, and 2C19. Evidence with drugs known to be metabolized by these enzymes suggests that fluoxetine strongly inhibits 2C9, moderately inhibits 2C19 and 3A4, and has no effect on 1A2 (Riesenman, 1995b; Nemeroff et al, 1996a; Shen, 1995).

d) In a controlled study of performance of 90 healthy volunteers, the effects of fluoxetine, amitriptyline, or placebo with diazepam were studied. Volunteers received one of six treatment combinations, and were given performance tests including a critical tracking test, divided attention test, visual search task, memory test, and vigilance test. Fluoxetine alone did not affect performance, but when fluoxetine was added to diazepam, there was a significant increase in the divided attention tracking error and significant impairment on the vigilance test. For amitriptyline alone and during coadministration with diazepam, significant impairment was observed. On most tests, the combination of amitriptyline and diazepam resulted in additive effects. The authors concluded that the combination of diazepam and an antidepressant may increase an individual's risk during driving and while performing other complex tasks (Moskowitz & Burns, 1988).

e) A case was reported in which an 83-year old man developed delirium after the addition of fluoxetine and diazepam to a regimen of warfarin, lisinopril, furosemide, potassium, digoxin, and acetaminophen. The patient was given fluoxetine 20 mg per day and diazepam 2.5 mg three to four times per day for symptoms of depression, anxiety, and insomnia. The patient then developed symptoms of drug delirium, including confusion, incoherence, and irrational speaking. The patient also developed an increased international normalized ratio (INR), after which fluoxetine was discontinued. The patient presented to the hospital with left-sided weakness and later died from complications of a large interparenchymal hemorrhage. The authors proposed that the addition of fluoxetine to the patient's regimen resulted in increased serum levels of both warfarin and diazepam, resulting in drug-induced delirium and loss of anticoagulant control (Dent & Orrock, 1997a).

3.5.1.BL Dibenzepin

1) Interaction Effect: tricyclic antidepressant toxicity (dry mouth, urinary retention, sedation) and an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)

2) Summary: Tricyclic antidepressants (TCAs) and fluoxetine have been shown to prolong the QTc interval at the recommended therapeutic dose (Prod Info Prozac(R), 2001h; Marshall & Forker, 1982). Even though no formal drug interaction studies have been done which demonstrate QT prolongation, the coadministration of tricyclic antidepressants and other drugs known to prolong the QTc interval, such as fluoxetine, is not recommended (Prod Info Elavil(R), 1999). In addition, concurrent use of fluoxetine and TCAs such as desipramine, nortriptyline, and imipramine has resulted in significant increases in TCA concentrations (Preskorn et al, 1994a; Preskorn et al, 1994a; Aranow et al, 1989a; Downs et al, 1989a; Goodnick, 1989a; Bell & Cole, 1988a).

3) Severity: major

4) Onset: unspecified

5) Substantiation: probable

6) Clinical Management: The concurrent administration of fluoxetine and a tricyclic antidepressant is not recommended.
7) Probable Mechanism: decreased tricyclic antidepressant metabolism; additive effects on QT prolongation
8) Literature Reports
a) Fluoxetine increased the level of tricyclic antidepressants (nortriptyline, imipramine, desipramine) in 4 patients. After the addition of fluoxetine, the ratio of antidepressant level to dose increased by 109% to 486% in the patients. Three patients developed clinical symptoms (anticholinergic effects, constipation, urinary hesitancy, sedation, unstable gait) as a result of the increased levels (Aranow et al, 1989).
b) Fluoxetine statistically and clinically significantly increased desipramine concentrations in 18 healthy subjects. When fluoxetine (20 mg daily) was added to desipramine (50 mg daily), the mean maximum concentration of desipramine increased by 278% and the area under the concentration-time curve increased by 342%. Desipramine trough concentrations continued to be 198% above baseline three weeks after fluoxetine was discontinued. The same study compared pharmacokinetics of desipramine when combined with sertraline. The impact of sertraline was modest, resulting in small and short-term increases in desipramine plasma concentrations (Preskorn et al, 1994).
c) A 75-year-old female experienced symptomatic increases in her desipramine serum concentrations when fluoxetine was added. Desipramine serum levels ranged from 109 to 150 ng/mL with oral doses of 300 mg at bedtime prior to fluoxetine therapy. Following the addition of oral fluoxetine 20 mg daily to the regimen, the desipramine serum level increased to 212 ng/mL within five days. The fluoxetine dose was increased to 40 mg/day three days later, and the desipramine serum level was 419 ng/mL after four days. A worsening of depression and severe fatigue coincided with the increases in desipramine serum levels. Withdrawal of fluoxetine and reduction in the desipramine dose to 200 mg daily reduced the desipramine serum level to 231 ng/mL within two weeks (Bell & Cole, 1988).
d) A 33-year-old depressed male developed adverse effects of dry mouth, tinnitus, and difficulties with alertness and memory while receiving fluoxetine 40 mg daily and desipramine 150 mg daily for five weeks; fluoxetine was discontinued and the blood levels of desipramine decreased from 938 to 48 ng/mL with resolution of clinical symptoms (Goodnick, 1989).
e) A 39-year-old female experienced symptomatic increases in her desipramine levels with concomitant fluoxetine therapy. Prior to fluoxetine therapy, the patient's measured levels of desipramine had ranged from 148 to 160 ng/mL on a regimen of 300 mg daily. Five weeks after the addition of fluoxetine 20 mg daily, she reported anticholinergic symptoms, sedation, and confusion with a desipramine level of 527 ng/mL. The desipramine dose was lowered to 200 mg/day; eleven days later, the level was 244 ng/mL; the patient reported decreased energy, impaired short-term memory, and some "garbled" speech, as well as an episode of nausea, dizziness, and syncope. The desipramine dose was reduced to 50 mg/day; the adverse effects resolved in six days. Eight days later, the desipramine level was 122 ng/mL (Downs et al, 1989).
f) Concomitant administration of fluoxetine and desipramine was reported to result in an increased desipramine level and new onset of delirium in a 69-year-old male within 10 days of the addition of fluoxetine to the patient's regimen (Preskorn et al, 1990).

3.5.1.BM 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.BN 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 PROZAC(R) oral capsules, delayed-release capsules, solution, 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 (Prod Info PROZAC(R) oral capsules, delayed-release capsules, solution, 2008).
3) Severity: major
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: When fluoxetine and an anticoagulant are given concurrently, monitor patient for signs of increased bleeding. Patients who are taking warfarin should be monitored closely for altered anticoagulant effects, including increased bleeding, when fluoxetine therapy is initiated or discontinued (Prod Info PROZAC(R) oral capsules, delayed-release capsules, solution, 2008).
7) Probable Mechanism: unknown
8) Literature Reports

a) Fluoxetine is thought to inhibit the cytochrome P450 2C9 isoenzyme (CYP2C9). This is the enzyme by which the more potent warfarin isomer, S-warfarin, is metabolized (Riesenman, 1995). In addition, both fluoxetine and warfarin are tightly bound to albumin. In combination, the possibility for protein-binding displacement of either drug is present (Prod Info Coumadin(R), 1999).

b) 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).

c) 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).

d) In 6 reported cases, INR increased during combined fluoxetine and warfarin therapy. In a seventh case, severe bruising of the lower legs occurred in a woman initially treated with fluoxetine and, secondarily, started on warfarin (Woolfrey et al, 1993; Claire et al, 1991).

e) An 83-year-old man died from cerebral hemorrhage secondary to increased warfarin concentrations. The patient had been taking warfarin 30 mg per week for atrial fibrillation with a target INR between 2 and 3. The patient's other drugs included lisinopril, furosemide, potassium, digoxin, and acetaminophen. After being seen for symptoms of depression, anxiety, and insomnia, the patient was given fluoxetine 20 mg per day and diazepam 2.5 mg 3 to 4 times per day. Eight days later, the patient's INR increased to 4.8, and the dose of warfarin was decreased to 27.5 mg per week. The patient was later seen for symptoms of drug delirium, including confusion, incoherence, and speaking irrationally. At this point, the INR was 3.64 and fluoxetine was discontinued. The next day the patient presented to the hospital with left-sided weakness and later died from complications of a large interparenchymal hemorrhage. The authors proposed that the addition of fluoxetine to the patient's regimen resulted in increased serum levels of both warfarin and diazepam, resulting in delirium and loss of anticoagulant control (Dent & Orrock, 1997).

3.5.1.BO 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.BP Digitoxin
1) Interaction Effect: an increased risk of digitoxin toxicity (nausea, vomiting, arrhythmias)
2) Summary: The administration of fluoxetine to a patient taking digitoxin, also tightly bound to plasma protein, may cause a shift in plasma concentrations of digitoxin (Prod Info Prozac(R), 1999c).
3) Severity: moderate
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: Patients receiving fluoxetine and digitoxin therapy concomitantly should be monitored for increasing levels of digitoxin, along with signs and symptoms of digitoxin toxicity.
7) Probable Mechanism: unknown

3.5.1.BQ Digoxin
1) Interaction Effect: an increased risk of digoxin toxicity (nausea, vomiting, arrhythmias)
2) Summary: One case report describes a 93-year-old female stabilized on digoxin who experienced toxic levels of digoxin after fluoxetine had been added to her regimen for depression. Rechallenge with fluoxetine again caused her digoxin levels to increase dramatically. While the mechanism of this interaction is not clear, it could be related to displacement of digoxin from binding sites or reduced clearance of digoxin (Leibovitz et al, 1998a).
3) Severity: moderate
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: Patients receiving fluoxetine and digoxin therapy concomitantly should be monitored for increasing levels of digoxin, along with signs and symptoms of digoxin toxicity, including anorexia.
7) Probable Mechanism: unknown
8) Literature Reports
a) Digoxin 0.125 mg daily was being administered to a 93-year-old female for congestive heart failure and paroxysmal atrial fibrillation. Digoxin levels ranged from 1.0 to 1.4 nmol/L during the two months preceding the initiation of fluoxetine 10 mg daily. Within one week, the patient complained of anorexia. Her digoxin level measured 4.2 nmol/L, while renal function and potassium levels remained unchanged. Both digoxin and fluoxetine were discontinued, and her digoxin level returned to normal in five days with resolution of the anorexia. During the next three weeks her digoxin serum levels ranged from 0.9 nmol/L to 1.4 nmol/L. Because the symptoms of depression persisted, fluoxetine was again initiated at 10 mg daily and the digoxin serum level was closely monitored. After two days of fluoxetine therapy, the digoxin level increased to 2.0 nmol/L, and after four days it was 2.8 nmol/L. Renal function remained unchanged, as did serum electrolytes. The patient again experienced anorexia, and treatment with fluoxetine was discontinued (Leibovitz et al, 1998).

3.5.1.BR Dihydroergotamine
1) Interaction Effect: an increased risk of ergotism (nausea, vomiting, vasospastic ischemia)
2) Summary: Because of the potential for serious toxicity including vasospasm that can occur with increased plasma concentrations of ergot derivatives, the concurrent use of fluoxetine and ergot derivatives is contraindicated. Fluoxetine and ergot derivatives are both metabolized by cytochrome P450 3A4 enzymes, and the competition for metabolism could result in an increased plasma concentration of the ergot derivative (Prod Info Cafergot(R), 2002).
3) Severity: contraindicated
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: The concurrent use of fluoxetine and ergot derivatives is contraindicated.

7) Probable Mechanism: inhibition of cytochrome P450 3A4- mediated ergot metabolism by fluoxetine

3.5.1.BS 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.BT 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.BU Disopyramide

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Even though no formal drug interaction studies have been done, the coadministration of Class Ia antiarrhythmics and other drugs known to prolong the QTc interval is not recommended (Prod Info Quinaglute Dura-tabs(R), 1999). Fluoxetine has demonstrated QT prolongation at therapeutic doses (Prod Info Prozac(R), 2001z).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of class Ia antiarrhythmic agents and agents that prolong the QT interval, such as fluoxetine, is not recommended.
7) Probable Mechanism: additive effects on QT prolongation

3.5.1.BV Dofetilide

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Even though no formal drug interaction studies have been done, the coadministration of Class III antiarrhythmics and other drugs known to prolong the QTc interval is not recommended (Allen et al, 2002; Prod Info Tikosyn(TM) dofetilide capsules, 1999; Prod Info Corvert(R), 1998). Fluoxetine has been shown to prolong the QTc interval at the recommended therapeutic dose (Prod Info Prozac(R), 2001a).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of class III antiarrhythmic agents and agents that

prolong the QT interval, such as fluoxetine, is not recommended.
7) Probable Mechanism: additive effects on QT prolongation

3.5.1.BW Dolasetron

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Though citing no data, the manufacturer of dolasetron recommends caution if dolasetron is administered with another drug which can prolong the QTc interval (Prod Info Anzemet(R), 1997). Fluoxetine has been shown to prolong the QTc interval at the recommended therapeutic dose (Prod Info Prozac(R), 2001y).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of fluoxetine and dolasetron is not recommended.
7) Probable Mechanism: additive effects on QT prolongation

3.5.1.BX Doxepin

1) Interaction Effect: tricyclic antidepressant toxicity (dry mouth, urinary retention, sedation) and an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Tricyclic antidepressants (TCAs) and fluoxetine have been shown to prolong the QTc interval at the recommended therapeutic dose (Prod Info Prozac(R), 2001h; Marshall & Forker, 1982). Even though no formal drug interaction studies have been done which demonstrate QT prolongation, the coadministration of tricyclic antidepressants and other drugs known to prolong the QTc interval, such as fluoxetine, is not recommended (Prod Info Elavil(R), 1999). In addition, concurrent use of fluoxetine and TCAs such as desipramine, nortriptyline, and imipramine has resulted in significant increases in TCA concentrations (Preskorn et al, 1994a; Preskorn et al, 1994a; Aranow et al, 1989a; Downs et al, 1989a; Goodnick, 1989a; Bell & Cole, 1988a).
3) Severity: major
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: The concurrent administration of fluoxetine and a tricyclic antidepressant is not recommended.
7) Probable Mechanism: decreased tricyclic antidepressant metabolism; additive effects on QT prolongation
8) Literature Reports

a) Fluoxetine increased the level of tricyclic antidepressants (nortriptyline, imipramine, desipramine) in 4 patients. After the addition of fluoxetine, the ratio of antidepressant level to dose increased by 109% to 486% in the patients. Three patients developed clinical symptoms (anticholinergic effects, constipation, urinary hesitancy, sedation, unstable gait) as a result of the increased levels (Aranow et al, 1989).

b) Fluoxetine statistically and clinically significantly increased desipramine concentrations in 18 healthy subjects. When fluoxetine (20 mg daily) was added to desipramine (50 mg daily), the mean maximum concentration of desipramine increased by 278% and the area under the concentration-time curve increased by 342%. Desipramine trough concentrations continued to be 198% above baseline three weeks after fluoxetine was discontinued. The same study compared pharmacokinetics of desipramine when combined with sertraline. The impact of sertraline was modest, resulting in small and short-term increases in desipramine plasma concentrations (Preskorn et al, 1994).

c) A 75-year-old female experienced symptomatic increases in her desipramine serum concentrations when fluoxetine was added. Desipramine serum levels ranged from 109 to 150 ng/mL with oral doses of 300 mg at bedtime prior to fluoxetine therapy. Following the addition of oral fluoxetine 20 mg daily to the regimen, the desipramine serum level increased to 212 ng/mL within five days. The fluoxetine dose was increased to 40 mg/day three days later, and the desipramine serum level was 419 ng/mL after four days. A worsening of depression and severe fatigue coincided with the increases in desipramine serum levels. Withdrawal of fluoxetine and reduction in the desipramine dose to 200 mg daily reduced the desipramine serum level to 231 ng/mL within two weeks (Bell & Cole, 1988).

d) A 33-year-old depressed male developed adverse effects of dry mouth, tinnitus, and difficulties with alertness and memory while receiving fluoxetine 40 mg daily and desipramine 150 mg daily for five weeks; fluoxetine was discontinued and the blood levels of desipramine decreased from 938 to 48 ng/mL with resolution of clinical symptoms (Goodnick, 1989).

e) A 39-year-old female experienced symptomatic increases in her desipramine levels with concomitant fluoxetine therapy. Prior to fluoxetine therapy, the patient's measured levels of desipramine had ranged from 148 to 160 ng/mL on a regimen of 300 mg daily. Five weeks after the addition of fluoxetine 20 mg daily, she reported anticholinergic symptoms, sedation, and confusion with a desipramine level of 527 ng/mL. The desipramine dose was lowered to 200 mg/day; eleven days later, the level was 244 ng/mL; the patient reported decreased energy, impaired short-term memory, and some "garbled" speech, as well as an episode of nausea, dizziness, and syncope. The desipramine dose was reduced to 50 mg/day; the adverse effects resolved in six days. Eight days later, the desipramine level was 122 ng/mL (Downs et al, 1989).

f) Concomitant administration of fluoxetine and desipramine was reported to result in an increased

desipramine level and new onset of delirium in a 69-year-old male within 10 days of the addition of fluoxetine to the patient's regimen (Preskorn et al, 1990).

3.5.1.BY Droperidol

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Droperidol has been shown to prolong the QTc interval at the recommended therapeutic dose. Even though no formal drug interaction studies have been done, the coadministration of droperidol and other drugs known to prolong the QTc interval, including fluoxetine is not recommended (Prod Info Inapsine(TM), 2001; Prod Info Prozac(R), 2001ab).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of droperidol and fluoxetine is not recommended.
7) Probable Mechanism: additive cardiac effects

3.5.1.BZ 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.CA Duloxetine

1) Interaction Effect: increased duloxetine and fluoxetine serum concentrations and an increased risk of serotonin syndrome
2) Summary: Duloxetine is a selective serotonin and norepinephrine reuptake inhibitor (SSNRI). The concomitant use of duloxetine with fluoxetine, an SSRI, is not recommended due to the potential for serotonin syndrome. In addition, the coadministration of duloxetine with fluoxetine is likely to increase the bioavailability of either drug, increasing the risk of serious adverse events. Duloxetine and fluoxetine are both substrates for, and moderately potent inhibitors of CYP2D6. Coadministration of duloxetine 40 mg once daily with another SSRI (the potent CYP2D6 inhibitor paroxetine 20 mg once daily) resulted in a 60% increase in the serum concentration of duloxetine (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 fluoxetine is not recommended due to the potential for development of serotonin syndrome. Additionally, concomitant use has resulted in increased duloxetine and fluoxetine serum levels (Prod Info CYMBALTA(R) delayed-release oral capsules, 2008).
7) Probable Mechanism: fluoxetine inhibition of CYP2D6-mediated duloxetine metabolism; additive serotonergic effects

3.5.1.CB 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.CC Enflurane
1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Even though no formal drug interaction studies have been done, enflurane should be coadministered cautiously with other drugs which are also known to prolong the QTc interval, including fluoxetine (Owens, 2001c; Prod Info Prozac(R), 2001n).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of enflurane with other agents that can prolong the QT interval, such as fluoxetine, is not recommended.
7) Probable Mechanism: additive effects on QT prolongation

3.5.1.CD 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 PROZAC(R) oral capsules, delayed-release capsules, solution, 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 (Prod Info PROZAC(R) oral capsules, delayed-release capsules, solution, 2008).
3) Severity: major
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: When fluoxetine and an anticoagulant are given concurrently, monitor patient for signs of increased bleeding. Patients who are taking warfarin should be monitored closely for altered anticoagulant effects, including increased bleeding, when fluoxetine therapy is initiated or discontinued (Prod Info PROZAC(R) oral capsules, delayed-release capsules, solution, 2008).
7) Probable Mechanism: unknown
8) Literature Reports
a) Fluoxetine is thought to inhibit the cytochrome P450 2C9 isoenzyme (CYP2C9). This is the enzyme by which the more potent warfarin isomer, S-warfarin, is metabolized (Riesenman, 1995). In addition, both fluoxetine and warfarin are tightly bound to albumin. In combination, the possibility for protein-binding displacement of either drug is present (Prod Info Coumadin(R), 1999).
b) 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).
c) 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).

d) In 6 reported cases, INR increased during combined fluoxetine and warfarin therapy. In a seventh case, severe bruising of the lower legs occurred in a woman initially treated with fluoxetine and, secondarily, started on warfarin (Woolfrey et al, 1993; Claire et al, 1991).

e) An 83-year-old man died from cerebral hemorrhage secondary to increased warfarin concentrations. The patient had been taking warfarin 30 mg per week for atrial fibrillation with a target INR between 2 and 3. The patient's other drugs included lisinopril, furosemide, potassium, digoxin, and acetaminophen. After being seen for symptoms of depression, anxiety, and insomnia, the patient was given fluoxetine 20 mg per day and diazepam 2.5 mg 3 to 4 times per day. Eight days later, the patient's INR increased to 4.8, and the dose of warfarin was decreased to 27.5 mg per week. The patient was later seen for symptoms of drug delirium, including confusion, incoherence, and speaking irrationally. At this point, the INR was 3.64 and fluoxetine was discontinued. The next day the patient presented to the hospital with left-sided weakness and later died from complications of a large interparenchymal hemorrhage. The authors proposed that the addition of fluoxetine to the patient's regimen resulted in increased serum levels of both warfarin and diazepam, resulting in delirium and loss of anticoagulant control (Dent & Orrock, 1997).

3.5.1.CE 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.CF 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.CG Ergoloid Mesylates

1) Interaction Effect: an increased risk of ergotism (nausea, vomiting, vasospastic ischemia)

2) Summary: Because of the potential for serious toxicity including vasospasm that can occur with increased plasma concentrations of ergot derivatives, the concurrent use of fluoxetine and ergot derivatives is contraindicated. Fluoxetine and ergot derivatives are both metabolized by cytochrome P450 3A4 enzymes, and the competition for metabolism could result in an increased plasma concentration of the ergot derivative (Prod Info Cafergot(R), 2002).

3) Severity: contraindicated

4) Onset: unspecified

5) Substantiation: probable

6) Clinical Management: The concurrent use of fluoxetine and ergot derivatives is contraindicated.

7) Probable Mechanism: inhibition of cytochrome P450 3A4- mediated ergot metabolism by fluoxetine

3.5.1.CH Ergonovine

1) Interaction Effect: an increased risk of ergotism (nausea, vomiting, vasospastic ischemia)
2) Summary: Because of the potential for serious toxicity including vasospasm that can occur with increased plasma concentrations of ergot derivatives, the concurrent use of fluoxetine and ergot derivatives is contraindicated. Fluoxetine and ergot derivatives are both metabolized by cytochrome P450 3A4 enzymes, and the competition for metabolism could result in an increased plasma concentration of the ergot derivative (Prod Info Cafergot(R), 2002).
3) Severity: contraindicated
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: The concurrent use of fluoxetine and ergot derivatives is contraindicated.
7) Probable Mechanism: inhibition of cytochrome P450 3A4- mediated ergot metabolism by fluoxetine

3.5.1.CI Ergotamine
1) Interaction Effect: an increased risk of ergotism (nausea, vomiting, vasospastic ischemia)
2) Summary: Because of the potential for serious toxicity including vasospasm that can occur with increased plasma concentrations of ergot derivatives, the concurrent use of fluoxetine and ergot derivatives is contraindicated. Fluoxetine and ergot derivatives are both metabolized by cytochrome P450 3A4 enzymes, and the competition for metabolism could result in an increased plasma concentration of the ergot derivative (Prod Info Cafergot(R), 2002).
3) Severity: contraindicated
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: The concurrent use of fluoxetine and ergot derivatives is contraindicated.
7) Probable Mechanism: inhibition of cytochrome P450 3A4- mediated ergot metabolism by fluoxetine

3.5.1.CJ Erythromycin
1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Erythromycin significantly increased the mean QTc interval versus baseline in a retrospective study of 49 patients (Oberg & Bauman, 1995a). Erythromycin has demonstrated QTc prolongation in combination with other drugs that prolong the QT interval (Prod Info PCE(R), 1997). Fluoxetine has been associated with QT prolongation (Prod Info Prozac(R), 2003a). Caution is advised with coadministration of drugs that potentially prolong the QTc interval.
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Caution is advised if erythromycin and fluoxetine are used concomitantly. Monitor QT interval at baseline and periodically during treatment.
7) Probable Mechanism: additive effects on QT prolongation
8) Literature Reports
a) Erythromycin significantly increased the QTc interval compared with baseline in a retrospective study of 49 patients. The erythromycin dose was 500 milligrams or 1 gram four times daily, with a mean of 15 doses received. Patients (n equal to 9) who received 60 mg/kg/day or more all developed increases in QT interval of 15% or greater. For all patients, the mean QTc interval increased from 432 milliseconds (msec) at baseline to 483 msec (p less than 0.01). In patients with delayed repolarization at baseline (n equal to 9), the QTc interval increased from 473 msec to 525 msec (p less than 0.01). In patients with heart disease (n equal to 30), all experienced an increase in QTc interval (mean of 15%), compared with an increase of 8% in patients without heart disease (p less than 0.05). In 5 patients (10%), the QTc interval was severely prolonged. One patient developed torsades de pointes attributed to erythromycin. Of 16 patients receiving cotrimoxazole concomitantly, 8 developed QT prolongation of 15% or greater (Oberg & Bauman, 1995).

3.5.1.CK 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.CL 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.CM 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.CN 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.CO 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.CP 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 fluoxetine, has the potential to cause serotonin syndrome (Schenck & Mahowald, 1996a). 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, 1991z). Until more data are available, fenfluramine should not be used in combination with fluoxetine.
3) Severity: major
4) Onset: rapid
5) Substantiation: theoretical
6) Clinical Management: Concurrent use of fenfluramine and fluoxetine 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 fluoxetine or other serotonin specific reuptake inhibitors.
7) Probable Mechanism: additive serotonergic effects

3.5.1.CQ 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.CR 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.CS Flecainide
1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Even though no formal drug interaction studies have been done, the coadministration of Class I antiarrhythmics and other drugs known to prolong the QTc interval is not recommended (Prod Info Tambocor(R) flecainide acetate, 1998). Fluoxetine has been shown to prolong the QTc interval at the recommended therapeutic dose (Prod Info Prozac(R), 2001w).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of class I antiarrhythmic agents and agents that prolong the QT interval, such as fluoxetine, is not recommended.
7) Probable Mechanism: additive effects on QT prolongation

3.5.1.CT 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.CU Fluconazole
1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Case reports have described QT prolongation and torsades de pointes associated with fluconazole (Khazan & Mathis, 2002; Wassmann et al, 1999). Fluoxetine has been shown to prolong the QTc interval at the recommended therapeutic dose (Prod Info Prozac(R), 2001q). Even though no formal drug interaction studies have been done, caution is advised if drugs known to prolong the QT interval are used concomitantly.
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Caution is advised if fluconazole and fluoxetine are used concomitantly.
7) Probable Mechanism: additive effects on QT prolongation

3.5.1.CV 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.CW 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 fluoxetine for depression. Upon discontinuation of fluoxetine, the parkinsonism resolved. A similar interaction has been observed when fluphenazine was given in combination with paroxetine or sertraline (Kurlan, 1998a).
3) Severity: moderate
4) Onset: delayed

5) Substantiation: probable
6) Clinical Management: Monitor patients receiving concurrent therapy with fluphenazine and fluoxetine for the development of drug-induced parkinsonism. Therapy with fluoxetine may need to be discontinued.
7) Probable Mechanism: inhibition of cytochrome P450-mediated fluphenazine metabolism by fluoxetine
8) Literature Reports
a) A 63-year-old female with chronic, multiple motor and vocal tics was successfully treated with fluphenazine 2.5 mg daily. When nortriptyline therapy for depression failed, the patient was started on fluoxetine 20 mg daily. After two weeks, she developed acute, severe parkinsonism manifesting as resting tremor, rigidity, bradykinesia, postural imbalance, and stooped posture. The parkinsonism resolved within three weeks of discontinuing the fluphenazine and the fluoxetine, but the tics reappeared (Kurlan, 1998).

3.5.1.CX 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.CY 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 PROZAC(R) oral capsules, delayed-release capsules, solution, 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 (Prod Info PROZAC(R) oral capsules, delayed-release capsules, solution, 2008).
3) Severity: major
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: When fluoxetine and an anticoagulant are given concurrently, monitor patient for signs of increased bleeding. Patients who are taking warfarin should be monitored closely for altered anticoagulant effects, including increased bleeding, when fluoxetine therapy is initiated or discontinued (Prod Info PROZAC(R) oral capsules, delayed-release capsules, solution, 2008).
7) Probable Mechanism: unknown
8) Literature Reports
a) Fluoxetine is thought to inhibit the cytochrome P450 2C9 isoenzyme (CYP2C9). This is the enzyme by which the more potent warfarin isomer, S-warfarin, is metabolized (Riesenman, 1995). In addition, both fluoxetine and warfarin are tightly bound to albumin. In combination, the possibility for protein-binding displacement of either drug is present (Prod Info Coumadin(R), 1999).
b) 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).

c) 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).

d) In 6 reported cases, INR increased during combined fluoxetine and warfarin therapy. In a seventh case, severe bruising of the lower legs occurred in a woman initially treated with fluoxetine and, secondarily, started on warfarin (Woolfrey et al, 1993; Claire et al, 1991).

e) An 83-year-old man died from cerebral hemorrhage secondary to increased warfarin concentrations. The patient had been taking warfarin 30 mg per week for atrial fibrillation with a target INR between 2 and 3. The patient's other drugs included lisinopril, furosemide, potassium, digoxin, and acetaminophen. After being seen for symptoms of depression, anxiety, and insomnia, the patient was given fluoxetine 20 mg per day and diazepam 2.5 mg 3 to 4 times per day. Eight days later, the patient's INR increased to 4.8, and the dose of warfarin was decreased to 27.5 mg per week. The patient was later seen for symptoms of drug delirium, including confusion, incoherence, and speaking irrationally. At this point, the INR was 3.64 and fluoxetine was discontinued. The next day the patient presented to the hospital with left-sided weakness and later died from complications of a large interparenchymal hemorrhage. The authors proposed that the addition of fluoxetine to the patient's regimen resulted in increased serum levels of both warfarin and diazepam, resulting in delirium and loss of anticoagulant control (Dent & Orrock, 1997).

3.5.1.CZ Foscarnet

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)

2) Summary: Foscarnet can prolong the QT interval in some patients, which may result in ventricular tachycardia, ventricular fibrillation, and torsades de pointes. Because fluoxetine may also prolong the QT interval and increase the risk of arrhythmias, the concurrent administration of foscarnet and fluoxetine is not recommended (Prod Info Prozac(R), 2001t; Prod Info Foscavir(R), 1998).

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: The concurrent administration of foscarnet and fluoxetine is not recommended.

7) Probable Mechanism: additive cardiac effects

3.5.1.DA Fosphenytoin

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

2) Summary: Fosphenytoin is a prodrug of phenytoin and the same interactions that occur with phenytoin are expected to occur with fosphenytoin (Prod Info Cerebyx(R), 1999). Several case reports indicate that concurrent use of fluoxetine and phenytoin can result in significantly increased phenytoin serum levels leading to toxicity (FDA, 1994c; Jalil, 1992c; Woods et al, 1994a). Alternatively, patients who are stabilized on fluoxetine and phenytoin therapy may experience subtherapeutic concentrations of phenytoin and loss of seizure control when fluoxetine is discontinued (Shad & Preskorn, 1999c).

3) Severity: moderate

4) Onset: delayed

5) Substantiation: established

6) Clinical Management: Monitor phenytoin serum levels with the addition of fluoxetine and periodically thereafter to assure stability; a lower fosphenytoin dosage may be required with concomitant therapy. Serum levels of phenytoin should be monitored following the discontinuation of fluoxetine; however, because of the long half-life of fluoxetine, decreases in phenytoin levels may not be clinically significant for a few weeks. Careful monitoring is required.

7) Probable Mechanism: decreased phenytoin metabolism

8) Literature Reports

a) Twenty-three reported cases of fluoxetine-phenytoin interactions that resulted in large increases in serum phenytoin levels and/or symptoms of phenytoin toxicity were evaluated. On the average, the adverse effects began within 2 weeks after fluoxetine was added to existing phenytoin therapy. The average increase in plasma levels in 9 evaluable cases was 161% (range 75 to 309%) and the maximum phenytoin serum concentration in 16 evaluable cases ranged from 22 to 53.5 mcg/mL

(therapeutic level, 10 to 20 mcg/mL) (FDA, 1994b).
b) An 84-year-old woman was stabilized on phenytoin 300 mg daily; after two months of treatment, fluoxetine 20 mg daily was added to her therapy and increased to 40 mg daily after 10 days (Jalil, 1992b). Within five days of starting fluoxetine, she developed vertigo, gait ataxia, diplopia, and altered mental status; her phenytoin serum level had increased from 15 to 35 mcg/mL. Both phenytoin and fluoxetine were gradually reduced and the signs and symptoms of toxicity abated. Four weeks later she was rechallenged with the same dose of fluoxetine without a return of toxicity.
c) In another case, a 57-year-old woman who had been stabilized on phenytoin 400 mg/d for a year (serum level, 11.5 mcg/mL) was given fluoxetine 20 mg/d (Jalil, 1992b). Ten days later she developed vomiting, vertigo, trunk ataxia, limb dysmetria, and multidirectional nystagmus, and the phenytoin serum level was 47 mcg/mL. Fluoxetine was discontinued and all signs and symptoms of toxicity disappeared over a 3 week period. At 4 weeks post-fluoxetine, the phenytoin serum level was 20 mcg/mL.
d) A 42-year-old male with a history of grand mal seizures and aggressive behavior was receiving phenytoin 200 mg daily and carbamazepine 600 mg daily without resolution of his problems. His phenytoin level was 2.0 ng/mL and his dose was subsequently increased to 400 mg daily. Fluoxetine 20 mg daily was added for aggression, and the patient experienced resolution of his behavioral problems and a cessation of his seizure activity. The phenytoin level ranged between 10.9 ng/mL and 15.7 ng/mL during fluoxetine therapy. However, the patient discontinued fluoxetine on his own and after a month experienced a recurrence of problems. Phenytoin concentration was measured at 6.6 ng/mL six weeks after the discontinuation of fluoxetine, despite no change in his phenytoin dose. This case report illustrates the need for close monitoring of phenytoin levels when fluoxetine is initiated and discontinued, since subtherapeutic levels of phenytoin may result if doses of phenytoin are not readjusted following the cessation of fluoxetine (Shad & Preskorn, 1999b).

3.5.1.DB 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.DC 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.DD 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. Fluoxetine is a known inhibitor of CYP2D6. In a population pharmacokinetic analysis

using a database of 852 Alzheimer's disease patients, several drugs which inhibit CYP2D6, including fluoxetine (N=48), demonstrated a 25-33% decrease in galantamine clearance. The resulting plasma concentration increase of galantamine may warrant caution when it is coadministered with fluoxetine. 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 fluoxetine 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.DE Gemifloxacin
1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Gemifloxacin should be avoided in patients receiving fluoxetine. Gemifloxacin has the potential to prolong the QT interval in some patients (Prod Info Factive(R), 2003). Additive effects on QT prolongation may occur with the concomitant use of fluoxetine and gemifloxacin (Varriale, 2001b).
3) Severity: major
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: The concurrent administration of two drugs that prolong the QT interval, such as gemifloxacin and fluoxetine, is not recommended.
7) Probable Mechanism: additive effects on QT prolongation

3.5.1.DF 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.DG Halofantrine
1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Halofantrine can prolong the QT interval in some patients, which may result in ventricular tachycardia, ventricular fibrillation, and torsades de pointes. Because fluoxetine has demonstrated QT prolongation at therapeutic doses and may increase the risk of arrhythmias, the concurrent administration of

halofantrine with fluoxetine is not recommended (Prod Info Prozac(R), 2001i; Prod Info Halfan(R), 1998).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of halofantrine and fluoxetine is not recommended.
7) Probable Mechanism: additive cardiac effects

3.5.1.DH Haloperidol
1) Interaction Effect: haloperidol toxicity (pseudoparkinsonism, akathisia, tongue stiffness) and an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Haloperidol is associated with QTc prolongation and torsade de pointes (Hassaballa & Balk, 2003; Prod Info Haldol(R), 2001). Fluoxetine has been shown to prolong the QTc interval at the recommended therapeutic dose (Prod Info Prozac(R), 2001x). Caution is advised with coadministration of drugs that potentially prolong the QTc interval. In addition, several case reports describe development of extrapyramidal symptoms when fluoxetine and haloperidol were taken together, possibly due to inhibition of haloperidol metabolism (Benazzi, 1996a; Goff et al, 1991a; Stein, 1991a; Tate, 1989a).
3) Severity: major
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: The concurrent administration of fluoxetine and haloperidol is not recommended.
7) Probable Mechanism: inhibition of haloperidol metabolism by fluoxetine; theoretical additive effects on QT prolongation
8) Literature Reports
a) Fluoxetine increased plasma concentrations of haloperidol in 8 outpatients. Patients received fluoxetine 20 mg daily for 10 days with maintenance doses of haloperidol (average dose, 14 mg per day). After ten days, mean plasma concentrations of haloperidol had increased by 20%. Extrapyramidal symptom scores did not change appreciably after the addition of fluoxetine although one patient developed mild akathisia and another developed tremors. Extrapyramidal symptoms were expected to increase because of indirect inhibition of dopamine synthesis by fluoxetine (Goff et al, 1991).
b) A 39-year-old male experienced tardive dyskinesia with concomitant fluoxetine and haloperidol therapy. He was taking fluoxetine 20 mg daily for 2 months, then haloperidol 2 mg twice daily was started and later lowered to 1 mg per day. Five months later during a routine examination, tardive dyskinesia was diagnosed. The suggested mechanism was the down-regulation of dopamine activity (Stein, 1991).
c) A 39-year-old female developed tardive dyskinesia associated with concomitant fluoxetine and haloperidol therapy. She had been taking haloperidol 2 to 5 mg a day for two years (both with and without benztropine) with occasional mild, reversible extrapyramidal symptoms. Five days before stopping haloperidol, she started taking fluoxetine, which was increased over several days to 40 mg twice a day. After two weeks of fluoxetine she took haloperidol 5 mg each on two consecutive days (along with continuation of fluoxetine). She then experienced severe tongue stiffness, parkinsonism, and akathisia. Both fluoxetine and haloperidol were withdrawn. During the next seven days her extrapyramidal symptoms gradually disappeared (Tate, 1989).
d) A 40-year-old male developed urinary retention while taking fluoxetine and haloperidol. During a recurrence of depression, the patient was treated with fluoxetine 20 mg per day, alprazolam 1.5 mg per day, and haloperidol 1 mg per day. The patient had previously taken fluoxetine and alprazolam without incident. Approximately one week after beginning therapy, the patient developed difficulty in voiding urine, dilated pupils, dry mouth, palpitations, restlessness, hand tremors, and insomnia. After discontinuation of haloperidol and alprazolam, side effects ceased within one week. The authors postulated that the interaction was due to fluoxetine inhibition of cytochrome CYP2D6, which metabolizes haloperidol (Benazzi, 1996).

3.5.1.DI Halothane
1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Even though no formal drug interaction studies have been done, halothane should be administered cautiously with other drugs which are also known to prolong the QTc interval, including fluoxetine (Owens, 2001; Prod Info Prozac(R), 2001).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of halothane with other agents that can prolong the QT interval, such as fluoxetine, is not recommended.
7) Probable Mechanism: additive effect on QT interval

3.5.1.DJ 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 PROZAC(R) oral capsules, delayed-release capsules, solution, 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 (Prod Info PROZAC(R) oral capsules, delayed-release capsules, solution, 2008).

3) Severity: major

4) Onset: delayed

5) Substantiation: probable

6) Clinical Management: When fluoxetine and an anticoagulant are given concurrently, monitor patient for signs of increased bleeding. Patients who are taking warfarin should be monitored closely for altered anticoagulant effects, including increased bleeding, when fluoxetine therapy is initiated or discontinued (Prod Info PROZAC(R) oral capsules, delayed-release capsules, solution, 2008).

7) Probable Mechanism: unknown

8) Literature Reports

a) Fluoxetine is thought to inhibit the cytochrome P450 2C9 isoenzyme (CYP2C9). This is the enzyme by which the more potent warfarin isomer, S-warfarin, is metabolized (Riesenman, 1995). In addition, both fluoxetine and warfarin are tightly bound to albumin. In combination, the possibility for protein-binding displacement of either drug is present (Prod Info Coumadin(R), 1999).

b) 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).

c) 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).

d) In 6 reported cases, INR increased during combined fluoxetine and warfarin therapy. In a seventh case, severe bruising of the lower legs occurred in a woman initially treated with fluoxetine and, secondarily, started on warfarin (Woolfrey et al, 1993; Claire et al, 1991).

e) An 83-year-old man died from cerebral hemorrhage secondary to increased warfarin concentrations. The patient had been taking warfarin 30 mg per week for atrial fibrillation with a target INR between 2 and 3. The patient's other drugs included lisinopril, furosemide, potassium, digoxin, and acetaminophen. After being seen for symptoms of depression, anxiety, and insomnia, the patient was given fluoxetine 20 mg per day and diazepam 2.5 mg 3 to 4 times per day. Eight days later, the patient's INR increased to 4.8, and the dose of warfarin was decreased to 27.5 mg per week. The patient was later seen for symptoms of drug delirium, including confusion, incoherence, and speaking irrationally. At this point, the INR was 3.64 and fluoxetine was discontinued. The next day the patient presented to the hospital with left-sided weakness and later died from complications of a large interparenchymal hemorrhage. The authors proposed that the addition of fluoxetine to the patient's regimen resulted in increased serum levels of both warfarin and diazepam, resulting in delirium and loss of anticoagulant control (Dent & Orrock, 1997).

3.5.1.DK Hydroquinidine

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)

2) Summary: Even though no formal drug interaction studies have been done, the coadministration of Class Ia antiarrhythmics and other drugs known to prolong the QTc interval is not recommended (Prod Info Quinaglute Dura-tabs(R), 1999). Fluoxetine has demonstrated QT prolongation at therapeutic doses (Prod Info Prozac(R), 2001z).

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: The concurrent administration of class Ia antiarrhythmic agents and agents that prolong the QT interval, such as fluoxetine, is not recommended.
7) Probable Mechanism: additive effects on QT prolongation

3.5.1.DL 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.DM 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.DN Ibutilide
1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Even though no formal drug interaction studies have been done, the coadministration of Class III antiarrhythmics and other drugs known to prolong the QTc interval is not recommended (Allen et al, 2002; Prod Info Tikosyn(TM) dofetilide capsules, 1999; Prod Info Corvert(R), 1998). Fluoxetine has been shown to prolong the QTc interval at the recommended therapeutic dose (Prod Info Prozac(R), 2001a).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of class III antiarrhythmic agents and agents that prolong the QT interval, such as fluoxetine, is not recommended.

7) Probable Mechanism: additive effects on QT prolongation

3.5.1.DO Iloperidone

1) Interaction Effect: increased plasma concentrations of iloperidone
2) Summary: Coadministration of iloperidone and fluoxetine 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: established
6) Clinical Management: If administered with fluoxetine, reduce iloperidone doses by one-half. Upon withdrawal of fluoxetine 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) Coadministration of fluoxetine 20 mg twice daily for 21 days and iloperidone 3 mg (single doses) in 23 healthy volunteers (ages 29 to 44 years) classified as CYP2D6 extensive metabolizers, increased the AUC of iloperidone and the P88 metabolite by 2- to 3-fold, and decreased the AUC of the P95 metabolite by one-half (Prod Info FANAPT(TM) oral tablets, 2009).

3.5.1.DP 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.DQ Imipramine

1) Interaction Effect: tricyclic antidepressant toxicity (dry mouth, urinary retention, sedation) and an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Tricyclic antidepressants (TCAs) and fluoxetine have been shown to prolong the QTc interval at the recommended therapeutic dose (Prod Info Prozac(R), 2001h; Marshall & Forker, 1982). Even though no formal drug interaction studies have been done which demonstrate QT prolongation, the coadministration of tricyclic antidepressants and other drugs known to prolong the QTc interval, such as fluoxetine, is not recommended (Prod Info Elavil(R), 1999). In addition, concurrent use of fluoxetine and TCAs such as desipramine, nortriptyline, and imipramine has resulted in significant increases in TCA concentrations (Preskorn et al, 1994a; Preskorn et al, 1994a; Aranow et al, 1989a; Downs et al, 1989a; Goodnick, 1989a; Bell & Cole, 1988a).
3) Severity: major
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: The concurrent administration of fluoxetine and a tricyclic antidepressant is not recommended.
7) Probable Mechanism: decreased tricyclic antidepressant metabolism; additive effects on QT prolongation
8) Literature Reports
a) Fluoxetine increased the level of tricyclic antidepressants (nortriptyline, imipramine, desipramine) in 4 patients. After the addition of fluoxetine, the ratio of antidepressant level to dose increased by 109% to 486% in the patients. Three patients developed clinical symptoms (anticholinergic effects, constipation, urinary hesitancy, sedation, unstable gait) as a result of the increased levels (Aranow et al, 1989).
b) Fluoxetine statistically and clinically significantly increased desipramine concentrations in 18 healthy subjects. When fluoxetine (20 mg daily) was added to desipramine (50 mg daily), the mean maximum concentration of desipramine increased by 278% and the area under the concentration-time curve increased by 342%. Desipramine trough concentrations continued to be 198% above baseline three weeks after fluoxetine was discontinued. The same study compared pharmacokinetics of desipramine when combined with sertraline. The impact of sertraline was modest, resulting in small and short-term increases in desipramine plasma concentrations (Preskorn et al, 1994).
c) A 75-year-old female experienced symptomatic increases in her desipramine serum concentrations when fluoxetine was added. Desipramine serum levels ranged from 109 to 150 ng/mL with oral doses of 300 mg at bedtime prior to fluoxetine therapy. Following the addition of oral fluoxetine 20 mg daily to the

regimen, the desipramine serum level increased to 212 ng/mL within five days. The fluoxetine dose was increased to 40 mg/day three days later, and the desipramine serum level was 419 ng/mL after four days. A worsening of depression and severe fatigue coincided with the increases in desipramine serum levels. Withdrawal of fluoxetine and reduction in the desipramine dose to 200 mg daily reduced the desipramine serum level to 231 ng/mL within two weeks (Bell & Cole, 1988).

d) A 33-year-old depressed male developed adverse effects of dry mouth, tinnitus, and difficulties with alertness and memory while receiving fluoxetine 40 mg daily and desipramine 150 mg daily for five weeks; fluoxetine was discontinued and the blood levels of desipramine decreased from 938 to 48 ng/mL with resolution of clinical symptoms (Goodnick, 1989).

e) A 39-year-old female experienced symptomatic increases in her desipramine levels with concomitant fluoxetine therapy. Prior to fluoxetine therapy, the patient's measured levels of desipramine had ranged from 148 to 160 ng/mL on a regimen of 300 mg daily. Five weeks after the addition of fluoxetine 20 mg daily, she reported anticholinergic symptoms, sedation, and confusion with a desipramine level of 527 ng/mL. The desipramine dose was lowered to 200 mg/day; eleven days later, the level was 244 ng/mL; the patient reported decreased energy, impaired short-term memory, and some "garbled" speech, as well as an episode of nausea, dizziness, and syncope. The desipramine dose was reduced to 50 mg/day; the adverse effects resolved in six days. Eight days later, the desipramine level was 122 ng/mL (Downs et al, 1989).

f) Concomitant administration of fluoxetine and desipramine was reported to result in an increased desipramine level and new onset of delirium in a 69-year-old male within 10 days of the addition of fluoxetine to the patient's regimen (Preskorn et al, 1990).

3.5.1.DR 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.DS 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.DT Insulin Aspart, Recombinant
1) Interaction Effect: hypoglycemia
2) Summary: Fluoxetine may increase the blood glucose-lowering effect of insulin and the susceptibility to hypoglycemia (Prod Info EXUBERA(R) inhalation powder inhaler, 2006; Prod Info NOVOLOG(R), 2005; Prod Info LEVEMIR(R) injection, 2005; Prod Info LANTUS(R) subcutaneous injection, 2004; Prod Info Apidra(TM), 2004).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Blood glucose levels should be closely monitored when fluoxetine is added or discontinued in a patient receiving insulin. Lower doses of insulin may be required with concomitant therapy.
7) Probable Mechanism: additive hypoglycemia

3.5.1.DU Insulin Detemir
1) Interaction Effect: hypoglycemia
2) Summary: Fluoxetine may increase the blood glucose-lowering effect of insulin and the susceptibility to hypoglycemia (Prod Info EXUBERA(R) inhalation powder inhaler, 2006; Prod Info NOVOLOG(R), 2005; Prod Info LEVEMIR(R) injection, 2005; Prod Info LANTUS(R) subcutaneous injection, 2004; Prod Info Apidra(TM), 2004).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Blood glucose levels should be closely monitored when fluoxetine is added or discontinued in a patient receiving insulin. Lower doses of insulin may be required with concomitant therapy.
7) Probable Mechanism: additive hypoglycemia

3.5.1.DV Insulin Glargine, Recombinant
1) Interaction Effect: hypoglycemia
2) Summary: Fluoxetine may increase the blood glucose-lowering effect of insulin and the susceptibility to hypoglycemia (Prod Info EXUBERA(R) inhalation powder inhaler, 2006; Prod Info NOVOLOG(R), 2005; Prod Info LEVEMIR(R) injection, 2005; Prod Info LANTUS(R) subcutaneous injection, 2004; Prod Info Apidra(TM), 2004).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Blood glucose levels should be closely monitored when fluoxetine is added or discontinued in a patient receiving insulin. Lower doses of insulin may be required with concomitant therapy.
7) Probable Mechanism: additive hypoglycemia

3.5.1.DW Insulin Glulisine
1) Interaction Effect: hypoglycemia
2) Summary: Fluoxetine may increase the blood glucose-lowering effect of insulin and the susceptibility to hypoglycemia (Prod Info EXUBERA(R) inhalation powder inhaler, 2006; Prod Info NOVOLOG(R), 2005; Prod Info LEVEMIR(R) injection, 2005; Prod Info LANTUS(R) subcutaneous injection, 2004; Prod Info Apidra(TM), 2004).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Blood glucose levels should be closely monitored when fluoxetine is added or discontinued in a patient receiving insulin. Lower doses of insulin may be required with concomitant therapy.
7) Probable Mechanism: additive hypoglycemia

3.5.1.DX Insulin Human Inhaled
1) Interaction Effect: hypoglycemia
2) Summary: Fluoxetine may increase the blood glucose-lowering effect of insulin and the susceptibility to hypoglycemia (Prod Info EXUBERA(R) inhalation powder inhaler, 2006; Prod Info NOVOLOG(R), 2005; Prod Info LEVEMIR(R) injection, 2005; Prod Info LANTUS(R) subcutaneous injection, 2004; Prod Info Apidra(TM), 2004).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Blood glucose levels should be closely monitored when fluoxetine is added or

discontinued in a patient receiving insulin. Lower doses of insulin may be required with concomitant therapy.
7) Probable Mechanism: additive hypoglycemia

3.5.1.DY Iproniazid

1) Interaction Effect: CNS toxicity or serotonin syndrome (hypertension, hyperthermia, myoclonus, mental status changes)
2) Summary: Concurrent administration or overlapping therapy with fluoxetine 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 (Prod Info Prozac(R), 1999f; Sternbach, 1991k; Coplan & Gorman, 1993i; Feighner et al, 1990i; Kline et al, 1989i; Suchowersky & de Vries, 1990i). Concomitant use is contraindicated.
3) Severity: contraindicated
4) Onset: rapid
5) Substantiation: probable
6) Clinical Management: Concurrent use of fluoxetine and iproniazid is contraindicated. Wait at least two weeks after discontinuing a MAO inhibitor before initiating fluoxetine therapy. In addition, wait at least five weeks after discontinuing fluoxetine before initiating therapy with a MAO inhibitor.
7) Probable Mechanism: inhibition of serotonin metabolism by monoamine oxidase
8) Literature Reports

a) Concomitant use of serotonin specific reuptake inhibitors and monoamine oxidase inhibitors can 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 (Sternbach, 1991j). If the syndrome is not recognized and correctly treated, death can result.

b) It has been suggested that fluoxetine therapy be discontinued for at least five weeks before beginning therapy with a monoamine oxidase inhibitor. A 28-year old woman discontinued fluoxetine for six weeks before starting therapy with tranylcypromine. Over the next few days the patient developed fever, paresthesias, confusion, abdominal cramping, and various other CNS symptoms. Upon discontinuation of tranylcypromine, the patient's symptoms began to resolve. Blood samples taken three days after discontinuation of tranylcypromine revealed no presence of fluoxetine; however, the norfluoxetine level was 84 ng/mL (Coplan & Gorman, 1993h).

c) Adverse reactions reported when fluoxetine was given concomitantly with phenelzine (n=9) or tranylcypromine (n=4) include tremor (50%), agitation or restlessness (42%), mental status changes (42%), myoclonus (33%), diarrhea (33%), and blood pressure changes (25%) (Feighner et al, 1990h). All but one of the patients were taking other medications (ie, benzodiazepines, neuroleptics, anticonvulsants, antidepressants) that may have contributed to the adverse reactions.

d) Ten hours after her last dose of fluoxetine, a 45-year-old woman began tranylcypromine therapy (Kline et al, 1989h). Headache, muscle contractions, insomnia, and unsteady gait were reported on the second day. Thioridazine and tryptophan were added to her therapy. The patient experienced fever, rigidity of the arms and legs, and hyperreflexia. She died in the intensive care unit of a hospital 44 hours later.

e) Two cases suggestive of an interaction between fluoxetine and selegiline have been reported. One case involved a first episode of mania being observed approximately one month after adding selegiline to fluoxetine therapy. 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 and selegiline. Both drugs were discontinued, with relatively quick resolution of symptoms. Rechallenge with fluoxetine alone occurred without incident (Suchowersky & de Vries, 1990h).

3.5.1.DZ Isocarboxazid

1) Interaction Effect: CNS toxicity or serotonin syndrome (hypertension, hyperthermia, myoclonus, mental status changes)
2) Summary: Concurrent administration or overlapping therapy with fluoxetine 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 (Prod Info Prozac(R), 1999i; Sternbach, 1991q; Coplan & Gorman, 1993o; Feighner et al, 1990o; Kline et al, 1989o; Suchowersky & de Vries, 1990o). Concomitant use is contraindicated (Prod Info Marplan(R), 1998).
3) Severity: contraindicated
4) Onset: rapid
5) Substantiation: theoretical
6) Clinical Management: Concurrent use of fluoxetine and a MAO inhibitor is contraindicated. Wait at least two weeks after discontinuing a MAO inhibitor before initiating fluoxetine therapy. In addition, wait at least five weeks after discontinuing fluoxetine before initiating therapy with a MAO inhibitor.
7) Probable Mechanism: inhibition of serotonin metabolism by monoamine oxidase
8) Literature Reports

a) Concomitant use of serotonin specific reuptake inhibitors and monoamine oxidase inhibitors can

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 (Sternbach, 1991p). If the syndrome is not recognized and correctly treated, death can result.

b) It has been suggested that fluoxetine therapy be discontinued for five weeks before beginning therapy with a monoamine oxidase inhibitor. However, one case report describes a 28-year old woman who had discontinued a 2-year fluoxetine regimen for six weeks before starting therapy with tranylcypromine. Over the next few days the patient developed fever, paresthesias, confusion, abdominal cramping, and various other CNS symptoms. Upon discontinuation of tranylcypromine, the patient's symptoms began to resolve. Blood samples taken three days after discontinuation of tranylcypromine revealed no presence of fluoxetine; however, the norfluoxetine level was 84 ng/mL (Coplan & Gorman, 1993n).

c) Adverse reactions reported when fluoxetine was given concomitantly with phenelzine (n=9) or tranylcypromine (n=4) include tremor (50%), agitation or restlessness (42%), mental status changes (42%), myoclonus (33%), diarrhea (33%), and blood pressure changes (25%) (Feighner et al, 1990n). All but one of the patients were taking other medications (ie, benzodiazepines, neuroleptics, anticonvulsants, antidepressants) that may have contributed to the adverse reactions.

d) Ten hours after her last dose of fluoxetine, a 45-year-old woman began tranylcypromine therapy (Kline et al, 1989n). Headache, muscle contractions, insomnia, and unsteady gait were reported on the second day. Thioridazine and tryptophan were added to her therapy. The patient experienced fever, rigidity of the arms and legs, and hyperreflexia. She died in the intensive care unit of a hospital 44 hours later.

e) Interactions between fluoxetine and selegiline were suggested in two case reports (Suchowersky & de Vries, 1990n). One case involved a first episode of mania being observed approximately one month after adding selegiline to fluoxetine therapy. 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 and selegiline. Both drugs were discontinued, with relatively quick resolution of symptoms. Rechallenge with fluoxetine alone occurred without incident.

3.5.1.EA Isoflurane

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)

2) Summary: Even though no formal drug interaction studies have been done, isoflurane should be administered cautiously with other drugs which are also known to prolong the QTc interval, including fluoxetine (Owens, 2001a; Prod Info Prozac(R), 2001k).

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: The concurrent administration of isoflurane with other agents that can prolong the QT interval, such as fluoxetine, is not recommended.

7) Probable Mechanism: additive effect on QT interval

3.5.1.EB 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.EC Isradipine

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)

2) Summary: Isradipine can prolong the QT interval in some patients, which may result in ventricular tachycardia, ventricular fibrillation, and torsades de pointes. Because fluoxetine may also prolong the QT interval and increase the risk of arrhythmias, the concurrent administration of isradipine with fluoxetine is not recommended (Prod Info DynaCirc(R), 2000).

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: The concurrent administration of isradipine and fluoxetine is not recommended.

7) Probable Mechanism: additive cardiac effects

3.5.1.ED 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.EE 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.EF 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.EG Levomethadyl
1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Any drug known to have the potential to prolong the QT interval should not be used with levomethadyl. Possible pharmacodynamic interactions can occur between levomethadyl and potentially arrhythmogenic agents such as fluoxetine that prolong the QT interval (Prod Info Orlaam(R), 2001).
3) Severity: contraindicated
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: Levomethadyl is contraindicated in patients being treated with fluoxetine as it may precipitate QT prolongation and interact with levomethadyl.
7) Probable Mechanism: unknown

3.5.1.EH 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.EI Lidoflazine
1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Lidoflazine and fluoxetine have been shown to prolong the QTc interval at the recommended therapeutic dose (Prod Info Prozac(R), 2001g; Hanley & Hampton, 1983). Even though no formal drug interaction studies have been done, the coadministration of drugs known to prolong the QTc interval is not recommended.
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of lidoflazine and fluoxetine is not recommended.
7) Probable Mechanism: additive effects on QT prolongation

3.5.1.EJ Linezolid
1) Interaction Effect: increased risk of serotonin syndrome (hypertension, hyperthermia, myoclonus, mental status changes)
2) Summary: Linezolid is a reversible, nonselective monoamine oxidase inhibitor (MAOI). Concurrent administration or overlapping therapy with fluoxetine and a MAOI 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. There have been spontaneous reports of serotonin syndrome associated with concomitant use of linezolid and serotonergic agents, including fluoxetine (Thomas et al, 2004; Steinberg & Morin, 2007; Prod Info ZYVOX(R) IV injection, oral tablets, oral suspension, 2008; Prod Info PROZAC(R) oral capsules, oral solution, 2006). If these agents are used concomitantly, monitor for serotonin syndrome effects, including confusion, delirium, restlessness, tremors, blushing, diaphoresis, and hyperpyrexia. If symptoms occur, consider discontinuation of either one or both of the agents (Prod Info ZYVOX(R) IV injection, oral tablets, oral suspension, 2008). A washout period of 2 weeks is usually recommended following discontinuation of

an MAOI and initiation of fluoxetine. Following discontinuation of fluoxetine, a washout period of 5 weeks is usually recommended prior to initiation of an MAOI (Prod Info PROZAC(R) oral capsules, oral solution, 2006).

3) Severity: contraindicated

4) Onset: rapid

5) Substantiation: probable

6) Clinical Management: Unless carefully monitored for serotonin syndrome, linezolid should not be administered to patients taking fluoxetine(Prod Info ZYVOX(R) IV injection, oral tablets, oral suspension, 2008). A washout period of 2 weeks is usually recommended following discontinuation of an MAOI and initiation of fluoxetine. Following discontinuation of fluoxetine, a washout period of 5 weeks is usually recommended prior to initiation of an MAOI (Prod Info PROZAC(R) oral capsules, oral solution, 2006). If fluoxetine and linezolid are used concomitantly, monitor closely for symptoms of 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). Serotonin syndrome can be life-threatening. If serotonin syndrome develops, discontinue the offending agents and provide supportive care and other therapy as necessary (Boyer & Shannon, 2005).

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

8) Literature Reports

a) A 4-year-old female patient, weighing 12.8 kg, experienced serotonin syndrome-like symptoms following concomitant use of linezolid and fluoxetine. Eleven days after receiving fluoxetine 5 mg daily for acute stress disorder in response to a burn injury, the patient received oral linezolid 140 mg every 12 hours. Two days later, she was premedicated with oral fentanyl 200 mcg prior to a wound debridement procedure. Shortly afterwards, she became agitated and had myoclonus in her arms and legs. She also had mydriasis, was unable to visually track across midline, and her gaze deviated to the lower left quadrant. Discontinuation of fluoxetine and initiation of oral diphenhydramine 25 mg led to partial improvement in symptoms. Subsequently, linezolid was discontinued and replaced with an alternate antibiotic. Symptoms of agitation, myoclonic movements, and nystagmus resolved over the next 2 days (Thomas et al, 2004).

b) The concomitant administration of fluoxetine and linezolid was associated with mild symptoms of serotonin syndrome in a 23-year-old male as described in a case report. The patient, who had recently achieved complete remission of acute myelogenous leukemia and was admitted for maintenance chemotherapy, routinely received treatment with oral fluoxetine 60 mg once daily, oral methadone 75 mg once daily, oral voriconazole 300 mg twice daily, transdermal nicotine patch 21 mg (changed daily), oral lorazepam 2 mg twice daily (with 1 mg doses as needed every 4 hours), and oral quetiapine 200 mg every evening. On day 9 of admission, the fluoxetine dose was increased to 80 mg daily for mood instability, and linezolid 600 mg every 12 hours was initiated on day 43. Within 12 hours of initiating linezolid, the patient experienced physical discomfort and severe abdominal pain (described as feeling like a "runner's cramp" and making it "difficult to breathe"). The discomfort continued following another 4 doses of linezolid over the next day. On day 47, linezolid was discontinued, after a total of 6 linezolid doses, and the pain and other symptoms resolved within 48 hours. During linezolid therapy, vital signs and laboratory results were unremarkable, except for chemotherapy-induced neutropenia, thrombocytopenia, and anemia (Steinberg & Morin, 2007).

c) A retrospective chart review identified one highly probable case of serotonin syndrome in a patient who received concomitant therapy with linezolid and venlafaxine, followed by citalopram. Charts of 72 inpatients who received linezolid and an SSRI or venlafaxine within 14 days of each other were reviewed for a diagnosis of serotonin syndrome (SS) using the Sternbach and the Hunter Serotonin Toxicity criteria. Of these patients, 52 (72%) were treated concomitantly with linezolid and an SSRI or venlafaxine. Four patients met the criteria for having either high or low probability of SS. Of these, one case involved an 81-year-old woman who was diagnosed with a high probability of having SS after receiving concomitant linezolid and venlafaxine followed by citalopram. Linezolid was given for a vancomycin-resistant Enterococcus urinary tract infection. When the patient presented, she refused to eat, was confused as to time and place, and began shouting. Although she appeared to have met 6 of the Sternbach criteria and 4 of the Hunter criteria for SS, a diagnosis of SS was not documented in her chart. Her blood pressure was 180 mm Hg with a heart rate of 120 beats/min, and a respiratory rate of 50 breaths/min. The following day, she barely spoke and could not be aroused; additional symptoms included lethargy, extremity twitching and jerking, eyes rolled back in her head, and labored breathing. Linezolid was discontinued, and she was sedated and intubated. Five days following onset of symptoms and 2 days after linezolid was stopped, she was extubated and had returned to baseline mental status with the ability to communicate (Taylor et al, 2006).

d) In one case report, a 39-year-old female experienced symptoms of serotonin syndrome after concomitant treatment with fluoxetine and linezolid. She was admitted to the emergency room after being found unresponsive at home. This patient had a history of depression, suicide attempts and alcohol dependency. Before admission, her medications consisted of disulfiram, fluoxetine, buspirone, cyclobenzaprine, and folate. All medications were discontinued upon admission. The patient was given two doses of physostigmine for anticholinergic symptoms believed to be caused by a cyclobenzaprine overdose. Two days after admission, the patient became sedated, developed tachycardia, and had sporadic agitation presumably due to alcohol withdrawal. She was given lorazepam and haloperidol for

the alcohol withdrawal and agitation. On day five, she was intubated for respiratory depression thought to be from either pneumonia or respiratory suppression from lorazepam. The patient received vancomycin for methicillin-resistant staphylococcus aureus (sputum) and on day thirteen, was extubated and her mental status improved. On day eighteen, vancomycin was changed to linezolid. Immediate changes in her mental status were apparent. She experienced convulsions, tremors, weakness, and perspiration. After two doses of linezolid, the patient had a temperature of 98 degrees, blood pressure of 140/90, a heart rate of 170, and respirations of 18. Linezolid was discontinued and the vancomycin regimen restarted. The patient was diagnosed with benzodiazepine withdrawal, neuroleptic syndrome, sepsis, meningitis, and serotonin syndrome. Serotonin syndrome was diagnosed as a likely drug interaction between linezolid and fluoxetine (Morales & Vermette, 2005).

3.5.1.EK 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), 2003). 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.EL Lorcainide

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)

2) Summary: Even though no formal drug interaction studies have been done, the coadministration of Class I antiarrhythmics and other drugs known to prolong the QTc interval is not recommended (Prod Info Tambocor(R) flecainide acetate, 1998). Fluoxetine has been shown to prolong the QTc interval at the recommended therapeutic dose (Prod Info Prozac(R), 2001w).

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: The concurrent administration of class I antiarrhythmic agents and agents that prolong the QT interval, such as fluoxetine, is not recommended.

7) Probable Mechanism: additive effects on QT prolongation

3.5.1.EM 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.EN 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.EO 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.EP Mefloquine

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)

2) Summary: Fluoxetine has been shown to prolong the QTc interval at the recommended therapeutic dose (Prod Info Prozac(R), 2001p). Even though no formal drug interaction studies have been done, caution is advised if mefloquine is used with other drugs which can prolong the QTc interval (Prod Info Lariam(R), 1999).

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: The concurrent administration of fluoxetine and mefloquine is not recommended.

7) Probable Mechanism: additive effects on QT prolongation

3.5.1.EQ 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.ER Meperidine

1) Interaction Effect: an increased risk of serotonin syndrome

2) Summary: A 43-year-old male on fluoxetine every other day experienced serotonin syndrome immediately after intravenous meperidine was administered (Tissot, 2003). If fluoxetine and meperidine are used concomitantly, monitor closely for symptoms of serotonin syndrome. Serotonin syndrome can be life-threatening. If serotonin syndrome develops, discontinue the offending agents and provide supportive care and other therapy as necessary (Boyer & Shannon, 2005).

3) Severity: major

4) Onset: rapid

5) Substantiation: probable

6) Clinical Management: A case of serotonin syndrome was reported with coadministration of fluoxetine and meperidine and therefore, concomitant use is discouraged (Tissot, 2003). If fluoxetine and meperidine are used concomitantly, monitor closely for symptoms of serotonin syndrome such as neuromuscular abnormalities (including hyper-reflexia, tremor, muscle rigidity, clonus, peripheral hypertonicity, and shivering), autonomic hyperactivity (including tachycardia, mydriasis, diaphoresis, the presence of bowel sounds, and diarrhea), and mental status changes (including agitation and delirium). Serotonin syndrome can be life-threatening. If serotonin syndrome develops, discontinue the offending agents and provide supportive care and other therapy as necessary (Boyer & Shannon, 2005).

7) Probable Mechanism: additive pharmacologic effects

8) Literature Reports

a) A 43-year-old male on fluoxetine every other day experienced serotonin syndrome immediately after intravenous meperidine was administered. His other medications were rosiglitazone and fenofibrate. His medical history includes type 2 diabetes, dyslipidemia, and recurrent episodes of pancreatitis. Prior to this adverse event he received meperidine and midazolam, while not on fluoxetine, without any sequela. Before an endoscopy procedure he was administered intravenous midazolam and 50 mg of intravenous meperidine. He immediately became agitated and restless. He was unable to follow verbal commands because of confusion. Blood pressure (180/100 mm Hg) and heart rate (130 bpm) increased and oxygen saturation decreased to 95%. He had diaphoresis and dilated pupils. Within 10 minutes his blood pressure started to decrease. He had an episode of diarrhea. Over the next 10 to 15 minutes, his agitation subsided, he remained sleepy and confused, and blood pressure and heart continued to decrease to baseline. His temperature was 98.4 degrees Farenheit. After 60 to 90 minutes his sensorium appeared to clear and diaphoresis resolved. The patient remained afebrile with stable vital signs over the next 24 hours. He was treated with hydromorphone for abdominal pain without any adverse reaction. Several weeks later he received fentanyl, midazolam, and propofol pre-endoscopy without any event, but had not taken fluoxetine for 2 weeks before the procedure (Tissot, 2003).

3.5.1.ES Mesoridazine

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)

2) Summary: Fluoxetine has been shown to prolong the QTc interval at the recommended therapeutic dose (Prod Info Prozac(R), 2001ad). Although citing no data, the manufacturer of mesoridazine states that concomitant use with other drugs which prolong the QT interval is contraindicated (Prod Info Serentil(R),

2000).
3) Severity: contraindicated
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of fluoxetine and mesoridazine is contraindicated.
7) Probable Mechanism: additive effects on QT prolongation

3.5.1.ET Methylergonovine
1) Interaction Effect: an increased risk of ergotism (nausea, vomiting, vasospastic ischemia)
2) Summary: Because of the potential for serious toxicity including vasospasm that can occur with increased plasma concentrations of ergot derivatives, the concurrent use of fluoxetine and ergot derivatives is contraindicated. Fluoxetine and ergot derivatives are both metabolized by cytochrome P450 3A4 enzymes, and the competition for metabolism could result in an increased plasma concentration of the ergot derivative (Prod Info Cafergot(R), 2002).
3) Severity: contraindicated
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: The concurrent use of fluoxetine and ergot derivatives is contraindicated.
7) Probable Mechanism: inhibition of cytochrome P450 3A4- mediated ergot metabolism by fluoxetine

3.5.1.EU 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.EV Methysergide
1) Interaction Effect: an increased risk of ergotism (nausea, vomiting, vasospastic ischemia)
2) Summary: Because of the potential for serious toxicity including vasospasm that can occur with increased plasma concentrations of ergot derivatives, the concurrent use of fluoxetine and ergot derivatives is contraindicated. Fluoxetine and ergot derivatives are both metabolized by cytochrome P450 3A4 enzymes, and the competition for metabolism could result in an increased plasma concentration of the ergot derivative (Prod Info Cafergot(R), 2002).
3) Severity: contraindicated
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: The concurrent use of fluoxetine and ergot derivatives is contraindicated.
7) Probable Mechanism: inhibition of cytochrome P450 3A4- mediated ergot metabolism by fluoxetine

3.5.1.EW Metoprolol
1) Interaction Effect: an increased risk of metoprolol adverse effects (shortness of breath, bradycardia, hypotension, acute heart failure)
2) Summary: To date, little information is available related to the effects of combined fluoxetine and metoprolol. A case report described a possible interaction between metoprolol and fluoxetine resulting in bradycardia (Walley et al, 1993a). Fluoxetine is a potent inhibitor of hepatic cytochrome P450 2D6, the isoenzyme that catalyzes metoprolol metabolism (DeVane, 1994). Additional research is needed to further assess the effect of fluoxetine on metoprolol pharmacokinetics.
3) Severity: moderate
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: Atenolol should be considered for fluoxetine-treated patients who require a beta blocker. If metoprolol and fluoxetine are coadministered, monitor patients for metoprolol adverse effects. A reduction in the metoprolol dose may be necessary.
7) Probable Mechanism: inhibition of hepatic metabolism of metoprolol
8) Literature Reports
a) A case report described a possible interaction between metoprolol and fluoxetine resulting in bradycardia. A patient with angina that was controlled with metoprolol 100 mg daily developed lethargy

and bradycardia within two days after fluoxetine 20 mg per day was added to his therapy. Fluoxetine was discontinued and metoprolol was replaced with sotalol 80 mg twice daily. A week later fluoxetine was reinstituted without recurrence of the bradycardia. Fluoxetine is known to inhibit hepatic metabolism. Metoprolol is extensively metabolized via hepatic cytochrome P450 isoenzymes (CYP2D6 and possibly CYP3A). Sotalol does not undergo significant hepatic metabolism (Walley et al, 1993).

3.5.1.EX 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.EY Mirtazapine

1) Interaction Effect: an increased risk of serotonin syndrome
2) Summary: Concurrent use of fluoxetine and mirtazapine resulted in serotonin syndrome in a 75-year-old woman. She experience dizziness, headache, nausea, dry mouth, intense anxiety and agitation with suicidal ideas. Other symptoms were difficulty walking, marked resting tremor of the hands, and insomnia (Benazzi, 1998). If fluoxetine and mirtazapine are used together, monitor closely for symptoms of serotonin syndrome. Serotonin syndrome can be life-threatening. If serotonin syndrome develops, discontinue the offending agents and provide supportive care and other therapy as necessary (Boyer & Shannon, 2005).
3) Severity: major
4) Onset: rapid
5) Substantiation: probable
6) Clinical Management: A case of serotonin syndrome was reported with concomitant use of fluoxetine and mirtazapine and therefore, concomitant use is discouraged (Benazzi, 1998). If fluoxetine and mirtazapine are used together, monitor closely for symptoms of serotonin syndrome such as neuromuscular abnormalities (including hyper-reflexia, tremor, muscle rigidity, clonus, peripheral hypertonicity, and shivering), autonomic hyperactivity (including tachycardia, mydriasis, diaphoresis, the presence of bowel sounds, and diarrhea), and mental status changes (including agitation and delirium). Serotonin syndrome can be life-threatening. If serotonin syndrome develops, discontinue the offending agents and provide supportive care and other therapy as necessary (Boyer & Shannon, 2005).
7) Probable Mechanism: potentially additive pharmacologic effects
8) Literature Reports
a) Within a few hours of starting mirtazapine and shortly after stopping fluoxetine, a 75-year-old woman experienced symptoms consistent with serotonin syndrome. Besides fluoxetine 20 mg/day, she was on chlorpromazine 75 mg/day, and lorazepam 2.5 mg/day for depression. Due to lack of response, fluoxetine was discontinued and soon afterward mirtazapine 30 mg/day was started and the dose of chlorpromazine was decreased to 50 mg/day. Within a few hours of starting mirtazapine, she experience dizziness, headache, nausea, dry mouth, intense anxiety and agitation with suicidal ideas. Other symptoms were difficulty walking, marked resting tremor of the hands, and insomnia. Over the next 3 days, she progressively worsened. Mirtazapine was discontinued on day 5. Her symptoms improved the following day. Fluoxetine 20 mg/day was restarted on day 7 with subsequent resolution of dizziness, nausea, headache, and agitation resolution over the following days. Over the next 10 days, tremor, anxiety, difficulty walking, dry mouth, and insomnia improved (Benazzi, 1998).

3.5.1.EZ Moclobemide

1) Interaction Effect: CNS toxicity or serotonin syndrome (hypertension, hyperthermia, myoclonus, mental status changes)
2) Summary: Concurrent administration or overlapping therapy with fluoxetine 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 (Prod Info Prozac(R), 1999k; Sternbach, 1991u; Coplan & Gorman, 1993r; Feighner et al, 1990r; Kline et al, 1989s; Suchowersky & de Vries, 1990s). Although not reported specifically with moclobemide in therapeutic doses, a similar interaction may occur. Concomitant use is contraindicated.
3) Severity: contraindicated

4) Onset: rapid
5) Substantiation: probable
6) Clinical Management: Concurrent use of fluoxetine and a MAO inhibitor is contraindicated. Wait at least two weeks after discontinuing a MAO inhibitor before initiating fluoxetine therapy. In addition, wait at least five weeks after discontinuing fluoxetine before initiating therapy with a MAO inhibitor.
7) Probable Mechanism: inhibition of serotonin metabolism by monoamine oxidase
8) Literature Reports

a) Concomitant use of serotonin specific reuptake inhibitors and monoamine oxidase inhibitors can produce a toxic reaction known as serotonin syndrome (Sternbach, 1991t). 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.

b) Ten hours after her last dose of fluoxetine, a 45-year-old woman began tranylcypromine therapy (Kline et al, 1989r). Headache, muscle contractions, insomnia, and unsteady gait were reported on the second day. Thioridazine and tryptophan were added to her therapy. The patient experienced fever, rigidity of the arms and legs, and hyperreflexia. She died in the intensive care unit of a hospital 44 hours later.

c) Two cases suggestive of an interaction between fluoxetine and selegiline, a selective monoamine oxidase B inhibitor, have been reported (Suchowersky & de Vries, 1990r). One case involved a first episode of mania being observed approximately one month after adding selegiline to fluoxetine therapy. 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 and selegiline. Both drugs were discontinued, with relatively quick resolution of symptoms. Rechallenge with fluoxetine alone occurred without incident.

d) In three of five cases of serotonin syndrome following overdoses, the drug combination that induced the fatal syndrome included moclobemide, a selective monoamine oxidase inhibitor, and citalopram. Of these three patients, moclobemide blood concentrations ranged from 5 to 50 times the therapeutic level, and citalopram concentrations ranged from normal to 5 times the therapeutic level (Neuvonen et al, 1993).

e) Moclobemide is a selective and reversible inhibitor of monoamine oxidase A (MAO-A). Based on animal experiments, it is believed that both MAO-A and MAO-B are essential for the development of serotonin syndrome. In an effort to assess the safety and pharmacodynamics of combined treatment of fluoxetine and moclobemide, 18 healthy subjects participated in a randomized, placebo-controlled, parallel study. All participants ingested a single oral dose of moclobemide 300 mg on days 1 and 24, fluoxetine 40 mg on days 2 through 8, and fluoxetine 20 mg on days 9 through 24. On day 16, subjects were randomized to receive either placebo or moclobemide on an ascending dose schedule. Doses of moclobemide started at 100 mg daily, and increased to 200 mg on day 17, 300 mg on day 18, and 600 mg on days 19 through 23. Steady-state fluoxetine plasma concentrations had been achieved when moclobemide therapy was initiated, and did not change with the addition or increasing doses of moclobemide. No patients experienced serotonin syndrome or any kind of a pharmacodynamic interaction between these two agents. Additionally, fluoxetine reduced serotonin uptake into platelets almost completely as expected, but moclobemide had no effect on serotonin uptake during single- or multiple-dose therapy. These study results suggest that a long wash-out period between treatment with moclobemide and fluoxetine is not necessary (Dingemanse et al, 1998).

f) An 82-year-old woman developed various serotonin syndrome symptoms after changing from fluoxetine to moclobemide therapy without a washout period in between. She experienced agitation, confusion, and tremor, progressing to inability to answer questions with any answer other than yes or no. After treatment with 4 mg cyproheptadine, her condition improved significantly (Chan et al, 1998a).

3.5.1.FA 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.FB 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.FC 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 PROZAC(R) oral capsules, delayed-release capsules, solution, 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 (Prod Info PROZAC(R) oral capsules, delayed-release capsules, solution, 2008).

3) Severity: major

4) Onset: delayed

5) Substantiation: probable

6) Clinical Management: When fluoxetine and an anticoagulant are given concurrently, monitor patient for signs of increased bleeding. Patients who are taking warfarin should be monitored closely for altered anticoagulant effects, including increased bleeding, when fluoxetine therapy is initiated or discontinued (Prod Info PROZAC(R) oral capsules, delayed-release capsules, solution, 2008).

7) Probable Mechanism: unknown

8) Literature Reports

a) Fluoxetine is thought to inhibit the cytochrome P450 2C9 isoenzyme (CYP2C9). This is the enzyme by which the more potent warfarin isomer, S-warfarin, is metabolized (Riesenman, 1995). In addition, both fluoxetine and warfarin are tightly bound to albumin. In combination, the possibility for protein-binding displacement of either drug is present (Prod Info Coumadin(R), 1999).

b) 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).

c) 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).

d) In 6 reported cases, INR increased during combined fluoxetine and warfarin therapy. In a seventh case, severe bruising of the lower legs occurred in a woman initially treated with fluoxetine and, secondarily, started on warfarin (Woolfrey et al, 1993; Claire et al, 1991).

e) An 83-year-old man died from cerebral hemorrhage secondary to increased warfarin concentrations. The patient had been taking warfarin 30 mg per week for atrial fibrillation with a target INR between 2 and 3. The patient's other drugs included lisinopril, furosemide, potassium, digoxin, and acetaminophen. After being seen for symptoms of depression, anxiety, and insomnia, the patient was given fluoxetine 20 mg per day and diazepam 2.5 mg 3 to 4 times per day. Eight days later, the patient's INR increased to 4.8, and the dose of warfarin was decreased to 27.5 mg per week. The patient was later seen for symptoms of drug delirium, including confusion, incoherence, and speaking irrationally. At this point, the INR was 3.64 and fluoxetine was discontinued. The next day the patient presented to the hospital with left-sided weakness and later died from complications of a large interparenchymal hemorrhage. The authors proposed that the addition of fluoxetine to the patient's regimen resulted in increased serum levels of both warfarin and diazepam, resulting in delirium and loss of anticoagulant control (Dent & Orrock, 1997).

3.5.1.FD 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.FE 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.FF 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 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). Closely monitor blood pressure in patients receiving fluoxetine and nebivolol concomitantly. Downward dose adjustments of nebivolol may be necessary (Prod Info BYSTOLIC (TM) oral tablets, 2007).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: established
6) Clinical Management: Coadministration of fluoxetine, a CYP2D6 inhibitor, and nebivolol led to increased exposure and plasma concentrations of d-nebivolol, the pharmacologically active isomer. 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.FG Nialamide

1) Interaction Effect: CNS toxicity or serotonin syndrome (hypertension, hyperthermia, myoclonus, mental status changes)
2) Summary: Concurrent administration or overlapping therapy with fluoxetine 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 (Prod Info Prozac(R), 1999e; Sternbach, 1991i; Coplan & Gorman, 1993g; Feighner et al, 1990g; Kline et al, 1989g; Suchowersky & de Vries, 1990g). Concomitant use is contraindicated.
3) Severity: contraindicated
4) Onset: rapid
5) Substantiation: probable
6) Clinical Management: Concurrent use of fluoxetine and nialamide is contraindicated. Wait at least two weeks after discontinuing a MAO inhibitor before initiating fluoxetine therapy. In addition, wait at least five weeks after discontinuing fluoxetine before initiating therapy with a MAO inhibitor.
7) Probable Mechanism: inhibition of serotonin metabolism by monoamine oxidase
8) Literature Reports

a) Concomitant use of serotonin specific reuptake inhibitors and monoamine oxidase inhibitors can 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, death can result.

b) It has been suggested that fluoxetine therapy be discontinued for at least five weeks before beginning therapy with a monoamine oxidase inhibitor. A 28-year old woman discontinued fluoxetine for six weeks before starting therapy with tranylcypromine. Over the next few days the patient developed fever, paresthesias, confusion, abdominal cramping, and various other CNS symptoms. Upon discontinuation of tranylcypromine, the patient's symptoms began to resolve. Blood samples taken three days after discontinuation of tranylcypromine revealed no presence of fluoxetine; however, the norfluoxetine level was 84 ng/mL (Coplan & Gorman, 1993f).

c) Adverse reactions reported when fluoxetine was given concomitantly with phenelzine (n=9) or tranylcypromine (n=4) include tremor (50%), agitation or restlessness (42%), mental status changes (42%), myoclonus (33%), diarrhea (33%), and blood pressure changes (25%) (Feighner et al, 1990f). All but one of the patients were taking other medications (ie, benzodiazepines, neuroleptics, anticonvulsants, antidepressants) that may have contributed to the adverse reactions.

d) Ten hours after her last dose of fluoxetine, a 45-year-old woman began tranylcypromine therapy (Kline et al, 1989f). Headache, muscle contractions, insomnia, and unsteady gait were reported on the second day. Thioridazine and tryptophan were added to her therapy. The patient experienced fever, rigidity of the arms and legs, and hyperreflexia. She died in the intensive care unit of a hospital 44 hours later.

e) 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 therapy. 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 and selegiline. Both drugs were discontinued, with relatively quick resolution of symptoms. Rechallenge with fluoxetine alone occurred without incident.

3.5.1.FH 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.FI 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.FJ Nortriptyline

1) Interaction Effect: tricyclic antidepressant toxicity (dry mouth, urinary retention, sedation) and an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)

2) Summary: Tricyclic antidepressants (TCAs) and fluoxetine have been shown to prolong the QTc interval at the recommended therapeutic dose (Prod Info Prozac(R), 2001h; Marshall & Forker, 1982). Even though no formal drug interaction studies have been done which demonstrate QT prolongation, the coadministration of tricyclic antidepressants and other drugs known to prolong the QTc interval, such as fluoxetine, is not recommended (Prod Info Elavil(R), 1999). In addition, concurrent use of fluoxetine and TCAs such as desipramine, nortriptyline, and imipramine has resulted in significant increases in TCA concentrations (Preskorn et al, 1994a; Preskorn et al, 1994a; Aranow et al, 1989a; Downs et al, 1989a; Goodnick, 1989a; Bell & Cole, 1988a).

3) Severity: major

4) Onset: unspecified

5) Substantiation: probable
6) Clinical Management: The concurrent administration of fluoxetine and a tricyclic antidepressant is not recommended.
7) Probable Mechanism: decreased tricyclic antidepressant metabolism; additive effects on QT prolongation
8) Literature Reports
a) Fluoxetine increased the level of tricyclic antidepressants (nortriptyline, imipramine, desipramine) in 4 patients. After the addition of fluoxetine, the ratio of antidepressant level to dose increased by 109% to 486% in the patients. Three patients developed clinical symptoms (anticholinergic effects, constipation, urinary hesitancy, sedation, unstable gait) as a result of the increased levels (Aranow et al, 1989).
b) Fluoxetine statistically and clinically significantly increased desipramine concentrations in 18 healthy subjects. When fluoxetine (20 mg daily) was added to desipramine (50 mg daily), the mean maximum concentration of desipramine increased by 278% and the area under the concentration-time curve increased by 342%. Desipramine trough concentrations continued to be 198% above baseline three weeks after fluoxetine was discontinued. The same study compared pharmacokinetics of desipramine when combined with sertraline. The impact of sertraline was modest, resulting in small and short-term increases in desipramine plasma concentrations (Preskorn et al, 1994).
c) A 75-year-old female experienced symptomatic increases in her desipramine serum concentrations when fluoxetine was added. Desipramine serum levels ranged from 109 to 150 ng/mL with oral doses of 300 mg at bedtime prior to fluoxetine therapy. Following the addition of oral fluoxetine 20 mg daily to the regimen, the desipramine serum level increased to 212 ng/mL within five days. The fluoxetine dose was increased to 40 mg/day three days later, and the desipramine serum level was 419 ng/mL after four days. A worsening of depression and severe fatigue coincided with the increases in desipramine serum levels. Withdrawal of fluoxetine and reduction in the desipramine dose to 200 mg daily reduced the desipramine serum level to 231 ng/mL within two weeks (Bell & Cole, 1988).
d) A 33-year-old depressed male developed adverse effects of dry mouth, tinnitus, and difficulties with alertness and memory while receiving fluoxetine 40 mg daily and desipramine 150 mg daily for five weeks; fluoxetine was discontinued and the blood levels of desipramine decreased from 938 to 48 ng/mL with resolution of clinical symptoms (Goodnick, 1989).
e) A 39-year-old female experienced symptomatic increases in her desipramine levels with concomitant fluoxetine therapy. Prior to fluoxetine therapy, the patient's measured levels of desipramine had ranged from 148 to 160 ng/mL on a regimen of 300 mg daily. Five weeks after the addition of fluoxetine 20 mg daily, she reported anticholinergic symptoms, sedation, and confusion with a desipramine level of 527 ng/mL. The desipramine dose was lowered to 200 mg/day; eleven days later, the level was 244 ng/mL; the patient reported decreased energy, impaired short-term memory, and some "garbled" speech, as well as an episode of nausea, dizziness, and syncope. The desipramine dose was reduced to 50 mg/day; the adverse effects resolved in six days. Eight days later, the desipramine level was 122 ng/mL (Downs et al, 1989).
f) Concomitant administration of fluoxetine and desipramine was reported to result in an increased desipramine level and new onset of delirium in a 69-year-old male within 10 days of the addition of fluoxetine to the patient's regimen (Preskorn et al, 1990).

3.5.1.FK Octreotide

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Octreotide and fluoxetine have been shown to prolong the QTc interval at the recommended therapeutic dose (Prod Info Prozac(R), 2001m; Prod Info Sandostatin(R), 1999). Even though no formal drug interaction studies have been done, the coadministration of drugs known to prolong the QTc interval is not recommended.
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of octreotide and fluoxetine is not recommended.
7) Probable Mechanism: additive effects on QT prolongation

3.5.1.FL 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.FM 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.FN Pargyline

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

2) Summary: Concurrent administration or overlapping therapy with fluoxetine 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 (Prod Info Prozac(R), 1999h; Sternbach, 1991o; Coplan & Gorman, 1993m; Feighner et al, 1990m; Kline et al, 1989m; Suchowersky & de Vries, 1990m). Concomitant use is contraindicated.

3) Severity: contraindicated

4) Onset: rapid

5) Substantiation: probable

6) Clinical Management: Concurrent use of fluoxetine and pargyline is contraindicated. Wait at least two weeks after discontinuing a MAO inhibitor before initiating fluoxetine therapy. In addition, wait at least five weeks after discontinuing fluoxetine before initiating therapy with a MAO inhibitor.

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

8) Literature Reports

a) Concomitant use of serotonin specific reuptake inhibitors and monoamine oxidase inhibitors can 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 (Sternbach, 1991n). If the syndrome is not recognized and correctly treated, death can result.

b) It has been suggested that fluoxetine therapy be discontinued for at least five weeks before beginning therapy with a monoamine oxidase inhibitor. A 28-year old woman discontinued fluoxetine for six weeks before starting therapy with tranylcypromine. Over the next few days the patient developed fever, paresthesias, confusion, abdominal cramping, and various other CNS symptoms. Upon discontinuation of tranylcypromine, the patient's symptoms began to resolve. Blood samples taken three days after discontinuation of tranylcypromine revealed no presence of fluoxetine; however, the norfluoxetine level was 84 ng/mL (Coplan & Gorman, 1993l).

c) Adverse reactions reported when fluoxetine was given concomitantly with phenelzine (n=9) or tranylcypromine (n=4) include tremor (50%), agitation or restlessness (42%), mental status changes (42%), myoclonus (33%), diarrhea (33%), and blood pressure changes (25%) (Feighner et al, 1990l). All but one of the patients were taking other medications (ie, benzodiazepines, neuroleptics, anticonvulsants, antidepressants) that may have contributed to the adverse reactions.
d) Ten hours after her last dose of fluoxetine, a 45-year-old woman began tranylcypromine therapy (Kline et al, 1989l). Headache, muscle contractions, insomnia, and unsteady gait were reported on the second day. Thioridazine and tryptophan were added to her therapy. The patient experienced fever, rigidity of the arms and legs, and hyperreflexia. She died in the intensive care unit of a hospital 44 hours later.
e) 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 therapy. 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 and selegiline. Both drugs were discontinued, with relatively quick resolution of symptoms. Rechallenge with fluoxetine alone occurred without incident.

3.5.1.FO 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 PROZAC(R) oral capsules, delayed-release capsules, solution, 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 (Prod Info PROZAC(R) oral capsules, delayed-release capsules, solution, 2008).
3) Severity: major
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: When fluoxetine and an anticoagulant are given concurrently, monitor patient for signs of increased bleeding. Patients who are taking warfarin should be monitored closely for altered anticoagulant effects, including increased bleeding, when fluoxetine therapy is initiated or discontinued (Prod Info PROZAC(R) oral capsules, delayed-release capsules, solution, 2008).
7) Probable Mechanism: unknown
8) Literature Reports

a) Fluoxetine is thought to inhibit the cytochrome P450 2C9 isoenzyme (CYP2C9). This is the enzyme by which the more potent warfarin isomer, S-warfarin, is metabolized (Riesenman, 1995). In addition, both fluoxetine and warfarin are tightly bound to albumin. In combination, the possibility for protein-binding displacement of either drug is present (Prod Info Coumadin(R), 1999).
b) 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).
c) 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).
d) In 6 reported cases, INR increased during combined fluoxetine and warfarin therapy. In a seventh case, severe bruising of the lower legs occurred in a woman initially treated with fluoxetine and, secondarily, started on warfarin (Woolfrey et al, 1993; Claire et al, 1991).
e) An 83-year-old man died from cerebral hemorrhage secondary to increased warfarin concentrations.

The patient had been taking warfarin 30 mg per week for atrial fibrillation with a target INR between 2 and 3. The patient's other drugs included lisinopril, furosemide, potassium, digoxin, and acetaminophen. After being seen for symptoms of depression, anxiety, and insomnia, the patient was given fluoxetine 20 mg per day and diazepam 2.5 mg 3 to 4 times per day. Eight days later, the patient's INR increased to 4.8, and the dose of warfarin was decreased to 27.5 mg per week. The patient was later seen for symptoms of drug delirium, including confusion, incoherence, and speaking irrationally. At this point, the INR was 3.64 and fluoxetine was discontinued. The next day the patient presented to the hospital with left-sided weakness and later died from complications of a large interparenchymal hemorrhage. The authors proposed that the addition of fluoxetine to the patient's regimen resulted in increased serum levels of both warfarin and diazepam, resulting in delirium and loss of anticoagulant control (Dent & Orrock, 1997).

3.5.1.FP Paroxetine

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.FQ Pentamidine

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Pentamidine and fluoxetine have been shown to prolong the QTc interval at the recommended therapeutic dose (Prod Info Prozac(R), 2001f; Lindsay et al, 1990). Even though no formal drug interaction studies have been done, the coadministration of drugs known to prolong the QTc interval is not recommended.
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of pentamidine and fluoxetine is not recommended.
7) Probable Mechanism: additive effects on QT prolongation

3.5.1.FR Pentazocine

1) Interaction Effect: hypertension, diaphoresis, ataxia, flushing, nausea, dizziness, and anxiety
2) Summary: A case of neurologic effects associated with concomitant use of fluoxetine and pentazocine has been reported in the literature (Hansen et al, 1990a).
3) Severity: moderate
4) Onset: rapid
5) Substantiation: probable
6) Clinical Management: Until more data are available, concomitant use of fluoxetine and pentazocine should be undertaken with caution.
7) Probable Mechanism: unknown
8) Literature Reports
a) One study reported a case in which coadministration of fluoxetine and pentazocine was associated with a marked neurologic reaction. A 39-year-old male taking fluoxetine 40 mg daily was administered oral pentazocine 50 mg for a severe headache. Approximately 30 minutes after receiving the pentazocine, the patient became hypertensive, diaphoretic, flushed, ataxic, paresthetic, nauseated, lightheaded, and anxious. Although an interaction between fluoxetine and pentazocine may have occurred, a hypersensitivity to pentazocine alone was not ruled out (Hansen et al, 1990).
b) Fluoxetine administered seven days before surgery had no effect on kappa-opiate pentazocine analgesia but significantly attenuated the analgesia produced by morphine (p less than 0.05), a mu-opiate. The duration of action of morphine analgesia was shortened by the addition of fluoxetine. The authors point out that the effect of chronic fluoxetine administration on mu-opiate analgesia is not clear and further studies are needed (Gordon et al, 1994).

3.5.1.FS 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 PROZAC(R) oral capsules, delayed-release capsules, solution, 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 (Prod

Info PROZAC(R) oral capsules, delayed-release capsules, solution, 2008).
3) Severity: major
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: When fluoxetine and an anticoagulant are given concurrently, monitor patient for signs of increased bleeding. Patients who are taking warfarin should be monitored closely for altered anticoagulant effects, including increased bleeding, when fluoxetine therapy is initiated or discontinued (Prod Info PROZAC(R) oral capsules, delayed-release capsules, solution, 2008).
7) Probable Mechanism: unknown
8) Literature Reports
a) Fluoxetine is thought to inhibit the cytochrome P450 2C9 isoenzyme (CYP2C9). This is the enzyme by which the more potent warfarin isomer, S-warfarin, is metabolized (Riesenman, 1995). In addition, both fluoxetine and warfarin are tightly bound to albumin. In combination, the possibility for protein-binding displacement of either drug is present (Prod Info Coumadin(R), 1999).
b) 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).
c) 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).
d) In 6 reported cases, INR increased during combined fluoxetine and warfarin therapy. In a seventh case, severe bruising of the lower legs occurred in a woman initially treated with fluoxetine and, secondarily, started on warfarin (Woolfrey et al, 1993; Claire et al, 1991).
e) An 83-year-old man died from cerebral hemorrhage secondary to increased warfarin concentrations. The patient had been taking warfarin 30 mg per week for atrial fibrillation with a target INR between 2 and 3. The patient's other drugs included lisinopril, furosemide, potassium, digoxin, and acetaminophen. After being seen for symptoms of depression, anxiety, and insomnia, the patient was given fluoxetine 20 mg per day and diazepam 2.5 mg 3 to 4 times per day. Eight days later, the patient's INR increased to 4.8, and the dose of warfarin was decreased to 27.5 mg per week. The patient was later seen for symptoms of drug delirium, including confusion, incoherence, and speaking irrationally. At this point, the INR was 3.64 and fluoxetine was discontinued. The next day the patient presented to the hospital with left-sided weakness and later died from complications of a large interparenchymal hemorrhage. The authors proposed that the addition of fluoxetine to the patient's regimen resulted in increased serum levels of both warfarin and diazepam, resulting in delirium and loss of anticoagulant control (Dent & Orrock, 1997).

3.5.1.FT Phenelzine
1) Interaction Effect: CNS toxicity or serotonin syndrome (hypertension, hyperthermia, myoclonus, mental status changes)
2) Summary: Concurrent administration or overlapping therapy with fluoxetine 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 (Prod Info Prozac(R), 1999b; Sternbach, 1991g; Coplan & Gorman, 1993e; Feighner et al, 1990e; Kline et al, 1989e; Suchowersky & de Vries, 1990e). Concomitant use of phenelzine and fluoxetine is contraindicated. Allow at least five weeks between discontinuation of fluoxetine and initiation of phenelzine and at least 10 days between discontinuation of phenelzine and initiation of fluoxetine, or other serotoninergic agents (Prod Info Nardil(R), 1995).
3) Severity: contraindicated
4) Onset: rapid

5) Substantiation: theoretical
6) Clinical Management: Concurrent use of fluoxetine and phenelzine is contraindicated. Wait at least 14 days after discontinuing phenelzine before initiating fluoxetine therapy. In addition, wait at least five weeks after discontinuing fluoxetine before initiating therapy with a MAO inhibitor.
7) Probable Mechanism: inhibition of serotonin metabolism by monoamine oxidase
8) Literature Reports
a) Concomitant use of serotonin specific reuptake inhibitors and monoamine oxidase inhibitors can 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.
b) It has been suggested that fluoxetine therapy be discontinued for five weeks before beginning therapy with a monoamine oxidase inhibitor. However, one case report describes a 28-year old woman who had discontinued a 2-year fluoxetine regimen for six weeks before starting therapy with tranylcypromine. Over the next few days the patient developed fever, paresthesias, confusion, abdominal cramping, and various other CNS symptoms. Upon discontinuation of tranylcypromine, the patient's symptoms began to resolve. Blood samples taken three days after discontinuation of tranylcypromine revealed no presence of fluoxetine; however, the norfluoxetine level was 84 ng/mL (Coplan & Gorman, 1993d).
c) Adverse reactions reported when fluoxetine was given concomitantly with phenelzine (n=9) or tranylcypromine (n=4) include tremor (50%), agitation or restlessness (42%), mental status changes (42%), myoclonus (33%), diarrhea (33%), and blood pressure changes (25%) (Feighner et al, 1990d). All but one of the patients were taking other medications (ie, benzodiazepines, neuroleptics, anticonvulsants, antidepressants) that may have contributed to the adverse reactions.
d) Ten hours after her last dose of fluoxetine, a 45-year-old woman began tranylcypromine therapy (Kline et al, 1989d). Headache, muscle contractions, insomnia, and unsteady gait were reported on the second day. Thioridazine and tryptophan were added to her therapy. The patient experienced fever, rigidity of the arms and legs, and hyperreflexia. She died in the intensive care unit of a hospital 44 hours later.
e) Two cases suggestive of an interaction between fluoxetine and selegiline were reported (Suchowersky & de Vries, 1990d). One case involved a first episode of mania being observed approximately one month after adding selegiline to fluoxetine therapy. 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 and selegiline. Both drugs were discontinued, with relatively quick resolution of symptoms. Rechallenge with fluoxetine alone occurred without incident.

3.5.1.FU 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 PROZAC(R) oral capsules, delayed-release capsules, solution, 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 (Prod Info PROZAC(R) oral capsules, delayed-release capsules, solution, 2008).
3) Severity: major
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: When fluoxetine and an anticoagulant are given concurrently, monitor patient for signs of increased bleeding. Patients who are taking warfarin should be monitored closely for altered anticoagulant effects, including increased bleeding, when fluoxetine therapy is initiated or discontinued (Prod Info PROZAC(R) oral capsules, delayed-release capsules, solution, 2008).
7) Probable Mechanism: unknown
8) Literature Reports
a) Fluoxetine is thought to inhibit the cytochrome P450 2C9 isoenzyme (CYP2C9). This is the enzyme by which the more potent warfarin isomer, S-warfarin, is metabolized (Riesenman, 1995). In addition, both fluoxetine and warfarin are tightly bound to albumin. In combination, the possibility for protein-binding displacement of either drug is present (Prod Info Coumadin(R), 1999).
b) 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).

c) 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).

d) In 6 reported cases, INR increased during combined fluoxetine and warfarin therapy. In a seventh case, severe bruising of the lower legs occurred in a woman initially treated with fluoxetine and, secondarily, started on warfarin (Woolfrey et al, 1993; Claire et al, 1991).

e) An 83-year-old man died from cerebral hemorrhage secondary to increased warfarin concentrations. The patient had been taking warfarin 30 mg per week for atrial fibrillation with a target INR between 2 and 3. The patient's other drugs included lisinopril, furosemide, potassium, digoxin, and acetaminophen. After being seen for symptoms of depression, anxiety, and insomnia, the patient was given fluoxetine 20 mg per day and diazepam 2.5 mg 3 to 4 times per day. Eight days later, the patient's INR increased to 4.8, and the dose of warfarin was decreased to 27.5 mg per week. The patient was later seen for symptoms of drug delirium, including confusion, incoherence, and speaking irrationally. At this point, the INR was 3.64 and fluoxetine was discontinued. The next day the patient presented to the hospital with left-sided weakness and later died from complications of a large interparenchymal hemorrhage. The authors proposed that the addition of fluoxetine to the patient's regimen resulted in increased serum levels of both warfarin and diazepam, resulting in delirium and loss of anticoagulant control (Dent & Orrock, 1997).

3.5.1.FV 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 PROZAC(R) oral capsules, delayed-release capsules, solution, 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 (Prod Info PROZAC(R) oral capsules, delayed-release capsules, solution, 2008).

3) Severity: major

4) Onset: delayed

5) Substantiation: probable

6) Clinical Management: When fluoxetine and an anticoagulant are given concurrently, monitor patient for signs of increased bleeding. Patients who are taking warfarin should be monitored closely for altered anticoagulant effects, including increased bleeding, when fluoxetine therapy is initiated or discontinued (Prod Info PROZAC(R) oral capsules, delayed-release capsules, solution, 2008).

7) Probable Mechanism: unknown

8) Literature Reports

a) Fluoxetine is thought to inhibit the cytochrome P450 2C9 isoenzyme (CYP2C9). This is the enzyme by which the more potent warfarin isomer, S-warfarin, is metabolized (Riesenman, 1995). In addition, both fluoxetine and warfarin are tightly bound to albumin. In combination, the possibility for protein-binding displacement of either drug is present (Prod Info Coumadin(R), 1999).

b) 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).

c) 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).
d) In 6 reported cases, INR increased during combined fluoxetine and warfarin therapy. In a seventh case, severe bruising of the lower legs occurred in a woman initially treated with fluoxetine and, secondarily, started on warfarin (Woolfrey et al, 1993; Claire et al, 1991).
e) An 83-year-old man died from cerebral hemorrhage secondary to increased warfarin concentrations. The patient had been taking warfarin 30 mg per week for atrial fibrillation with a target INR between 2 and 3. The patient's other drugs included lisinopril, furosemide, potassium, digoxin, and acetaminophen. After being seen for symptoms of depression, anxiety, and insomnia, the patient was given fluoxetine 20 mg per day and diazepam 2.5 mg 3 to 4 times per day. Eight days later, the patient's INR increased to 4.8, and the dose of warfarin was decreased to 27.5 mg per week. The patient was later seen for symptoms of drug delirium, including confusion, incoherence, and speaking irrationally. At this point, the INR was 3.64 and fluoxetine was discontinued. The next day the patient presented to the hospital with left-sided weakness and later died from complications of a large interparenchymal hemorrhage. The authors proposed that the addition of fluoxetine to the patient's regimen resulted in increased serum levels of both warfarin and diazepam, resulting in delirium and loss of anticoagulant control (Dent & Orrock, 1997).

3.5.1.FW 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.FX Phenytoin

1) Interaction Effect: an increased risk of phenytoin toxicity (ataxia, hyperreflexia, nystagmus, tremor)
2) Summary: Several case reports indicate that concurrent use of fluoxetine and phenytoin can result in significantly increased phenytoin serum levels leading to toxicity (FDA, 1994a; Jalil, 1992a; Woods et al, 1994). Alternatively, patients who are stabilized on fluoxetine and phenytoin therapy may experience subtherapeutic concentrations of phenytoin and loss of seizure control when fluoxetine is discontinued (Shad & Preskorn, 1999a). During an in vitro study, the inhibitory effects of fluoxetine on cytochrome P450 2C9 were evaluated using p-hydroxylation of phenytoin as an established index reaction reflecting CYP2C9 activity. In vivo, p-hydroxylation of phenytoin depends on the formation of 5-(p-hydroxy-phenyl)-5-phenylhydantoin (HPPH). Fluoxetine, specifically the R-component of the racemic fluoxetine mixture, impaired the formation of HPPH, which can lead to an increase in steady-state phenytoin levels (Schmider et al, 1997).
3) Severity: moderate
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: Monitor phenytoin serum levels with the addition of fluoxetine and periodically thereafter to assure stability; lower phenytoin dosage may be required with concomitant therapy. Serum

levels of phenytoin should be monitored following the discontinuation of fluoxetine; however, because of the long half-life of fluoxetine, decreases in phenytoin levels may not be clinically significant for a few weeks. Careful monitoring is required.

7) Probable Mechanism: decreased phenytoin metabolism

8) Literature Reports

a) Twenty-three reported cases of fluoxetine-phenytoin interactions have resulted in large increases in serum phenytoin levels and/or symptoms of phenytoin toxicity. On the average, the adverse effects began within two weeks after fluoxetine was added to existing phenytoin therapy. The average increase in plasma levels in nine evaluable cases was 161% (range 75 to 309%) and the maximum phenytoin serum concentration in 16 evaluable cases ranged from 22 to 53.5 mcg/mL (therapeutic level, 10 to 20 mcg/mL) (FDA, 1994).

b) An 84-year-old woman was stabilized on phenytoin 300 mg daily. After two months of treatment, fluoxetine 20 mg daily was added to her therapy, and increased to 40 mg daily after 10 days (Jalil, 1992). Within five days of starting fluoxetine, she developed vertigo, gait ataxia, diplopia, and altered mental status; her phenytoin serum level had increased from 15 to 35 mcg/mL. Both phenytoin and fluoxetine were gradually reduced and the signs and symptoms of toxicity abated. Four weeks later she was rechallenged with the same dose of fluoxetine without a return of toxicity.

c) In another case, a 57-year-old woman who had been stabilized on phenytoin 400 mg daily for a year (serum level, 11.5 mcg/mL) was given fluoxetine 20 mg daily (Jalil, 1992). Ten days later she developed vomiting, vertigo, trunk ataxia, limb dysmetria, and multidirectional nystagmus, and the phenytoin serum level was 47 mcg/mL. Fluoxetine was discontinued and all signs and symptoms of toxicity disappeared over a three-week period. At four weeks post-fluoxetine, the phenytoin serum level was 20 mcg/mL.

d) A 42-year-old male with a history of grand mal seizures and aggressive behavior was receiving phenytoin 200 mg daily and carbamazepine 600 mg daily without resolution of his problems. His phenytoin level was 2.0 ng/mL and his dose was subsequently increased to 400 mg daily. Fluoxetine 20 mg daily was added for aggression, and the patient experienced resolution of his behavioral problems and a cessation of his seizure activity. The phenytoin level ranged between 10.9 ng/mL and 15.7 ng/mL during fluoxetine therapy. However, the patient discontinued fluoxetine on his own and after a month experienced a recurrence of problems. Phenytoin concentration was measured at 6.6 ng/mL six weeks after the discontinuation of fluoxetine, despite no change in his phenytoin dose. This case report illustrates the need for close monitoring of phenytoin levels when fluoxetine is initiated and discontinued, since subtherapeutic levels of phenytoin may result if doses of phenytoin are not readjusted following the cessation of fluoxetine (Shad & Preskorn, 1999).

3.5.1.FY Pimozide

1) Interaction Effect: bradycardia, somnolence, and potentially increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)

2) Summary: One case of bradycardia and somnolence resulting from concomitant fluoxetine and pimozide therapy has been reported (Ahmed et al, 1993). Although a specific interaction study has not been conducted with these agents, due to the potential for additive QT prolongation effects, the concomitant use of fluoxetine and pimozide is contraindicated (Prod Info PROZAC(R) oral capsule, oral pulvule, oral solution, oral tablet, 2005).

3) Severity: contraindicated

4) Onset: unspecified

5) Substantiation: probable

6) Clinical Management: Due to the possibility of additive effects on the QT interval, the concurrent administration of fluoxetine and pimozide is contraindicated.

7) Probable Mechanism: additive effects on QT prolongation

8) Literature Reports

a) One case has been reported in which concurrent use of pimozide 5 mg daily and fluoxetine 20 mg daily in an elderly patient resulted in severe bradycardia and somnolence. The pulse rate gradually returned to normal after discontinuation of pimozide; rechallenge with a lower pimozide dose and a higher fluoxetine dose also resulted in bradycardia (Ahmed et al, 1993).

3.5.1.FZ 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.GA Pirmenol

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Even though no formal drug interaction studies have been done, the coadministration of Class Ia antiarrhythmics and other drugs known to prolong the QTc interval is not recommended (Prod Info Quinaglute Dura-tabs(R), 1999). Fluoxetine has demonstrated QT prolongation at therapeutic doses (Prod Info Prozac(R), 2001z).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of class Ia antiarrhythmic agents and agents that prolong the QT interval, such as fluoxetine, is not recommended.
7) Probable Mechanism: additive effects on QT prolongation

3.5.1.GB 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.GC 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.GD Prajmaline
1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Even though no formal drug interaction studies have been done, the coadministration of Class Ia antiarrhythmics and other drugs known to prolong the QTc interval is not recommended (Prod Info Quinaglute Dura-tabs(R), 1999). Fluoxetine has demonstrated QT prolongation at therapeutic doses (Prod Info Prozac(R), 2001z).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of class Ia antiarrhythmic agents and agents that prolong the QT interval, such as fluoxetine, is not recommended.
7) Probable Mechanism: additive effects on QT prolongation

3.5.1.GE Probucol
1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Fluoxetine and probucol have been shown to prolong the QTc interval at the recommended therapeutic dose (Prod Info Prozac(R), 2001v; Gohn & Simmons, 1992; Prod Info Lorelco(R), 1991). Even though no formal drug interaction studies have been done, the coadministration of drugs known to prolong the QTc interval is not recommended.
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of fluoxetine and probucol is not recommended.
7) Probable Mechanism: additive effects on QT prolongation

3.5.1.GF Procainamide
1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Even though no formal drug interaction studies have been done, the coadministration of Class Ia antiarrhythmics and other drugs known to prolong the QTc interval is not recommended (Prod Info Quinaglute Dura-tabs(R), 1999). Fluoxetine has demonstrated QT prolongation at therapeutic doses (Prod Info Prozac(R), 2001z).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of class Ia antiarrhythmic agents and agents that prolong the QT interval, such as fluoxetine, is not recommended.
7) Probable Mechanism: additive effects on QT prolongation

3.5.1.GG Procarbazine
1) Interaction Effect: CNS toxicity or serotonin syndrome (hypertension, hyperthermia, myoclonus, mental status changes)
2) Summary: Concurrent administration or overlapping therapy with fluoxetine 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 (Prod Info Prozac(R), 1999; Sternbach, 1991b; Coplan & Gorman, 1993a; Feighner et al, 1990a; Kline et al, 1989a; Suchowersky & de Vries, 1990a). Concomitant use is contraindicated.
3) Severity: contraindicated
4) Onset: rapid
5) Substantiation: established
6) Clinical Management: Concurrent use of fluoxetine and procarbazine is contraindicated. Wait at least two weeks after discontinuing a MAO inhibitor before initiating fluoxetine therapy. In addition, wait at least five weeks after discontinuing fluoxetine before initiating therapy with a MAO inhibitor.
7) Probable Mechanism: inhibition of serotonin metabolism by monoamine oxidase
8) Literature Reports

a) Concomitant use of serotonin specific reuptake inhibitors and monoamine oxidase inhibitors can 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 (Sternbach, 1991a). If the syndrome is not recognized and correctly treated, death can result.
b) It has been suggested that fluoxetine therapy be discontinued for at least five weeks before beginning therapy with a monoamine oxidase inhibitor. A 28-year old woman discontinued fluoxetine for six weeks before starting therapy with tranylcypromine. Over the next few days the patient developed fever, paresthesias, confusion, abdominal cramping, and various other CNS symptoms. Upon discontinuation of tranylcypromine, the patient's symptoms began to resolve. Blood samples taken three days after discontinuation of tranylcypromine revealed no presence of fluoxetine; however, the norfluoxetine level was 84 ng/mL (Coplan & Gorman, 1993).
c) Adverse reactions reported when fluoxetine was given concomitantly with phenelzine (n=9) or tranylcypromine (n=4) include tremor (50%), agitation or restlessness (42%), mental status changes (42%), myoclonus (33%), diarrhea (33%), and blood pressure changes (25%) (Feighner et al, 1990). All but one of the patients were taking other medications (ie, benzodiazepines, neuroleptics, anticonvulsants, antidepressants) that may have contributed to the adverse reactions.
d) Ten hours after her last dose of fluoxetine, a 45-year-old woman began tranylcypromine therapy (Kline et al, 1989). Headache, muscle contractions, insomnia, and unsteady gait were reported on the second day. Thioridazine and tryptophan were added to her therapy. The patient experienced fever, rigidity of the arms and legs, and hyperreflexia. She died in the intensive care unit of a hospital 44 hours later.
e) Two cases reports suggested a possible interaction between fluoxetine and selegiline (Suchowersky & de Vries, 1990). One case involved a first episode of mania being observed approximately one month after adding selegiline to fluoxetine therapy. 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 and selegiline. Both drugs were discontinued, with relatively quick resolution of symptoms. Rechallenge with fluoxetine alone occurred without incident.

3.5.1.GH Prochlorperazine

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Although citing no data, the manufacturers of some phenothiazines state that concomitant use with other drugs which prolong the QT interval is not recommended. Q and T wave distortions have been observed in patients taking phenothiazines (Prod Info Compazine(R), 2002; Prod Info Stelazine(R), 2002; Prod Info Thorazine(R), 2002) . Other phenothiazines may have similar effects, though no reports are available. Fluoxetine has been shown to prolong the QTc interval at the recommended therapeutic dose (Prod Info Prozac(R), 2003).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of fluoxetine and a phenothiazine is not recommended.
7) Probable Mechanism: additive effects on QT prolongation

3.5.1.GI Propafenone

1) Interaction Effect: increased serum propafenone concentrations and an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Propafenone has been shown to prolong the QTc interval (Larochelle et al, 1984). Fluoxetine has been shown to prolong the QTc interval at the recommended therapeutic dose (Prod Info Prozac(R), 2001e). Even though no formal drug interaction studies have been done, caution is advised if drugs known to prolong the QT interval are used concomitantly. In addition, fluoxetine may inhibit cytochrome P450 2D6 (CYP2D6) and impair the metabolism of propafenone (Cai et al, 1999a).
3) Severity: major
4) Onset: rapid
5) Substantiation: probable
6) Clinical Management: Caution is advised if fluoxetine and propafenone are used concomitantly.
7) Probable Mechanism: inhibition of cytochrome P450 2D6-mediated propafenone metabolism; theoretical additive effects on QT prolongation
8) Literature Reports
a) The metabolism of propafenone enantiomers was altered after fluoxetine treatment in 9 healthy Chinese subjects. All subjects were extensive CYP2D6 metabolizers. Subjects received a single oral dose of propafenone 400 mg both before and after fluoxetine 20 mg daily for ten days. The oral clearance of both S- and P- enantiomers of propafenone decreased from approximately 75 L/hr to 50 L/hr and 107 L/hr to 70 L/hr, respectively. Compared to baseline, the elimination half life, peak concentration, and area under the curve for both enantiomers after fluoxetine therapy were significantly increased (Cai et al, 1999).

3.5.1.GJ Propranolol

1) Interaction Effect: an increased risk of complete heart block

2) Summary: Metabolism of propranolol occurs in the liver and is thought to involve cytochrome P450IID6 (CYP2D6). Fluoxetine is a potent inhibitor of CYP2D6 (DeVane, 1994a). It is theoretically possible that coadministered fluoxetine could inhibit propranolol metabolism, leading to elevated serum concentrations of this beta blocker and possible toxicity. One case report describes a man who developed complete heart block two weeks after fluoxetine was added to propranolol therapy (Drake & Gordon, 1994a).

3) Severity: minor

4) Onset: delayed

5) Substantiation: probable

6) Clinical Management: Fluoxetine should be prescribed cautiously to patients on propranolol therapy. A baseline electrocardiogram should be considered prior to the initiation of fluoxetine.

7) Probable Mechanism: impaired atrioventricular conduction

8) Literature Reports

a) A 53-year-old male experienced a loss of consciousness two weeks after fluoxetine 20 mg daily was prescribed for depression. Other medications included propranolol 40 mg twice daily for anxiety. He had no previous cardiac history. An electrocardiogram revealed a complete heart block, and fluoxetine and propranolol were both discontinued. Two days later, the patient reverted to sinus rhythm with a heart rate of 60 beats per minute. The heart block was attributed to the fluoxetine-propranolol combination, since sinus rhythm returned two days after the discontinuation of fluoxetine, and the patient had no previous complications from propranolol therapy. Because 5-hydroxytryptamine (5-HT) receptors are located in the atrium of the heart, fluoxetine may have potentiated the action of 5-HT, causing impaired atrioventricular conduction (Drake & Gordon, 1994).

3.5.1.GK 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.GL 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.GM Quetiapine

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)

2) Summary: Fluoxetine has been shown to prolong the QTc interval at the recommended therapeutic dose (Prod Info Prozac(R), 2001l). Even though no formal drug interaction studies have been done, the coadministration of antipsychotics and other drugs known to prolong the QTc interval, including fluoxetine, is not recommended. Several antipsychotic agents have demonstrated QT prolongation including amisulpride (Prod Info Solian(R), 1999), quetiapine (Owens, 2001b), sertindole (Agelink et al, 2001), sultopride (Lande et al, 1992), and zotepine (Sweetman, 2003).

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: The concurrent administration of fluoxetine and antipsychotics is not recommended.

7) Probable Mechanism: additive effects on QT prolongation

3.5.1.GN Quinidine

1) Interaction Effect: an increased risk of fluoxetine and quinidine toxicity and an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)

2) Summary: Even though no formal drug interaction studies have been done, the coadministration of Class IA antiarrhythmics such as quinidine and other drugs known to prolong the QTc interval is not recommended (Prod Info Quinaglute Dura-tabs(R), 1999a). Fluoxetine has demonstrated QT prolongation at therapeutic doses (Prod Info Prozac(R), 2001af). In addition, quinidine inhibits CYP2D6 which may reduce fluoxetine metabolism (Stevens & Wrighton, 1993b) and fluoxetine inhibits CYP3A4, which may reduce quinidine metabolism (Nemeroff et al, 1996).

3) Severity: moderate

4) Onset: delayed

5) Substantiation: theoretical

6) Clinical Management: The concurrent administration of Class Ia antiarrhythmic agents, such as quinidine, and agents that prolong the QT interval, such as fluoxetine, is not recommended.

7) Probable Mechanism: altered fluoxetine or quinidine metabolism; additive effects on QT prolongation

8) Literature Reports

a) In vitro studies found that quinidine, a potent inhibitor of CYP2D6, inhibited fluoxetine N-demethylation by 20% (Stevens & Wrighton, 1993a). While indicating that fluoxetine is, in part, metabolized by CYP2D6, this study showed that much of fluoxetine metabolism may occur via alternate pathways.

3.5.1.GO 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 fluoxetine, 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 not allow concomitant use of fluoxetine; the combination of rasagiline and fluoxetine should be avoided. Wait at least two weeks after discontinuing rasagiline before initiating fluoxetine therapy. Wait at least five weeks or more, especially if fluoxetine has been used chronically and/or at high doses, after discontinuing fluoxetine before initiating therapy with rasagiline (Prod Info AZILECT(R) oral tablets, 2006).

3) Severity: major

4) Onset: unspecified

5) Substantiation: probable

6) Clinical Management: Concurrent use of fluoxetine and rasagiline should be avoided. Wait at least two weeks after discontinuing rasagiline before initiating fluoxetine therapy. Wait at least five weeks or more, especially if fluoxetine has been used chronically and/or at high doses, after discontinuing fluoxetine before initiating therapy with rasagiline.

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

3.5.1.GP 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 PROZAC(R) oral capsules, delayed-release capsules, solution, 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 (Prod Info PROZAC(R) oral capsules, delayed-release capsules, solution, 2008).

3) Severity: major

4) Onset: delayed

5) Substantiation: probable

6) Clinical Management: When fluoxetine and an anticoagulant are given concurrently, monitor patient for signs of increased bleeding. Patients who are taking warfarin should be monitored closely for altered anticoagulant effects, including increased bleeding, when fluoxetine therapy is initiated or discontinued (Prod Info PROZAC(R) oral capsules, delayed-release capsules, solution, 2008).

7) Probable Mechanism: unknown

8) Literature Reports

a) Fluoxetine is thought to inhibit the cytochrome P450 2C9 isoenzyme (CYP2C9). This is the enzyme by which the more potent warfarin isomer, S-warfarin, is metabolized (Riesenman, 1995). In addition, both fluoxetine and warfarin are tightly bound to albumin. In combination, the possibility for protein-binding displacement of either drug is present (Prod Info Coumadin(R), 1999).

b) 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).

c) 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).

d) In 6 reported cases, INR increased during combined fluoxetine and warfarin therapy. In a seventh case, severe bruising of the lower legs occurred in a woman initially treated with fluoxetine and, secondarily, started on warfarin (Woolfrey et al, 1993; Claire et al, 1991).

e) An 83-year-old man died from cerebral hemorrhage secondary to increased warfarin concentrations. The patient had been taking warfarin 30 mg per week for atrial fibrillation with a target INR between 2 and 3. The patient's other drugs included lisinopril, furosemide, potassium, digoxin, and acetaminophen. After being seen for symptoms of depression, anxiety, and insomnia, the patient was given fluoxetine 20 mg per day and diazepam 2.5 mg 3 to 4 times per day. Eight days later, the patient's INR increased to 4.8, and the dose of warfarin was decreased to 27.5 mg per week. The patient was later seen for symptoms of drug delirium, including confusion, incoherence, and speaking irrationally. At this point, the INR was 3.64 and fluoxetine was discontinued. The next day the patient presented to the hospital with left-sided weakness and later died from complications of a large interparenchymal hemorrhage. The authors proposed that the addition of fluoxetine to the patient's regimen resulted in increased serum levels of both warfarin and diazepam, resulting in delirium and loss of anticoagulant control (Dent & Orrock, 1997).

3.5.1.GQ Risperidone

1) Interaction Effect: increased plasma concentrations of risperidone

2) Summary: Concomitant use of fluoxetine (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 fluoxetine. One study demonstrated increased risperidone levels in patients treated concurrently with fluoxetine and risperidone (Prod Info RISPERDAL(R) oral tablets, oral solution, orally disintegrating tablets, 2008; Spina et al, 2002). Monitoring the patient for increased risperidone plasma levels side effects may be necessary (Spina et al, 2002). The risperidone dose should be reevaluated if fluoxetine is initiated or discontinued (Prod Info RISPERDAL(R) oral tablets, oral solution, orally disintegrating tablets, 2008) (Spina et al, 2002a).

3) Severity: moderate

4) Onset: unspecified

5) Substantiation: probable

6) Clinical Management: Concomitant use of fluoxetine 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). Carefully monitor patients for increased plasma risperidone levels and side effects (serotonin syndrome, extrapyramidal symptoms, and cardiotoxicity) when fluoxetine is coadministered with risperidone (Spina et al, 2002). Reevaluate the dose of risperidone when concomitant fluoxetine is initiated or discontinued (Prod Info RISPERDAL(R) oral tablets, oral solution, orally disintegrating tablets, 2008).

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

8) Literature Reports

a) Fluoxetine (a CYP2D6 inhibitor) 20 mg/day has been shown to increase the plasma concentration of risperidone (a CYP2D6 substrate) 2.5- to 2.8-fold. Fluoxetine did not affect the concentration of 9-hydroxyrisperidone. The dosage of risperidone should be reevaluated when fluoxetine is initiated or discontinued (Prod Info RISPERDAL(R) oral tablets, oral solution, orally disintegrating tablets, 2008).

b) Fluoxetine, an 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 an open, 4-week, pharmacokinetic study including 9 patients with schizophrenia or schizoaffective disorder, depressive type, risperidone concentrations increased when fluoxetine was coadministered with risperidone. Patients were stabilized on a fixed dose of risperidone 4 to 6 mg/day for at least four weeks and received adjunctive fluoxetine therapy 20 mg/day for the management of concomitant depression. Mean plasma risperidone concentrations increased from 12 ng/mL at baseline to 49 nanograms (ng)/mL (p less than 0.01) at week 2, and 56 ng/mL (p less than 0.01) at week 4. Plasma concentrations of 9-hydroxyrisperidone (9-OH-risperidone) showed no significant increase at 4 weeks compared with baseline. After 4 weeks of concurrent therapy, the active moiety (risperidone plus 9-OH-risperidone) was increased by 75% (range: 9% to 204%, p less than 0.01) compared with baseline. The mean plasma risperidone to 9-OH-risperidone ratio also increased significantly. Two patients experienced Parkinsonian symptoms during week 2 of concomitant therapy and were treated with anticholinergic medication. The authors suggest that monitoring plasma risperidone levels may be warranted in patients receiving concomitant fluoxetine and risperidone treatment (Spina et al, 2002).

3.5.1.GR Ritonavir

1) Interaction Effect: alterations in cardiac and/or neurologic function

2) Summary: Coadministration of fluoxetine 30 mg twice daily for eight days and ritonavir 600 mg as a single dose in 16 patients resulted in a 19% increase in the area under the concentration-time curve (AUC) of ritonavir but no changes in the ritonavir maximum concentration (Cmax). However, post-marketing experience has revealed reports of cardiac and neurologic events when ritonavir and fluoxetine have been coadministered (Prod Info Norvir(R), 1999).

3) Severity: moderate

4) Onset: delayed

5) Substantiation: established

6) Clinical Management: Monitor the patient for changes in cardiac and/or neurologic function.

7) Probable Mechanism: unknown

3.5.1.GS 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.GT 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.GU Selegiline
1) Interaction Effect: CNS toxicity or serotonin syndrome (hypertension, hyperthermia, myoclonus, mental status changes)
2) Summary: Concurrent administration or overlapping therapy with fluoxetine and selegiline 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 (Prod Info Prozac(R), 1999g; Sternbach, 1991m; Coplan & Gorman, 1993k; Feighner et al, 1990k; Kline et al, 1989k; Suchowersky & de Vries, 1990k). Concomitant use is contraindicated. A minimum of 14 days should elapse after discontinuing selegiline before initiating therapy with fluoxetine. At least five weeks should elapse after discontinuing fluoxetine prior to initiating of treatment with selegiline (Prod Info EMSAM(R) transdermal patch, 2006).
3) Severity: contraindicated
4) Onset: rapid
5) Substantiation: theoretical
6) Clinical Management: Concurrent use of fluoxetine and selegiline is contraindicated. Wait at least two weeks after discontinuing selegiline before initiating fluoxetine therapy. In addition, wait at least five weeks after discontinuing fluoxetine before initiating therapy with selegiline.
7) Probable Mechanism: inhibition of serotonin metabolism by monoamine oxidase
8) Literature Reports
a) Concomitant use of serotonin specific reuptake inhibitors and monoamine oxidase inhibitors can 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 (Sternbach, 1991l). If the syndrome is not recognized and correctly treated, death can result.
b) It has been suggested that fluoxetine therapy be discontinued for five weeks before beginning therapy with a monoamine oxidase inhibitor. However, one case report describes a 28-year old woman

who had discontinued a 2-year fluoxetine regimen for six weeks before starting therapy with tranylcypromine. Over the next few days the patient developed fever, paresthesias, confusion, abdominal cramping, and various other CNS symptoms. Upon discontinuation of tranylcypromine, the patient's symptoms began to resolve. Blood samples taken three days after discontinuation of tranylcypromine revealed no presence of fluoxetine; however, the norfluoxetine level was 84 ng/mL (Coplan & Gorman, 1993j).
c) Adverse reactions reported when fluoxetine was given concomitantly with phenelzine (n=9) or tranylcypromine (n=4) include tremor (50%), agitation or restlessness (42%), mental status changes (42%), myoclonus (33%), diarrhea (33%), and blood pressure changes (25%) (Feighner et al, 1990j). All but one of the patients were taking other medications (ie, benzodiazepines, neuroleptics, anticonvulsants, antidepressants) that may have contributed to the adverse reactions.
d) Ten hours after her last dose of fluoxetine, a 45-year-old woman began tranylcypromine therapy (Kline et al, 1989j). Headache, muscle contractions, insomnia, and unsteady gait were reported on the second day. Thioridazine and tryptophan were added to her therapy. The patient experienced fever, rigidity of the arms and legs, and hyperreflexia. She died in the intensive care unit of a hospital 44 hours later.
e) Two cases suggestive of an interaction between fluoxetine and selegiline were reported (Suchowersky & de Vries, 1990j). One case involved a first episode of mania being observed approximately one month after adding selegiline to fluoxetine therapy. 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 and selegiline. Both drugs were discontinued, with relatively quick resolution of symptoms. Rechallenge with fluoxetine alone occurred without incident.

3.5.1.GV Sematilide

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Even though no formal drug interaction studies have been done, the coadministration of Class III antiarrhythmics and other drugs known to prolong the QTc interval is not recommended (Allen et al, 2002; Prod Info Tikosyn(TM) dofetilide capsules, 1999; Prod Info Corvert(R), 1998). Fluoxetine has been shown to prolong the QTc interval at the recommended therapeutic dose (Prod Info Prozac(R), 2001a).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of class III antiarrhythmic agents and agents that prolong the QT interval, such as fluoxetine, is not recommended.
7) Probable Mechanism: additive effects on QT prolongation

3.5.1.GW Sertindole

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Fluoxetine has been shown to prolong the QTc interval at the recommended therapeutic dose (Prod Info Prozac(R), 2001l). Even though no formal drug interaction studies have been done, the coadministration of antipsychotics and other drugs known to prolong the QTc interval, including fluoxetine, is not recommended. Several antipsychotic agents have demonstrated QT prolongation including amisulpride (Prod Info Solian(R), 1999), quetiapine (Owens, 2001b), sertindole (Agelink et al, 2001), sultopride (Lande et al, 1992), and zotepine (Sweetman, 2003).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of fluoxetine and antipsychotics is not recommended.
7) Probable Mechanism: additive effects on QT prolongation

3.5.1.GX 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.GY 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, 1991).

3.5.1.GZ Sotalol

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)

2) Summary: Even though no formal drug interaction studies have been done, the coadministration of Class III antiarrhythmics and other drugs known to prolong the QTc interval is not recommended (Allen et al, 2002; Prod Info Tikosyn(TM) dofetilide capsules, 1999; Prod Info Corvert(R), 1998). Fluoxetine has been shown to prolong the QTc interval at the recommended therapeutic dose (Prod Info Prozac(R), 2001a).

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: The concurrent administration of class III antiarrhythmic agents and agents that prolong the QT interval, such as fluoxetine, is not recommended.

7) Probable Mechanism: additive effects on QT prolongation

3.5.1.HA Spiramycin

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)

2) Summary: Spiramycin and fluoxetine have been shown to prolong the QTc interval at the recommended therapeutic dose (Prod Info Prozac(R), 2001j; Stramba-Badiale et al, 1997). Even though no formal drug interaction studies have been done, the coadministration of drugs known to prolong the QTc interval is not recommended.

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: The concurrent administration of spiramycin and fluoxetine is not recommended.

7) Probable Mechanism: additive effects on QT prolongation

3.5.1.HB 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.HC Sulfamethoxazole

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)

2) Summary: Cotrimoxazole and fluoxetine have been shown to prolong the QTc interval at the recommended therapeutic dose (Prod Info Prozac(R), 2001ah; Lopez et al, 1987). Even though no formal drug interaction studies have been done, the coadministration of drugs known to prolong the QTc interval is not recommended.

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: The concurrent administration of cotrimoxazole and fluoxetine is not

recommended.
7) Probable Mechanism: additive effects on QT prolongation

3.5.1.HD 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.HE 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.HF 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.HG Sultopride
1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Fluoxetine has been shown to prolong the QTc interval at the recommended therapeutic dose (Prod Info Prozac(R), 2001l). Even though no formal drug interaction studies have been done, the coadministration of antipsychotics and other drugs known to prolong the QTc interval, including fluoxetine, is not recommended. Several antipsychotic agents have demonstrated QT prolongation including amisulpride (Prod Info Solian(R), 1999), quetiapine (Owens, 2001b), sertindole (Agelink et al, 2001), sultopride (Lande et al, 1992), and zotepine (Sweetman, 2003).

3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of fluoxetine and antipsychotics is not recommended.
7) Probable Mechanism: additive effects on QT prolongation

3.5.1.HH Sumatriptan

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 and a serotonin specific reuptake inhibitor (SSRI) (Prod Info Imitrex(R), 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 sumatriptan, and an SSRI, such as fluoxetine, 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) In the Canadian post-marketing surveillance program of fluoxetine, six cases of suspected drug interactions with sumatriptan have been reported. Of these cases, two are strongly suggestive of a drug interaction. Patients demonstrated symptoms consistent with serotonin syndrome (Joffe & Sokolov, 1997).

3.5.1.HI 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.HJ Tamoxifen

1) Interaction Effect: decreased tamoxifen efficacy
2) Summary: A retrospective analysis revealed a 1.9-fold higher breast cancer recurrence rate in patients receiving a CYP2D6 inhibitor concomitantly with tamoxifen than those receiving tamoxifen alone (Aubert, Stanek, and Yao, 2009). Coadministration of tamoxifen with a potent CYP2D6 inhibitor, such as fluoxetine, may inhibit the CYP2D6-mediated metabolism of tamoxifen to the active metabolite, endoxifen. Monitor patients receiving a CYP2D6 inhibitor concomitantly with tamoxifen closely for loss of tamoxifen efficacy.
3) Severity: moderate

4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Coadministration of fluoxetine and tamoxifen may result in decreased concentrations of endoxifen (active metabolite of tamoxifen), thereby decreasing tamoxifen efficacy. If administered concurrently, monitor closely for decreased tamoxifen efficacy.
7) Probable Mechanism: inhibition of CYP2D6-mediated tamoxifen metabolism to endoxifen (active metabolite)
8) Literature Reports
a) A retrospective analysis of breast cancer patients revealed a 1.9-fold higher 2-year recurrence rate of breast cancer in patients receiving concomitant therapy with tamoxifen and a CYP2D6 inhibitor compared with those receiving tamoxifen therapy alone. Based on medical and pharmacy claims data, 1928 patients who were new to tamoxifen therapy in a 30-month period and who had follow-up data for at least 24 months were included in the analysis. Among these patients, 353 (median age, 53 years) received tamoxifen concurrently with a CYP2D6 inhibitor and 945 (median age, 52 years) received tamoxifen alone. Disease recurrence was identified by diagnosis and insurance billing codes for mastectomy, lumpectomy, lymph node dissection, or radiation therapy, occurring at least 6 months after initiation of tamoxifen therapy. The 2-year breast cancer recurrence rate was 13.9% in women receiving concomitant tamoxifen and CYP2D6 inhibitor therapy compared with 7.5% in women receiving tamoxifen alone (95% CI, 1.33 to 2.76, p=0.001; hazard ratio, 1.92). Intervention procedures in the tamoxifen/CYP2D6 inhibitor group to treat breast cancer included mastectomy (54%), lumpectomy (36%), and radiation therapy (47%); corresponding intervention rates in the tamoxifen only group were 52%, 38%, and 46%, respectively (Aubert, Stanek, and Yao, 2009).

3.5.1.HK Tamsulosin
1) Interaction Effect: an increase in tamsulosin plasma exposure
2) Summary: In vitro data have shown that tamsulosin is primarily metabolized by CYP2D6 and CYP3A4 hepatic isozymes. Coadministration with cimetidine, a mild inhibitor of CYP450 enzymes, resulted in moderate increases in tamsulosin plasma exposure. Although no pharmacokinetic studies have been conducted with moderate or strong CYP2D6 inhibitors, such as fluoxetine, use caution if these agents are coadministered with tamsulosin, particularly at tamsulosin doses exceeding 0.4 mg (Prod Info FLOMAX(R) oral capsules, 2007). Patients should be monitored for increased tamsulosin adverse effects such as postural hypotension, dizziness, and syncope.
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Due to the potential for increased tamsulosin plasma exposures, use caution when moderate or strong CYP2D6 inhibitors, such as fluoxetine, are coadministered with tamsulosin, particularly at tamsulosin doses higher than 0.4 mg (Prod Info FLOMAX(R) oral capsules, 2007). Monitor patients for increased tamsulosin adverse effects (postural hypotension, dizziness, and episodes of syncope).
7) Probable Mechanism: potential inhibition of CYP2D6-mediated tamsulosin metabolism

3.5.1.HL 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.HM Tedisamil
1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Even though no formal drug interaction studies have been done, the coadministration of Class III antiarrhythmics and other drugs known to prolong the QTc interval is not recommended (Allen et al, 2002; Prod Info Tikosyn(TM) dofetilide capsules, 1999; Prod Info Corvert(R), 1998). Fluoxetine has been shown to prolong the QTc interval at the recommended therapeutic dose (Prod Info Prozac(R), 2001a).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical

6) Clinical Management: The concurrent administration of class III antiarrhythmic agents and agents that prolong the QT interval, such as fluoxetine, is not recommended.
7) Probable Mechanism: additive effects on QT prolongation

3.5.1.HN Telithromycin
1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Even though no formal drug interaction studies have been done, telithromycin should be coadministered cautiously with other drugs which are also known to prolong the QTc interval, including fluoxetine (Owens, 2001d; Prod Info Prozac(R), 2001o).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of telithromycin with other agents that can prolong the QT interval, such as fluoxetine, is not recommended.
7) Probable Mechanism: additive effects on QT prolongation

3.5.1.HO 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.HP 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.HQ Terfenadine

1) Interaction Effect: cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)

2) Summary: Although 2 cases have been reported in which concomitant terfenadine and fluoxetine resulted in cardiac toxicity in patients with no previous heart disease, a study of 12 healthy males demonstrated no significant pharmacokinetic or pharmacodynamic interaction between fluoxetine and terfenadine (Swims, 1993a; Marchiando & Cook, 1995a; Bergstrom et al, 1997a). Terfenadine and fluoxetine have been reported to cause QT prolongation at therapeutic doses. The administration of terfenadine with any other medication that may prolong the QT interval is contraindicated (Prod Info Seldane(R), 1997).

3) Severity: contraindicated

4) Onset: delayed

5) Substantiation: probable

6) Clinical Management: The concomitant administration of fluoxetine and terfenadine is contraindicated.

7) Probable Mechanism: decreased terfenadine metabolism

8) Literature Reports

a) In a study of 12 healthy male volunteers, fluoxetine did not inhibit the metabolism of terfenadine. Fluoxetine 60 mg daily was given for nine days. Terfenadine 60 mg was given alone and after eight days of the nine-day fluoxetine regimen. A high dose of fluoxetine was given to test the probability of interaction rigorously. Subject were monitored for changes in terfenadine pharmacokinetics and adverse effects. Concomitant fluoxetine resulted in a slight decrease in terfenadine plasma concentration. In addition, the area under the plasma concentration time curve for terfenadine was significantly decreased by fluoxetine. No change in blood pressure, heart rate, or cardiac electrographic tracings (EKG) were observed. One subjected reported dizziness after taking terfenadine alone and one subject had an abnormal EKG at baseline and during all observations during the study (Bergstrom et al, 1997).

b) A 39-year old woman experienced cardiac toxicity due to a possible interaction of terfenadine and fluoxetine (Marchiando & Cook, 1995). The patient's medications included acyclovir, beclomethasone, pseudoephedrine, and ibuprofen. During hospitalization for a substance abuse treatment program, the patient was started on fluoxetine 40 mg daily, terfenadine 60 mg twice daily, and disulfiram 250 mg daily. Approximately 14 days later, the patient underwent a routine electrocardiogram (ECG) study that revealed a prolonged QT interval of 550 milliseconds. The patient was asymptomatic and had no prior history of heart disease. Terfenadine was discontinued, and an ECG taken one week later revealed a normal QT interval.

c) A case report describes a possible interaction with terfenadine and fluoxetine in a 41-year-old male who experienced irregular heartbeat, skipped beats, and shortness of breath a month after institution of fluoxetine 20 mg daily; he had no previous history of heart disease. His drug regimen included fluoxetine, terfenadine 60 mg twice daily, ibuprofen 800 mg three times daily, misoprostol 100 mcg four times daily, Midrin(R) (acetaminophen 325 mg, dichloralphenazone 100 mg, isometheptene mucate 65 mg) as needed, and ranitidine 150 mg twice daily. A 24-hour Holter monitor showed intermittent frequent sinus tachycardia, three isolated atrial premature contractions, and three couplets. Terfenadine was discontinued and his previously reported symptoms did not reoccur. Fluoxetine is a known enzyme inhibitor and may have inhibited terfenadine metabolism resulting in the cardiac abnormalities seen in this patient (Swims, 1993).

3.5.1.HR Tetrabenazine

1) Interaction Effect: increased exposure to tetrabenazine

2) Summary: Caution should be used when administering a strong CYP2D6 inhibitor (eg, fluoxetine, paroxetine) to a patient taking tetrabenazine (a CYP2D6 substrate), and the daily dose of tetrabenazine should be halved if fluoxetine 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 fluoxetine 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 fluoxetine is necessary. Concomitant use of fluoxetine 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 fluoxetine

3.5.1.HS Thioridazine

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac

arrest)
2) Summary: Fluoxetine inhibits the metabolism of thioridazine through inhibition of CYP2D6. The resulting elevated levels of thioridazine may enhance QT prolongation (Prod Info Mellaril(R), 2000). Fluoxetine has been shown to prolong the QTc interval at the recommended therapeutic dose (Prod Info Prozac(R), 2001ae). Although citing no data, the manufacturer of thioridazine states that concomitant use with other drugs which prolong the QT interval is contraindicated (Prod Info Mellaril(R), 2000).
3) Severity: contraindicated
4) Onset: rapid
5) Substantiation: probable
6) Clinical Management: The concurrent administration of fluoxetine and thioridazine is contraindicated.
7) Probable Mechanism: inhibition of cytochrome P450 2D6-mediated thioridazine metabolism; additive effects on QT prolongation

3.5.1.HT 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.HU 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.HV 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 PROZAC(R) oral capsules, delayed-release capsules, solution, 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 (Prod Info PROZAC(R) oral capsules, delayed-release capsules, solution, 2008).
3) Severity: major
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: When fluoxetine and an anticoagulant are given concurrently, monitor patient for signs of increased bleeding. Patients who are taking warfarin should be monitored closely for altered

anticoagulant effects, including increased bleeding, when fluoxetine therapy is initiated or discontinued (Prod Info PROZAC(R) oral capsules, delayed-release capsules, solution, 2008).
7) Probable Mechanism: unknown
8) Literature Reports
a) Fluoxetine is thought to inhibit the cytochrome P450 2C9 isoenzyme (CYP2C9). This is the enzyme by which the more potent warfarin isomer, S-warfarin, is metabolized (Riesenman, 1995). In addition, both fluoxetine and warfarin are tightly bound to albumin. In combination, the possibility for protein-binding displacement of either drug is present (Prod Info Coumadin(R), 1999).
b) 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).
c) 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).
d) In 6 reported cases, INR increased during combined fluoxetine and warfarin therapy. In a seventh case, severe bruising of the lower legs occurred in a woman initially treated with fluoxetine and, secondarily, started on warfarin (Woolfrey et al, 1993; Claire et al, 1991).
e) An 83-year-old man died from cerebral hemorrhage secondary to increased warfarin concentrations. The patient had been taking warfarin 30 mg per week for atrial fibrillation with a target INR between 2 and 3. The patient's other drugs included lisinopril, furosemide, potassium, digoxin, and acetaminophen. After being seen for symptoms of depression, anxiety, and insomnia, the patient was given fluoxetine 20 mg per day and diazepam 2.5 mg 3 to 4 times per day. Eight days later, the patient's INR increased to 4.8, and the dose of warfarin was decreased to 27.5 mg per week. The patient was later seen for symptoms of drug delirium, including confusion, incoherence, and speaking irrationally. At this point, the INR was 3.64 and fluoxetine was discontinued. The next day the patient presented to the hospital with left-sided weakness and later died from complications of a large interparenchymal hemorrhage. The authors proposed that the addition of fluoxetine to the patient's regimen resulted in increased serum levels of both warfarin and diazepam, resulting in delirium and loss of anticoagulant control (Dent & Orrock, 1997).

3.5.1.HW Tipranavir
1) Interaction Effect: increased fluoxetine plasma concentrations
2) Summary: Although the drug interaction between fluoxetine and tipranavir/ritonavir has not been studied, coadministration of fluoxetine with tipranavir/ritonavir may result in increased fluoxetine plasma concentrations. Fluoxetine 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 fluoxetine and tipranavir/ritonavir may increase fluoxetine plasma concentrations. Use caution when these agents are coadministered and consider adjusting the fluoxetine dose as needed upon initiation of tipranavir/ritonavir (Prod Info APTIVUS(R) oral capsules, solution, 2008).
7) Probable Mechanism: unknown

3.5.1.HX 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.HY 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.HZ Toloxatone
1) Interaction Effect: CNS toxicity or serotonin syndrome (hypertension, hyperthermia, myoclonus, mental status changes)
2) Summary: Concurrent administration or overlapping therapy with fluoxetine 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 (Prod Info Prozac(R), 1999a; Sternbach, 1991d; Coplan & Gorman, 1993c; Feighner et al, 1990c; Kline et al, 1989c; Suchowersky & de Vries, 1990c). 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 fluoxetine and toloxatone is contraindicated. Wait at least two weeks after discontinuing a MAO inhibitor before initiating fluoxetine therapy. In addition, wait at least five weeks after discontinuing fluoxetine before initiating therapy with a MAO inhibitor.
7) Probable Mechanism: inhibition of serotonin metabolism by monoamine oxidase
8) Literature Reports
a) Concomitant use of serotonin specific reuptake inhibitors and monoamine oxidase inhibitors can 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 (Sternbach, 1991c). If the syndrome is not recognized and correctly treated, death can result.
b) It has been suggested that fluoxetine therapy be discontinued for at least five weeks before beginning therapy with a monoamine oxidase inhibitor. A 28-year old woman discontinued fluoxetine for six weeks before starting therapy with tranylcypromine. Over the next few days the patient developed fever, paresthesias, confusion, abdominal cramping, and various other CNS symptoms. Upon discontinuation of tranylcypromine, the patient's symptoms began to resolve. Blood samples taken three days after discontinuation of tranylcypromine revealed no presence of fluoxetine; however, the norfluoxetine level was 84 ng/mL (Coplan & Gorman, 1993b).

c) Adverse reactions reported when fluoxetine was given concomitantly with phenelzine (n=9) or tranylcypromine (n=4) include tremor (50%), agitation or restlessness (42%), mental status changes (42%), myoclonus (33%), diarrhea (33%), and blood pressure changes (25%) (Feighner et al, 1990b). All but one of the patients were taking other medications (ie, benzodiazepines, neuroleptics, anticonvulsants, antidepressants) that may have contributed to the adverse reactions.
d) Ten hours after her last dose of fluoxetine, a 45-year-old woman began tranylcypromine therapy (Kline et al, 1989b). Headache, muscle contractions, insomnia, and unsteady gait were reported on the second day. Thioridazine and tryptophan were added to her therapy. The patient experienced fever, rigidity of the arms and legs, and hyperreflexia. She died in the intensive care unit of a hospital 44 hours later.
e) 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 therapy. 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 and selegiline. Both drugs were discontinued, with relatively quick resolution of symptoms. Rechallenge with fluoxetine alone occurred without incident.

3.5.1.IA Tramadol

1) Interaction Effect: an increased risk of seizures and serotonin syndrome (hypertension, hyperthermia, myoclonus, mental status changes); increased concentrations of tramadol and decreased concentrations of tramadol active metabolite, M1
2) Summary: Seizures and serotonin syndrome have been reported in patients using tramadol. Some medications, including fluoxetine, are known to reduce the seizure threshold. The risk of seizures and serotonin syndrome may be enhanced when fluoxetine and tramadol therapy are combined (Prod Info Ultram(R), 2001). Fluoxetine is also an inhibitor of CYP2D6, and concomitant administration with tramadol may result in increases of tramadol concentrations and decreases in active metabolite, M1, concentrations. This may cause an increase in side effects or a reduction in the analgesic effect of tramadol (Prod Info ULTRAM(R)ER extended-release oral tablets, 2005).
3) Severity: major
4) Onset: rapid
5) Substantiation: probable
6) Clinical Management: Caution should be used if tramadol is to be administered to patients receiving concomitant fluoxetine 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. Also, monitor patients for signs and symptoms of narcotic toxicity (extreme sedation, respiratory depression), as well as decreased analgesic effect of tramadol.
7) Probable Mechanism: increased concentration of serotonin in the nervous system and periphery; inhibition of CYP2D6 metabolism of tramadol to M1 active metabolite by quinidine
8) Literature Reports

a) The combination of tramadol and fluoxetine may result in serotonin syndrome and mania. A 72-year-old female with no cognitive deficits had been treated with fluoxetine for the past 10 years. She was prescribed tramadol 150 mg daily for articular pain. After 18 days of combination therapy the patient began to feel nervous, had a temperature of 37.2 C, piloerection, and muscular contractions. She discontinued tramadol and 21 days later her physical symptoms disappeared. She was still agitated, euphoric, hyperactive, had rapid speech, paranoid ideation, and slept less than 3 hours a day. She was hospitalized and haloperidol treatment was initiated, however, her symptoms continued. She was readmitted one week later and treatment with olanzapine was initiated. Two weeks later she became euthymic and continued olanzapine therapy after being released from the hospital. The potential for inducing mania and serotonergic syndrome when using tramadol combined with SSRIs must be considered (Gonzalez-Pinto, 2001).

3.5.1.IB Tranylcypromine

1) Interaction Effect: CNS toxicity or serotonin syndrome (hypertension, hyperthermia, myoclonus, mental status changes)
2) Summary: Concurrent administration or overlapping therapy with fluoxetine 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 (Prod Info Prozac(R), 1999j; Sternbach, 1991s; Coplan & Gorman, 1993q; Feighner et al, 1990q; Kline et al, 1989q; Suchowersky & de Vries, 1990q; Sternbach, 1988a). Concomitant use is contraindicated.
3) Severity: contraindicated
4) Onset: rapid
5) Substantiation: probable
6) Clinical Management: Concurrent use of fluoxetine and tranylcypromine is contraindicated. Wait at least two weeks after discontinuing a MAO inhibitor before initiating fluoxetine therapy. In addition, wait at least five weeks after discontinuing fluoxetine before initiating therapy with a MAO inhibitor.
7) Probable Mechanism: inhibition of serotonin metabolism by monoamine oxidase

8) Literature Reports

a) Concomitant use of serotonin specific reuptake inhibitors and monoamine oxidase inhibitors can produce a toxic reaction known as serotonin syndrome (Sternbach, 1991r). Serotonin syndrome is a condition of serotonergic hyperstimulation and manifests as restlessness, myoclonus, changes in mental status, hyperreflexia, diaphoresis, shivering, and tremor (Sternbach, 1991r). If the syndrome is not recognized and correctly treated, death can result.

b) It has been suggested that fluoxetine therapy be discontinued for five weeks before beginning therapy with a monoamine oxidase inhibitor. However, one case report describes a 28-year old woman who had discontinued a 2-year fluoxetine regimen for six weeks before starting therapy with tranylcypromine. Over the next few days the patient developed fever, paresthesias, confusion, abdominal cramping, and various other CNS symptoms. Upon discontinuation of tranylcypromine, the patient's symptoms began to resolve. Blood samples taken three days after discontinuation of tranylcypromine revealed no presence of fluoxetine; however, the norfluoxetine level was 84 ng/mL (Coplan & Gorman, 1993p).

c) Adverse reactions reported when fluoxetine was given concomitantly with phenelzine (n=9) or tranylcypromine (n=4) include tremor (50%), agitation or restlessness (42%), mental status changes (42%), myoclonus (33%), diarrhea (33%), and blood pressure changes (25%) (Feighner et al, 1990p). All but one of the patients were taking other medications (ie, benzodiazepines, neuroleptics, anticonvulsants, antidepressants) that may have contributed to the adverse reactions.

d) Ten hours after her last dose of fluoxetine, a 45-year-old woman began tranylcypromine therapy (Kline et al, 1989p). Headache, muscle contractions, insomnia, and unsteady gait were reported on the second day. Thioridazine and tryptophan were added to her therapy. The patient experienced fever, rigidity of the arms and legs, and hyperreflexia. She died in the intensive care unit of a hospital 44 hours later.

e) Two cases suggestive of an interaction between fluoxetine and selegiline were reported (Suchowersky & de Vries, 1990p). One case involved a first episode of mania being observed approximately one month after adding selegiline to fluoxetine therapy. 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 and selegiline. Both drugs were discontinued, with relatively quick resolution of symptoms. Rechallenge with fluoxetine alone occurred without incident.

f) A 31-year-old female received fluoxetine 20 mg daily for 14 days, and was subsequently discontinued due to nausea and restlessness (Sternbach, 1988). The administration of tranylcypromine 10 mg daily commenced two days following the discontinuation of fluoxetine. Four days later, the patient increased tranylcypromine to 20 mg daily and developed a serotonin-like syndrome two to three hours later. Following the discontinuation of tranylcypromine, all signs and symptoms resolved within 24 hours.

3.5.1.IC Trazodone

1) Interaction Effect: trazodone toxicity (sedation, dry mouth, urinary retention) or serotonin syndrome (hypertension, hyperthermia, myoclonus, mental status changes)

2) Summary: When given concurrently, trazodone and fluoxetine have been reported to be therapeutically effective with and without side effects (Metz & Shader, 1990; Swerdlow & Andia, 1989; Neirenberg et al, 1992; Maes et al, 1997a). Coadministration of trazodone and fluoxetine has been reported to result in speech dysfunction in a 43-year old man following traumatic brain injury (Patterson et al, 1997a). There have also been several reports of serotonin syndrome due to interactions between selective serotonin reuptake inhibitors and antidepressants (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, 1991y). Further clinical studies are necessary to determine the incidence and implications of serotonin syndrome associated with this drug combination.

3) Severity: major

4) Onset: delayed

5) Substantiation: probable

6) Clinical Management: Due to the potential for impairment in trazodone metabolism, patients should be monitored for any signs of trazodone toxicity. Occasional dosage reductions of trazodone may be required. Serotonin syndrome, characterized by hypertension, hyperthermia, myoclonus, and mental status changes, may also occur during concomitant therapy.

7) Probable Mechanism: decreased trazodone clearance

8) Literature Reports

a) Five cases of elevated antidepressant levels, four involving tricyclic antidepressants (nortriptyline, imipramine, desipramine) and one involving trazodone, have been reported. After the addition of fluoxetine, the ratio of antidepressant level to dose increased by 109% to 486% in the patients on tricyclics and by 31% in the patient on trazodone. The trazodone-treated patient developed sedation and unstable gait (Aranow et al, 1989b).

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).
c) Serotonin syndrome was also 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).
d) A 43-year-old male with traumatic brain injury developed speech dysfunction during therapy with fluoxetine and trazodone. The patient was being treated with trazodone 150 mg at bedtime for chronic pain as a result of a fall. After undergoing a comprehensive psychiatric evaluation as part of rehabilitation, fluoxetine 20 mg every morning was added to the patient's regimen for treatment of symptoms of depression. Within one week of starting therapy with fluoxetine, the patient began to slur his speech and later exhibited a slow rate of speech, increased pause length, prolongation of initial phonemes, and word-finding difficulties. After discontinuation of fluoxetine and tapering of trazodone therapy, the patient had marked improvement in speech difficulty and returned to normal over the next week (Patterson et al, 1997).
e) The pharmacokinetic effect of trazodone and fluoxetine cotherapy was studied in 27 inpatients with a major depressive episode. All were treated with trazodone 100 mg daily, followed one week later with the addition of fluoxetine 20 mg daily, pindolol 7.5 mg daily, or placebo for four weeks. Pindolol and placebo had no significant effect on the plasma concentrations of trazodone or its active metabolite, meta-chlorophenylpiperazine (mCPP). However, when fluoxetine was combined with trazodone, levels of mCPP increased from a mean baseline value of 11.3 ng/mL to 38.3 ng/mL in four weeks. This increase was also associated with an improvement in the clinical response to the antidepressants (Maes et al, 1997).

3.5.1.ID Trifluoperazine

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Although citing no data, the manufacturers of some phenothiazines state that concomitant use with other drugs which prolong the QT interval is not recommended. Q and T wave distortions have been observed in patients taking phenothiazines (Prod Info Compazine(R), 2002; Prod Info Stelazine(R), 2002; Prod Info Thorazine(R), 2002) . Other phenothiazines may have similar effects, though no reports are available. Fluoxetine has been shown to prolong the QTc interval at the recommended therapeutic dose (Prod Info Prozac(R), 2003).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of fluoxetine and a phenothiazine is not recommended.
7) Probable Mechanism: additive effects on QT prolongation

3.5.1.IE Trimethoprim

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Cotrimoxazole and fluoxetine have been shown to prolong the QTc interval at the recommended therapeutic dose (Prod Info Prozac(R), 2001ah; Lopez et al, 1987). Even though no formal drug interaction studies have been done, the coadministration of drugs known to prolong the QTc interval is not recommended.
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of cotrimoxazole and fluoxetine is not recommended.
7) Probable Mechanism: additive effects on QT prolongation

3.5.1.IF Trimipramine

1) Interaction Effect: tricyclic antidepressant toxicity (dry mouth, urinary retention, sedation) and an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Tricyclic antidepressants (TCAs) and fluoxetine have been shown to prolong the QTc interval at the recommended therapeutic dose (Prod Info Prozac(R), 2001h; Marshall & Forker, 1982). Even though no formal drug interaction studies have been done which demonstrate QT prolongation, the coadministration of tricyclic antidepressants and other drugs known to prolong the QTc interval, such as fluoxetine, is not recommended (Prod Info Elavil(R), 1999). In addition, concurrent use of fluoxetine and TCAs such as

desipramine, nortriptyline, and imipramine has resulted in significant increases in TCA concentrations (Preskorn et al, 1994a; Preskorn et al, 1994a; Aranow et al, 1989a; Downs et al, 1989a; Goodnick, 1989a; Bell & Cole, 1988a).
3) Severity: major
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: The concurrent administration of fluoxetine and a tricyclic antidepressant is not recommended.
7) Probable Mechanism: decreased tricyclic antidepressant metabolism; additive effects on QT prolongation
8) Literature Reports
a) Fluoxetine increased the level of tricyclic antidepressants (nortriptyline, imipramine, desipramine) in 4 patients. After the addition of fluoxetine, the ratio of antidepressant level to dose increased by 109% to 486% in the patients. Three patients developed clinical symptoms (anticholinergic effects, constipation, urinary hesitancy, sedation, unstable gait) as a result of the increased levels (Aranow et al, 1989).
b) Fluoxetine statistically and clinically significantly increased desipramine concentrations in 18 healthy subjects. When fluoxetine (20 mg daily) was added to desipramine (50 mg daily), the mean maximum concentration of desipramine increased by 278% and the area under the concentration-time curve increased by 342%. Desipramine trough concentrations continued to be 198% above baseline three weeks after fluoxetine was discontinued. The same study compared pharmacokinetics of desipramine when combined with sertraline. The impact of sertraline was modest, resulting in small and short-term increases in desipramine plasma concentrations (Preskorn et al, 1994).
c) A 75-year-old female experienced symptomatic increases in her desipramine serum concentrations when fluoxetine was added. Desipramine serum levels ranged from 109 to 150 ng/mL with oral doses of 300 mg at bedtime prior to fluoxetine therapy. Following the addition of oral fluoxetine 20 mg daily to the regimen, the desipramine serum level increased to 212 ng/mL within five days. The fluoxetine dose was increased to 40 mg/day three days later, and the desipramine serum level was 419 ng/mL after four days. A worsening of depression and severe fatigue coincided with the increases in desipramine serum levels. Withdrawal of fluoxetine and reduction in the desipramine dose to 200 mg daily reduced the desipramine serum level to 231 ng/mL within two weeks (Bell & Cole, 1988).
d) A 33-year-old depressed male developed adverse effects of dry mouth, tinnitus, and difficulties with alertness and memory while receiving fluoxetine 40 mg daily and desipramine 150 mg daily for five weeks; fluoxetine was discontinued and the blood levels of desipramine decreased from 938 to 48 ng/mL with resolution of clinical symptoms (Goodnick, 1989).
e) A 39-year-old female experienced symptomatic increases in her desipramine levels with concomitant fluoxetine therapy. Prior to fluoxetine therapy, the patient's measured levels of desipramine had ranged from 148 to 160 ng/mL on a regimen of 300 mg daily. Five weeks after the addition of fluoxetine 20 mg daily, she reported anticholinergic symptoms, sedation, and confusion with a desipramine level of 527 ng/mL. The desipramine dose was lowered to 200 mg/day; eleven days later, the level was 244 ng/mL; the patient reported decreased energy, impaired short-term memory, and some "garbled" speech, as well as an episode of nausea, dizziness, and syncope. The desipramine dose was reduced to 50 mg/day; the adverse effects resolved in six days. Eight days later, the desipramine level was 122 ng/mL (Downs et al, 1989).
f) Concomitant administration of fluoxetine and desipramine was reported to result in an increased desipramine level and new onset of delirium in a 69-year-old male within 10 days of the addition of fluoxetine to the patient's regimen (Preskorn et al, 1990).

3.5.1.IG Tryptophan
1) Interaction Effect: serotonin syndrome (hypertension, hyperthermia, myoclonus, mental status changes)
2) Summary: Tryptophan is metabolized to serotonin, and fluoxetine, a selective serotonin reuptake inhibitor (SSRI), increases serotonergic activity (Steiner & Fontaine, 1986a; Boyer & Blumhardt, 1992). It is possible that combining these agents may result in excessive serotonin leading to a condition known as "serotonin syndrome".
3) Severity: major
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: If tryptophan and fluoxetine are coadministered, monitor patients for signs of serotonin syndrome (hypertension, hyperthermia, myoclonus, mental status changes). It may be necessary to reduce doses of one or both agents or to discontinue tryptophan.
7) Probable Mechanism: additive adverse effects
8) Literature Reports
a) In a case series, the concurrent use of fluoxetine 50 to 100 mg daily and L-tryptophan 1 to 4 g daily resulted in all five patients experiencing central nervous system toxicity (agitation, poor concentration, nausea, diarrhea, paresthesias, palpitations, chills, headaches, aggressive behavior, and severe insomnia) within a few days. Tryptophan was discontinued and the symptoms disappeared (Steiner & Fontaine, 1986).
b) Concurrent paroxetine (another SSRI) and tryptophan have been linked to headache, nausea, sweating, and dizziness (Prod Info Paxil(R), 1999). L-tryptophan administration increases serotonin

concentration in the central nervous system and paroxetine inhibits serotonin reuptake. Patients who receive potent serotonin reuptake inhibitors should be advised not to take L-tryptophan.

3.5.1.IH 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.II Vasopressin

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)

2) Summary: Fluoxetine and vasopressin have been shown to prolong the QTc interval at the recommended therapeutic dose (Prod Info Prozac(R), 2001b; Jacoby & Wiegman, 1990). Even though no formal drug interaction studies have been done, the coadministration of drugs known to prolong the QTc interval is not recommended.

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: The concurrent administration of fluoxetine and vasopressin is not recommended.

7) Probable Mechanism: additive effects on QT prolongation

3.5.1.IJ Venlafaxine

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest) and an increased risk of serotonin syndrome (hypertension, hyperthermia, myoclonus, mental status changes)

2) Summary: Venlafaxine and fluoxetine have been shown to prolong the QTc interval at the recommended therapeutic dose (Prod Info Prozac(R), 2001s; Prod Info Effexor(R) XR, 2000). Even though no formal drug interaction studies have been done, the coadministration of drugs known to prolong the QTc interval is not recommended. In addition, the concurrent use of venlafaxine and fluoxetine may result in serotonin syndrome (Chan et al, 1998).

3) Severity: major

4) Onset: rapid

5) Substantiation: theoretical

6) Clinical Management: The concurrent administration of venlafaxine and fluoxetine is not recommended.

7) Probable Mechanism: additive effects on QT prolongation; additive serotonergic effect

3.5.1.IK 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 PROZAC(R) oral capsules, delayed-release capsules, solution, 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 (Prod Info PROZAC(R) oral capsules, delayed-release capsules, solution, 2008).

3) Severity: major

4) Onset: delayed

5) Substantiation: probable
6) Clinical Management: When fluoxetine and an anticoagulant are given concurrently, monitor patient for signs of increased bleeding. Patients who are taking warfarin should be monitored closely for altered anticoagulant effects, including increased bleeding, when fluoxetine therapy is initiated or discontinued (Prod Info PROZAC(R) oral capsules, delayed-release capsules, solution, 2008).
7) Probable Mechanism: unknown
8) Literature Reports
a) Fluoxetine is thought to inhibit the cytochrome P450 2C9 isoenzyme (CYP2C9). This is the enzyme by which the more potent warfarin isomer, S-warfarin, is metabolized (Riesenman, 1995). In addition, both fluoxetine and warfarin are tightly bound to albumin. In combination, the possibility for protein-binding displacement of either drug is present (Prod Info Coumadin(R), 1999).
b) 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).
c) 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).
d) In 6 reported cases, INR increased during combined fluoxetine and warfarin therapy. In a seventh case, severe bruising of the lower legs occurred in a woman initially treated with fluoxetine and, secondarily, started on warfarin (Woolfrey et al, 1993; Claire et al, 1991).
e) An 83-year-old man died from cerebral hemorrhage secondary to increased warfarin concentrations. The patient had been taking warfarin 30 mg per week for atrial fibrillation with a target INR between 2 and 3. The patient's other drugs included lisinopril, furosemide, potassium, digoxin, and acetaminophen. After being seen for symptoms of depression, anxiety, and insomnia, the patient was given fluoxetine 20 mg per day and diazepam 2.5 mg 3 to 4 times per day. Eight days later, the patient's INR increased to 4.8, and the dose of warfarin was decreased to 27.5 mg per week. The patient was later seen for symptoms of drug delirium, including confusion, incoherence, and speaking irrationally. At this point, the INR was 3.64 and fluoxetine was discontinued. The next day the patient presented to the hospital with left-sided weakness and later died from complications of a large interparenchymal hemorrhage. The authors proposed that the addition of fluoxetine to the patient's regimen resulted in increased serum levels of both warfarin and diazepam, resulting in delirium and loss of anticoagulant control (Dent & Orrock, 1997).

3.5.1.IL 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.IM Ziprasidone
1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac

arrest)
2) Summary: Even though no formal drug interaction studies have been done, ziprasidone should not be coadministered with other drugs which are also known to prolong the QTc interval, including fluoxetine (Prod Info Geodon(TM), 2002; Prod Info Prozac(R), 2001ag).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of ziprasidone with other agents that can prolong the QT interval, such as fluoxetine, is not recommended.
7) Probable Mechanism: additive cardiac effects
8) Literature Reports
a) It has been shown that ziprasidone prolongs the QTc and that this represents a risk of potentially fatal ventricular dysrhythmias (Anon, 2000). QT prolongation is dose-related. It is not yet known whether ziprasidone will cause torsades de pointes or increase the rate of sudden death. In clinical trials ziprasidone increased the QTc interval, compared to placebo, by approximately 10 milliseconds (msec) at the highest dose (160 milligrams). Baseline QTc interval increased 9 to 14 msec more with ziprasidone than with risperidone, olanzapine, quetiapine, and haloperidol, but QTc interval was 14 msec less than that observed with thioridazine (Prod Info Geodon(R), 2002).

3.5.1.IN Zolmitriptan
1) Interaction Effect: an increased risk of serotonin syndrome and an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Zolmitriptan and fluoxetine have been shown to prolong the QTc interval at the recommended therapeutic dose (Prod Info Prozac(R), 2001d; Prod Info Zomig(R), 2001). Even though no formal drug interaction studies have been done, the coadministration of drugs known to prolong the QTc interval is not recommended. Additionally, 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: unspecified
5) Substantiation: theoretical
6) Clinical Management: Coadministration of a triptan, such as zolmitriptan, and an SSRI, such as fluoxetine, 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). Additionally, concurrent administration of zolmitriptan and fluoxetine may result in an increased risk of cardiotoxicity due to additive QT prolongation effects.
7) Probable Mechanism: additive pharmacologic effects resulting in excessive serotonergic stimulation; additive effects on QT prolongation
8) Literature Reports
a) The pharmacokinetics of zolmitriptan were unaffected by 4 weeks of pretreatment with fluoxetine 20 mg/day (Prod Info Zomig(R), 2003).

3.5.1.IO Zolpidem
1) Interaction Effect: an increased risk of hallucinations
2) Summary: Short-term combined therapy with fluoxetine and zolpidem was determined to be safe by a study involving 29 healthy women. After a single dose of zolpidem followed by one washout day, the subjects were given a daily dose of fluoxetine on days three through 27, then zolpidem was added each evening on days 28 through 32. There were no significant changes in either fluoxetine or zolpidem plasma concentrations, and both medications were tolerated well, either individually or combined (Allard et al, 1998a). However, the publication of five case reports from the Washington Poison Center elucidates potential interactions between zolpidem and various antidepressant medications. Five patients reported hallucinations after concurrent use of zolpidem and antidepressant medication. The hallucination episodes all lasted longer than one hour, but resolved without further sequelae (Elko et al, 1998a).
3) Severity: moderate
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: Observe patients for hallucinatory activity. Alternative anti-insomnia medication may be warranted.
7) Probable Mechanism: unknown
8) Literature Reports
a) A study conducted by Lorex Pharmaceuticals and Boston Research and Science Consulting demonstrates the safety of concomitant short-term therapy with fluoxetine and zolpidem. In this study,

29 healthy female volunteers were given a single evening dose of zolpidem 10 mg, followed by one washout day. This was followed by a daily morning dose of fluoxetine 20 mg on days 3 through 27. On days 28 through 32, a daily evening dose of zolpidem was added. Steady state plasma concentrations of fluoxetine and norfluoxetine were reached on day 24 of fluoxetine dosing as determined by serial venous blood sampling. There were no significant differences in area under concentration curve (AUC), peak concentration (Cmax), or time to reach peak concentration (Tmax) after one or five consecutive doses of zolpidem in conjunction with fluoxetine administration. The following pharmacokinetic mean parameters were observed for zolpidem: AUC 917.04 ng/hr/mL on day 28, 978.77 ng/hr/mL on day 32, Cmax 167.94 ng/mL on day 28, 175.91 ng/mL on day 32, Tmax 1.67 hr on day 28, 1.54 hr on day 32. For fluoxetine the following were noted: AUC 2674.53 ng/hr/mL on day 27, 2879.63 ng/hr/mL on day 32, Cmax 133.48 ng/mL on day 27, 142.23 ng/mL on day 32, Tmax 8.28 hr on day 27, 9.04 hr on day 32. The only statistically significant difference was a higher half-life value for zolpidem on day 32, the fifth consecutive dose of zolpidem in the presence of fluoxetine (Allard et al, 1998).

b) The Washington Poison Center reports that they received five different calls from patients experiencing hallucinations after concurrent use of zolpidem and antidepressant medication. Four of the five reports came from patients taking serotonin reuptake inhibitors in addition to zolpidem. The antidepressant medications being taken were desipramine, fluoxetine, sertraline, venlafaxine, and bupropion. In each case, the hallucinatory activity lasted longer than one hour, but the patients' symptoms resolved without further sequelae. The authors concluded that the mechanism by which zolpidem might cause hallucinations has not been firmly established (Elko et al, 1998).

3.5.1.IP 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).

3.5.1.IQ Zotepine

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)

2) Summary: Fluoxetine has been shown to prolong the QTc interval at the recommended therapeutic dose (Prod Info Prozac(R), 2001l). Even though no formal drug interaction studies have been done, the coadministration of antipsychotics and other drugs known to prolong the QTc interval, including fluoxetine, is not recommended. Several antipsychotic agents have demonstrated QT prolongation including amisulpride (Prod Info Solian(R), 1999), quetiapine (Owens, 2001b), sertindole (Agelink et al, 2001), sultopride (Lande et al, 1992), and zotepine (Sweetman, 2003).

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: The concurrent administration of fluoxetine and antipsychotics is not recommended.

7) Probable Mechanism: additive effects on QT prolongation

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) Fluoxetine Hydrochloride

1) Therapeutic

a) ATTENTION DEFICIT HYPERACTIVITY DISORDER (ADHD)

1) Reduction in 3 essential features consistent with ADHD:

a) Inappropriate inattention (manifested as inability to finish tasks, listening, easily distracted, difficulty at concentrating with schoolwork or other tasks).

b) Impulsivity (which may be manifested as acting or engaging in dangerous activities before thinking, shifting from activity to activity, difficulty in organizing work, requiring significant supervision, calling out in class frequently, difficulty awaiting a turn in games or group situations.

c) Hyperactivity (evident by excessive running about or climbing, difficulty sitting still or staying seated, excessive movement, talks excessively)

2) Improvement in cognitive performance (i.e., reading, memory and mathematical skills)

3) All children should receive a drug-free trial every year.

b) BULIMIA

1) Reduction or resolution of signs/symptoms associated with bulimia (binge eating, purging episodes, inconspicuous eating, frequent weight swings, suicide attempts, kleptomania, laxative/diuretic abuse, and associated medical complications).

c) DEPRESSION

1) Improvement in target symptoms associated with depression (depressed mood, suicidal thoughts or intent, change in appetite, lack of energy, change in sleep patterns, lack of pleasure/interest in usual activities, feeling of excessive guilt/worthlessness, psychomotor retardation or agitation, difficulties in thinking/concentration/memory).

d) NARCOLEPSY

1) Reduction in daytime sedation with sleep attacks

2) Reduction in fatigue, impaired performance

3) Improved night time sleep

4) Resolution/improvement of cataplexy (characterized by muscle weakness and/or paralysis, sleep paralysis, and hypnagogic hallucinations)

e) PANIC ATTACKS

1) Reduction or resolution of signs/symptoms consistent with panic disorder (dyspnea, palpitations, dizziness, trembling, sweating, choking, nausea, paresthesias, depersonalization, hot and/or cold flashes, chest pain or discomfort, fear of dying, or experiencing an uncontrolled feeling).

f) POSTTRAUMATIC STRESS DISORDER

1) Reduction or resolution of flashbacks, recollections, and dreams of the traumatic event.

2) Reduction or resolution of sleep disturbances, outbursts of anger, hypervigilance, emotional numbing, guilt, inability to concentrate, and the physiological reaction (e.g., sweating) upon re-exposure to the event (e.g., nightmare).

g) OBSESSIVE-COMPULSIVE DISORDER

1) Reduction or resolution of recurrent and persistent impulses, ideas or thoughts that are intrusive and senseless.

2) Reduction or resolution of repetitive and intentional behaviors performed in response to obsessive thoughts.

h) PREMENSTRUAL SYNDROME

1) Reduction or resolution of signs/symptoms associated with premenstrual syndrome (i.e., tension, irritability, dysphoria, fatigue, anxiety, crying, depression, restlessness, craving for sweet/salty foods, binge eating, headache).

i) SOCIAL PHOBIA

1) Reduction or resolution of fear (may be manifested as nervousness, nausea, sweating, headaches) surrounding social encounters

j) TRICHOTILLOMANIA

1) Reduction or resolution of alopecia and hair pulling

2) Toxic

a) 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 (US Food and Drug Administration, 2004; Anon, 2004). .
b) 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 (US Food and Drug Administration, 2004; Anon, 2004).
c) Psychosis, hypomania or mania, hallucinations, euphoria, akathisia or ataxia
d) Seizures
e) Suicidal ideation
f) SIADH/hyponatremia
g) Sexual dysfunction (anorgasmia/delayed orgasm, inhibited ejaculation, and impotency)
h) Visual disturbances may develop and require withdrawal of therapy

4.2 Patient Instructions

A) Fluoxetine (By mouth)

Fluoxetine

Treats depression, obsessive compulsive disorder (OCD), eating disorders, and panic disorders. Sarafem® treats premenstrual dysphoric disorder (PMDD), which is mood disorders and physical symptoms that occur 1 to 2 weeks before a woman's menstrual period. 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 fluoxetine, or if you are also using pimozide. You should not use this medicine if you have used an MAO inhibitor (MAOI) such as Eldepryl®, Marplan®, Nardil®, or Parnate® within the past 14 days. Do not take an MAO inhibitor or thioridazine while you are using this medicine and for at least 5 weeks after you stop taking this medicine.

How to Use This Medicine:
Capsule, Delayed Release Capsule, Tablet, Liquid
Your doctor will tell you how much of this medicine to use and how often. Your dose may need to be changed several times in order to find out what works best for you. Do not use more medicine or use it more often than your doctor tells you to.Some people need to take this medicine every day, and some people need to take it only once a week. Make sure you understand your own schedule.
You may need to take this medicine for up to 4 weeks before you start feeling better.
Measure the oral liquid medicine with a marked measuring spoon, oral syringe, or medicine cup.
You may take this medicine with or without food. Take your medicine at the same time each day.
Swallow the delayed-release capsule whole. Do not crush, break, or chew it.
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:
For people who take this medicine every day (Prozac® or Sarafem®): If you miss a dose or forget to take your medicine, take it as soon as you can. If it is almost time for your next dose, wait until then to take the medicine and skip the missed dose. Do not use extra medicine to make up for a missed dose.
For people who take this medicine once a week (Prozac® Weekly): If you miss a dose or forget to take your medicine, take it as soon as you can. Then go back to your regular schedule the next week. 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 alprazolam (Xanax®), diazepam (Valium®), digoxin (Lanoxin®), flecainide (Tambocor®), linezolid (Zyvox®), St. John's wort, sumatriptan (Imitrex®), tramadol (Ultram®), tryptophan, vinblastine, medicine for seizures (such as carbamazepine, phenytoin, Dilantin®, or Tegretol®), or a blood thinner (such as warfarin or Coumadin®).

Tell your doctor if you are using other medicines to treat depression (such as amitriptyline, desipramine, doxepin, imipramine, lithium, nortriptyline, pimozide, Orap®, Pamelor®, or Sinequan®), medicine to treat mental illness (such as clozapine, haloperidol, Clozaril®, or Haldol®), or a medicine called flecainide (Tambocor®) for heart rhythm problems.
Make sure your doctor knows if you are also using any pain or arthritis medicines, sometimes called "NSAIDs" (such as aspirin, ibuprofen, naproxen, Advil®, Aleve®, Bextra®, Celebrex®, Ecotrin®, or Motrin®).
Also tell your doctor if you have used an MAO inhibitor such as Eldepryl®, Marplan®, Nardil®, or Parnate® within the past 14 days.
Tell your doctor if you are using any medicines that make you sleepy. These include sleeping pills, cold and allergy medicine, narcotic pain relievers, and sedatives.
Do not drink alcohol while you are using this medicine.

Warnings While Using This Medicine:
Make sure your doctor knows if you are pregnant, planning to become pregnant, or breastfeeding. Tell your doctor if you have seizures, diabetes, heart disease, liver disease, hyponatremia (low sodium in the blood), bleeding problems, manic disorder, or recent heart attack.
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 get 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.
If you develop a skin rash, even a mild one, stop taking this medicine and call your doctor right away.
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.
Blistering, peeling, red skin rash.
Change in how much or how often you urinate.
Chest pain, pounding or uneven heartbeat.
Confusion, weakness, and muscle twitching.
Dry mouth, increased thirst, muscle cramps, nausea, or vomiting.
Feelings of intense anxiety, agitation, or irritability.
Fever, chills, body aches, or weakness.
Painful, prolonged erection of your penis.
Unusual bleeding, bruising, or weakness.
Vomiting blood or something that looks like coffee grounds.

If you notice these less serious side effects, talk with your doctor:
Changes in appetite with weight gain or loss.
Decreased interest in sex.
Dry mouth, sore throat, or yawning more than usual.
Ear pain or ringing in your ears.
Headache.
Nausea, diarrhea, constipation, or upset stomach.
Nervousness, shakiness, or sweating.
Trouble having sex.
Trouble sleeping.

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

4.3 Place In Therapy

A) SUMMARY

1) Fluoxetine has received approval by the United States Food and Drug Administration for treating bulimia nervosa, depression, obsessive compulsive disorder, and premenstrual dysphoria. Fluoxetine 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. Fluoxetine differs from other

SSRIs with regard to its pharmacokinetic profile; it has a longer half-life partly due to the extremely long half-life of its active metabolite. In comparative clinical trials with other SSRIs, fluoxetine had a slower onset of antidepressant action than other agents. Compared to other SSRIs, fluoxetine does NOT appear to have a higher incidence of most adverse effects. Fluoxetine is not the first choice of an antidepressant for severely depressed patients because it has a slower onset of action than other agents. If it was used previously and was effective in these patients, a higher starting dose may be tried. Also, fluoxetine may NOT be the best agent for patients with agitation. However, fluoxetine may be especially useful in poorly compliant patients or in patients who previously experienced withdrawal reactions. Ultimately, the selection of an SSRI is dependent on clinical judgement and response of patients to previous therapy (Edwards & Anderson, 1999).

2) Fluoxetine is as effective for treating typical or endogenous depression as the tricyclic antidepressants (TCAs) and is comparable to clomipramine for obsessive-compulsive behavior. Advantages of fluoxetine over the TCAs include minimal anticholinergic effects, lack of orthostatic hypotension, minimal sedation, and no association with prolonged cardiac conduction time. The disadvantages of this agent compared to the TCAs are induction of nervousness or anxiety, insomnia, gastrointestinal disturbances, and headaches. Fluoxetine has been noted to induce weight loss, which may be an advantage or disadvantage depending on the circumstances. The drug may be especially beneficial in geriatric patients due to a low incidence of postural hypotension and a lack of cardiovascular effects. Its single or twice daily dosing may improve compliance in some patients. Seizures do not appear to be a problem with therapeutic doses.

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. 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 (Joffe et al, 1996).

4.4 Mechanism of Action / Pharmacology

A) MECHANISM OF ACTION

1) Fluoxetine is a "second-generation" antidepressant agent which is a specific inhibitor of serotonin reuptake (Stark et al, 1985). The chemical structure of fluoxetine differs from that of tricyclic antidepressants (Chouinard, 1985); the drug is a non-tricyclic compound with the chemical name of N-methyl-3-phenyl-3(alpha, alpha, alpha-trifluoro-p-tolyl)-oxy-propylamine hydrochloride (Bremner, 1984).

2) Fluoxetine has been demonstrated to be a specific inhibitor of serotonin uptake in vitro and in vivo in man and animals (Lemberger et al, 1978; Lemberger et al, 1978a; Wong et al, 1974; Fuller et al, 1977; Stark et al, 1985; Lemberger et al, 1987) while producing little effect on the noradrenergic system (Wong et al, 1975; Lemberger et al, 1978; Wong et al, 1974; Stark et al, 1985; Fuller & Wong, 1987). The drug has been shown to have little affinity for muscarinic, histaminic H1, serotonergic 5-HT1 or 5-HT2, or noradrenergic alpha-1 or alpha-2 receptors (Stark et al, 1985; Lemberger et al, 1987). Fluoxetine is reportedly 100 times more potent as an inhibitor of serotonin uptake than norepinephrine or dopamine uptake in in vitro studies; inhibition of serotonin uptake has occurred in vivo without affecting norepinephrine uptake (Stark et al, 1985). The drug has minimal anticholinergic and antihistaminic effects.

3) The inhibition of serotonin uptake produced by fluoxetine correlates with plasma concentrations. Doses of 20 to 30 mg daily for 7 days in healthy volunteers produced a 65% inhibition of serotonin uptake into platelets, which correlated with fluoxetine plasma concentrations of 55 ng/mL; endogenous serotonin content of platelets had decreased from 100% to 70% after 7 days of treatment. With doses of 20 to 30 mg daily for 28 days, 80% inhibition of serotonin uptake into platelets was observed, corresponding to plasma levels of 80 ng/mL; corresponding endogenous serotonin content at 28 days had decreased by 80% (Lemberger et al, 1985a).

4) Evidence for serotonin deficiency in depressive disorders stems primarily from 1) measurement of decreased serotonin levels in brain samples from postmortem depressed patients, 2) measurement of a decrease in the serotonin metabolite (5-hydroxyindoleacetic acid) in CSF prior to and after probenecid in depressed patients, and 3) demonstration of benefits of administration of 5-hydroxytryptophan, or drugs that increase serotonin concentrations in the synaptic cleft (MAO inhibitors) (Stark et al, 1985; van Praag, 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 is 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) A review article discussed the rational treatment of depression and included a discussion of each class of antidepressants (Cohen, 1997).

7) Pharmacologic comparisons of the various selective serotonin reuptake inhibitors and their potential therapeutic distinctions were provided in a review (Finley, 1994).

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

4.5 Therapeutic Uses

Fluoxetine

Fluoxetine Hydrochloride

4.5.A Fluoxetine

Anorexia nervosa

Cataplexy - Narcolepsy

4.5.A.1 Anorexia nervosa

See Drug Consult reference: ANOREXIA NERVOSA - DRUG THERAPY

4.5.A.2 Cataplexy - Narcolepsy

See Drug Consult reference: NARCOLEPSY AND CATAPLEXY - DRUG THERAPY

4.5.B Fluoxetine Hydrochloride

Alcoholism - Depression

Anorexia nervosa

Anxiety disorder of childhood

Attention deficit hyperactivity disorder

Autistic disorder

Bipolar disorder; Adjunct

Body dysmorphic disorder

Bulimia nervosa

Cancer - Depression

Cerebrovascular accident, Mortality

Cerebrovascular accident, Post

Cerebrovascular accident, Post - Depression

Chronic fatigue syndrome

Depersonalization disorder

Depression - Diabetes mellitus

Depression - HIV infection

Diabetic neuropathy

Dysthymia

Fibromyalgia

Headache

Hot sweats

Huntington's disease

Major depressive disorder

Myocardial infarction; Prophylaxis

Obesity

Obsessive-compulsive disorder

Panic disorder

Picking own skin

Postpartum depression

Posttraumatic stress disorder

Premature ejaculation

Premenstrual dysphoric disorder

Raynaud's phenomenon

Schizophrenia; Adjunct

Seasonal affective disorder

Severe major depression with psychotic features

Slow channel syndrome

Social phobia

Tinnitus

Trichotillomania

Vasovagal syncope; Prophylaxis

4.5.B.1 Alcoholism - Depression

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, fluoxetine was significantly better than placebo for relieving symptoms of major depression associated with alcohol dependence.

c) Adult:

1) In a 12-week study of patients (n=51) with major depression and alcohol dependence, fluoxetine resulted in a significantly greater improvement in depression and a reduction in alcohol consumption compared to placebo. Fluoxetine demonstrated significant improvement on the 24-item Hamilton Rating Scale for Depression (HAM-D-24) but not the Beck Depression Inventory (BDI) compared to placebo; however, differences for the HAM-D-24 and BDI were significant from baseline to study completion for fluoxetine. All parameters of alcohol consumption showed significant improvement with fluoxetine compared to placebo. Patients were randomly assigned to placebo or fluoxetine 20 milligrams (mg) daily which could be titrated to 40 mg daily. Fluoxetine was tolerated well; no patient left the study due to adverse effects. Additional large studies are needed to assess the long-term efficacy of fluoxetine in a less severely depressed population of alcoholics (Cornelius et al, 1997).

4.5.B.2 Anorexia nervosa

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:

Ineffective in the treatment of patients with anorexia nervosa (n=93) following weight restoration during a randomized, double-blind trial (Walsh et al, 2006)
Ineffective during a small (n=31), placebo-controlled trial when added to a structured psychological and behavioral program (Attia et al, 1998)

c) Adult:

1) Results from a randomized, double blind study failed to demonstrate any benefit of fluoxetine over placebo in the treatment of patients with anorexia nervosa following weight restoration. Prior to randomization, patients (mean age, 23 +/- 4.6 years; mean body mass index (BMI), 15.4 +/-1.8 kilograms/square meter (kg/m(2)); mean length of illness, 56.5 +/-44.7 months) received inpatient or intensive outpatient treatment and were eligible to participate in the study once they regained weight to a minimum BMI of 19 kg/m(2). Patients were then randomized to an initial dose of fluoxetine 20 milligrams (mg) (n=49) or placebo (n=44) orally daily. The dose of fluoxetine was increased to 60 mg daily over 1 week and could be further increased to 80 mg daily if the patient's clinical status deteriorated. Patients were treated on an outpatient basis for up to 1 year. All patients received cognitive behavioral therapy. The primary outcome measure was time-to-relapse. Approximately 57% of patients dropped out of the study early, with similar completion rates in each arm (p=0.98). The mean fluoxetine dose at the end of the study was 63.5 +/- 15.8 mg daily. In the most conservative analysis of time-to-relapse, which classified all patients who terminated early as having relapsed, there was no significant difference between fluoxetine and placebo (p=0.64). Less conservative analyses led to similar results. The percentage of patients who maintained a BMI of at least 18.5 kg/m(2) and remained in the study for 1 year was 26.5% and 31.5% for fluoxetine and placebo, respectively (p=0.57). When treatment was terminated prematurely, there were no significant differences between patients with regard to BMI or psychological state. At the end of the study, 45% and 43% of the fluoxetine and placebo groups, respectively, had not relapsed (Walsh et al, 2006).

2) In a small, placebo-controlled study (n=31), fluoxetine was no more effective than placebo for patients with anorexia nervosa who were also receiving inpatient psychological and behavioral therapy. The initial dose of fluoxetine was 20 milligrams (mg) daily which was increased over 1 week to 60 mg daily. At 7 weeks (study end-point), the mean dose of fluoxetine and placebo was 56 and 58.7 mg/day, respectively. Therapy was tolerated well. Results of this study are similar to others which used antidepressants for anorexia nervosa. All of the studies were similar with regard to small sample size, short duration, and addition to behavior therapy. None of the studies have addressed the issue of whether antidepressants are better than placebo if behavior therapy is omitted (Attia et al, 1998).

4.5.B.3 Anxiety disorder of childhood

a) Overview

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

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:

Fluoxetine 10 to 60 milligrams/day was effective in the treatment of overanxious disorder, social phobia, or separation anxiety disorder in an analysis of twenty-one patients ages 11 to 17 years of age (Birmaher et al, 1994).

4.5.B.4 Attention deficit hyperactivity disorder

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 single, uncontrolled, trial (n=22), fluoxetine showed some benefit in attention deficit hyperactivity disorder (ADHD) as assessed by both global clinical impressions and parent questionnaires. However, up to one-third of all patients experienced side effects during treatment. Larger studies with better patient controls will be needed to assess the usefulness of fluoxetine in this condition (Barrickman et al, 1991).

4.5.B.5 Autistic 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:
The efficacy of fluoxetine for treating idiopathic autism in children has been demonstrated in a long-term trial

c) Pediatric:
1) Twenty-two of 37 children with idiopathic autism experienced improvements in behavior (mood and temperament), social skills, language, cognition, and adaptive skills when treated in an open-label trial with fluoxetine. In these patients, the ideal dose of fluoxetine ranged from 0.2 milligrams/kilogram/day (mg/kg) to 1.4 mg/kg/day for a mean duration of 21 months. Improvements were measured through various tests and through the observations of those who dealt with the patient on a regular basis. Eleven children were considered to have an excellent response, 11 had a good response, and 15 had no long-term improvements. Fluoxetine was discontinued in those children not responding due to the development of hyperactivity, agitation, and lethargy. Discontinuation of fluoxetine was also attempted in responders; however, regression generally followed. A strong correlation existed between those responding positively to treatment with fluoxetine and those with a family history of major affective disorders. Those that had responded previously remained on fluoxetine for over 1 year and were still demonstrating improvements. After completion of the initial study 31 additional patients were treated with fluoxetine. An additional 4 patients had an excellent response to fluoxetine therapy (22% of the overall 68 patients), an additional 22 patients had a good response (49%), and an additional 5 patients had no long-term improvement (29%). Fluoxetine was found to be an effective treatment option for idiopathic autism in 71% of the total 68 patients studied (DeLong GR, Teague LA & Kamran MM, 1998).

4.5.B.6 Bipolar disorder; Adjunct

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:
Twice weekly dosing overcame depression without inducing mood switching in a single case

c) Adult:
1) Twice weekly dosing with fluoxetine overcame depression in a 59-year-old woman with type I bipolar disorder without causing mood switching. In a manic state and with psychotic behaviors, the woman was hospitalized and treated with lithium 600 milligrams (mg) twice daily, olanzapine 5 mg at bedtime, and clonazepam 0.5 mg twice daily. She became calmer and rational and reported that she had been depressed. On hospital day 12, she was given fluoxetine 10 mg each morning, while continuing the other medications. Twenty-two days later she was diagnosed as manic. Fluoxetine was reduced to 10 mg twice weekly. Her manic symptoms rapidly subsided. She remained euthymic thereafter. At 13 days after the reduction of fluoxetine, her fluoxetine blood concentration was less than 20 micrograms per liter; norfluoxetine was 53 micrograms per liter. At discharge 60 days after admission, her medications were oral lithium 600 mg twice daily, oral olanzapine 5 mg at bedtime, oral clonazepam 1 mg at bedtime, and oral fluoxetine 10 mg every Monday and Thursday. At 9-month follow-up, she remained euthymic (Megna & Devitt, 2001).

4.5.B.7 Body dysmorphic disorder

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:
Fluoxetine was safe and more effective than placebo in the treatment of body dysmorphic disorder

c) Adult:

1) In a 12-week, double-blind, placebo controlled study, fluoxetine was more effective than placebo in the treatment of body dysmorphic disorder (BDD). After establishing the diagnosis of BDD, patients were divided into matched fluoxetine (n=34) and placebo groups (n=33). Study participants in the active treatment group received fluoxetine 20 milligrams (mg) daily for two weeks and an additional 20 mg per day every 10 days as tolerated to a maximum of 80 mg per day. At eight weeks of treatment there was a statistically significant (p less than 0.001) decrease in the Yale-Brown Obsessive Compulsive Scale modified for BDD (BDD-YBOCS) score of 35% versus 14% for the fluoxetine (54% response rate) and placebo groups, (18% response rate) respectively. Treatment outcome was not affected by the presence of personality disorder, obsessive-compulsive disorder, depression, or BDD severity or duration. There was also no difference in response between delusional and non-delusional patients to fluoxetine, but delusional patients were less likely to respond to placebo. The mean dose of fluoxetine by study end was 78 mg/day (range 20-80 mg/day) and the mean response time was 7.7 weeks (range 2 to 12 weeks). Drowsiness and stomach/abdominal discomfort were the only adverse effects that occurred significantly more frequently with fluoxetine treatment (Phillips et al, 2002).

4.5.B.8 Bulimia nervosa

FDA Labeled Indication

a) Overview

FDA Approval: Adult, yes; 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:

Indicated for the treatment of binge-eating and vomiting behaviors in patients with moderate to severe bulimia nervosa (Prod Info PROZAC(R) oral pulvule, oral solution, oral tablet, oral delayed-release capsule, 2005)

Fluoxetine is effective in the treatment of bulimia; beneficial effects may be seen as early as one week after initiation of therapy

In a small, open-label study, fluoxetine therapy reduced symptoms of bulimia nervosa in pediatric patients

c) Adult:

1) Continued fluoxetine treatment, relative to placebo treatment, was associated with a significant reduction of relapse in patients who had responded acutely to treatment with fluoxetine for bulimia nervosa. Patients with DSM-IV diagnosis of bulimia nervosa, purging type, who showed a 50% or greater reduction in vomiting episodes during at least 1 of the last 2 weeks of 8 weeks of acute treatment with fluoxetine (60 milligrams (mg) per day) were regarded as responders and were entered into a 52-week randomized, double-blind study to observe relapse rates. Relapse was defined as a return to baseline frequency of vomiting for 2 consecutive weeks. Of the 150 responders (65% of the original 232 participants), 76 continued to receive fluoxetine 60 mg/day and 74 received placebo. The fluoxetine group had fewer relapses in the first 3 months (p less than 0.04). Thereafter, the difference between the groups remained at 14% to 18% but was not statistically significant due to the high attrition rates. By the end of 52 weeks, 33% of the fluoxetine group and 51% of the placebo group had relapsed. Among fluoxetine-treated patients, there was no difference in relapse rates between depressed and non-depressed patients. Statistically significant differences favoring fluoxetine were observed for vomiting episodes, binge-eating episodes, Clinical Global Impression (CGI) severity and improvement scores, and the Yale-Brown-Cornell Eating Disorder Scale total score. The rate of discontinuation because of adverse events was similar for the 2 groups. In the first 3 months, 8 patients of the fluoxetine group and 15 of the placebo group discontinued because of poorer than expected efficacy (Romano et al, 2002).

2) Addition of medication to psychological therapy resulted in greater improvement in binge eating, vomiting, and depression than psychological therapy alone (Walsh et al, 1997). In this complex study, patients (n=120) meeting criteria for bulimia nervosa and using self-induced vomiting were randomly assigned to the following treatments: (1) cognitive-behavioral therapy with placebo; (2) cognitive-behavioral therapy with medication; (3) supportive psychotherapy with placebo; (4) supportive psychotherapy with medication; or (5) medication alone. Patients receiving medication began treatment with desipramine with titration to 300 milligrams/day, if tolerated. Patients with intolerable side effects or a less than 75% decrease in binge eating were switched to fluoxetine 60 mg/day; 74% of patients received fluoxetine. Major study results were: (1) Cognitive-behavioral therapy was more effective than supportive psychotherapy; (2) Cognitive-behavioral therapy plus medication was more effective than medication alone; and (3) Use of a stepped approach to drug therapy improved the benefit of medication. Limitations of this study are a short evaluation period, inability to maintain blinding due to differences in drug side effects, and reliability of patient reporting.

3) Fluoxetine 60 to 80 milligrams/day was effective in the treatment of BULIMIA nervosa in an uncontrolled study involving 10 patients (Freeman & Hampson, 1987).

4) Among obese subjects treated with fluoxetine and behavior modification, those classified as binge-eaters lost half the weight lost by those who were not so classified at the end of the year-long trial; this difference was not statistically significant (Marcus et al, 1990).

d) Pediatric:

1) Fluoxetine therapy was effective in the treatment of pediatric patients with bulimia nervosa. In a small, prospective, open-label study, ten female patients, 12 to 18 years of age (mean age, 16.2 years), with bulimia nervosa (n=8) or eating disorder not otherwise specified (n=2) received fluoxetine 60 milligrams (mg)/day (initial, 20 mg/day, titrated to 60 mg/day by day 7) for 8 weeks with concurrent psychotherapy. From baseline to week 8, the mean number of weekly binges was significantly reduced from 4.1 to 0 (p less than 0.01) and the mean number of weekly purges decreased from 6.4 to 0.4 (p less than 0.005). Significant improvements were also observed for several other outcome measures, including the Eating Attitudes Test, Eating Disorder Inventory, and the Self-report For Childhood Anxiety Related Disorders (p less than 0.05, all values). Body mass index, body weight, and scores for the Body Shape Questionnaire and Beck Depression Inventory were not significantly changed from baseline to week 8 (p=ns). Clinical Global Impression-Improvement Scale scores were "much improved" for 2 patients, "improved" for 5 patients, and "slightly improved" for 3 patients. Fluoxetine was generally well tolerated. The most common adverse events included headache (n=4), drowsiness (n=4), difficulty falling asleep (n=5), and difficulty staying asleep (n=4) (Kotler et al, 2003).

4.5.B.9 Cancer - Depression

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:

Possibly effective in improving quality of life and reducing depressive symptoms in cancer patients

c) Adult:

1) The results of one study suggest that fluoxetine therapy may be effective in improving quality of life and reducing depressive symptoms in patients with advanced cancer. In a randomized, double-blind, placebo-controlled study, patients (n=163) with advanced incurable malignancies and at least minimal depressive symptoms received fluoxetine (20 milligrams once daily in the morning) or placebo for 12 weeks. Quality of life (measured via the Functional Assessment of Cancer Therapy-General (FACT-G) scale) and depression (assessed via the Brief Zung Self-rating Depression Scale (BZSDS)) were measured at baseline and every 3 to 6 weeks. Fluoxetine-treated patients showed statistically significant improvements in scores for both the FACT-G (p=0.05) and the BZSDS (p=0.0005) as compared with placebo however, clinically significant improvements (defined as a 6-point difference in best-change score) between groups were not found. Vomiting was more commonly reported by patients taking fluoxetine (33%) as compared with placebo (4.6%) (Fisch et al, 2003).

4.5.B.10 Cerebrovascular accident, Mortality

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:

Antidepressant treatment given during the first six months following stroke increased long-term survival in depressed and non-depressed patients

c) Adult:

1) Treatment with nortriptyline or fluoxetine during the first six months following stroke significantly increased long-term survival in depressed and non-depressed patients. In a randomized, double-blind, placebo-controlled study, patients (n=104) who had suffered a stroke within the previous 6 months received fluoxetine (initial, 10 milligrams (mg)/day, titrated to 40 mg/day over 9 weeks), nortriptyline (initial, 25 mg/day, titrated to 100 mg/day over 6 weeks), or placebo for 12 weeks. According to the intent-to-treat analysis, significantly more patients treated with an antidepressant were alive at 9 years follow-up as compared with patients who received placebo (59.2% vs 36.4%, respectively; p=0.03). Of patients who completed the full 12- week treatment period (n=81), 67.9% of antidepressant-treated patients and 35.7% of placebo-treated patients were alive at the 9-year follow- up (p=0.005). The likelihood of long-term survival was higher for patients who received antidepressant therapy as compared with placebo for both depressed and non-depressed patients (p=0.02, both values). Of the 50 patients that died during the 9-year follow-up, the percentage of deaths attributable to vascular causes (ie, cardiovascular disease and recurrent stroke) was significantly higher in patients given placebo as compared to patients who received antidepressant therapy (87.8% vs 35.3%, respectively, p=0.0005) (Jorge et al, 2003).

4.5.B.11 Cerebrovascular accident, Post

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:

Improved motor performance after stroke reported in a limited number of patients
In a limited number of patients, fluoxetine was effective for post-stroke emotionalism

c) Adult:

1) A single dose of fluoxetine 20 milligrams, in comparison to placebo, was associated with cerebral activation and improved motor performance in 8 patients with single ischemic lacunar infarction and resultant pure motor hemiplegia. The increase in cerebral activation was localized in the sensorimotor cortex contralateral to the paralysis. Decreases in activation occurred in other areas, including the cerebellum bilaterally and the contralesional caudate nucleus. Improvement in motor performance was evident in speed of execution of specific muscle movements and in strength. Also, improvement in task performance with practice was evident with fluoxetine and not with placebo (Pariente et al, 2001).

2) Fluoxetine reduced post-stroke emotionalism in 8 of 9 patients compared to none of the control patients (Brown et al, 1998). Twenty patients with emotionalism of greater than 4 weeks duration were randomly assigned to fluoxetine 20 milligrams daily or placebo for 10 days. One patient receiving fluoxetine stopped treatment due to a generalized rash. Ratings on the modified Lawson and MacLeod scale and patient self-rating scale were significantly lower in the fluoxetine than placebo group (p=0.011; p=0.049). By day 10, a 50% reduction in the frequency of emotional outbursts was reported by 8 of 9 fluoxetine-treated patients and 0 of 10 placebo-treated patients.

3) Within a few months of a stroke, two Chinese patients developed pathologic crying which improved rapidly after starting fluoxetine 10 or 20 milligrams (mg) daily. The first patient reported 2 months of uncontrollable crying spells which were not associated with depression. On the fifth day of fluoxetine treatment, the crying spells ceased and did not return during 4 months of therapy. The second patient also denied depression and responded to fluoxetine within 1 week. Since fluoxetine and other selective serotonin reuptake inhibitors have been effective for this disorder, an abnormality of the serotonin system or partial destruction of the serotonergic raphe nuclei in the brain stem are possibly associated with this disorder (Low & Chong, 1998).

4.5.B.12 Cerebrovascular accident, Post - Depression

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:

FLUOXETINE may prevent post-stroke depression

c) Adult:

1) Based on a randomized, double-blind trial (n=48), a 12-week course of oral FLUOXETINE or NORTRIPTYLINE appeared to provide effective prophylaxis against depression in non-depressed patients within 6 months onset of acute stroke (either thromboembolic or hemorrhagic); however, there was a tendency for depression to develop after the course of fluoxetine or nortriptyline was finished, especially in nortriptyline- treated subjects. Subjects were followed for 21 months after the 3- month treatment period. FLUOXETINE-treated subjects (n=17) were given daily doses of 10 milligrams (mg) for the first 3 weeks (wk), 20 mg (wk 4 to 6), 30 mg (wk 7 to 9), and 40 mg (wk 10 to 12). NORTRIPTYLINE- treated subjects (n=15) received daily doses of 25 mg (wk 1), 50 mg (wk 2 to 3), 75 mg (wk 4 to 6), and 100 mg (wk 7 to 12). Nortriptyline- treated patients received therapeutic drug monitoring to maintain serum levels at 50 to 120 mg/milliliter. Dosages were reduced if side effects developed, which happened for 6 subjects (2 fluoxetine, 4 nortriptyline). Assessments were made using the Present State Exam (PSE) and the Hamilton Depression scale (Ham-D). During the 12-wk treatment period, no cases of major depression were reported. Minor depression occurred in 3 (20.0%) of fluoxetine-treated subjects, 1 (7.7%) nortriptyline-treated subject, and 5 (33.3%) placebo-treated subjects. Two of three depressed fluoxetine-treated subjects dropped out before completing 3 months of therapy. For those who completed 3 months of treatment, the rate of depression was significantly higher in the control group compared with a combined fluoxetine-nortriptyline group (5 of 15 versus 2 of 26; p=0.036). Six months after treatment ended, rates of depression were higher in the combined active treatment group compared with controls (p=0.047). No significant between-group differences were seen at 1 and 2 years. Using time-by-treatment analysis, Ham-D scores were lower in the active group compared with the placebo group during months 0 to 3 (p=0.026). For months 3 to 9, Ham-D scores were significantly declining in the nortriptyline group compared with controls (p=0.022) and were trending lower in the fluoxetine group (p=0.09 versus placebo). After 1 year and 2 years, no significant differences were seen across the 3 groups. The authors emphasized that patients treated

prophylactically with nortriptyline post-stroke need careful monitoring, and might be helped by a longer course of therapy or a more gradual withdrawal of the drug (Narushima et al, 2002).

4.5.B.13 Chronic fatigue syndrome

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:

Despite earlier case reports of efficacy of fluoxetine in the treatment of chronic fatigue syndrome, a randomized, controlled trial of fluoxetine in both depressed and non-depressed chronic fatigue syndrome patients demonstrated no beneficial effect. Patients were treated with fluoxetine 20 mg daily for a period of 8 weeks. None of the symptoms of chronic fatigue syndrome, including fatigue, depression, functional impairment, sleep disturbances, cognitions, and physical activity, improved in either the depressed or non-depressed subgroup (Vercoulen et al, 1996).

4.5.B.14 Depersonalization disorder

a) Overview

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

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:

In a case report, fluoxetine relieved chronic symptoms of depersonalization.

c) Adult:

1) A 27-year-old man with a 10-year history of depersonalization, depression, and anxiety with panic attacks noted marked improvement in symptoms 2 to 3 months after starting fluoxetine 20 milligrams (mg) daily. Alprazolam 0.5 mg 3 times daily was started a few months before fluoxetine but only decreased the frequency of panic attacks. Previous treatment with imipramine and psychotherapy was ineffective. Alprazolam 0.25 mg and fluoxetine 20 mg daily were continued for 2 years with complete remission of depersonalization and panic attacks; depression also improved (Ratliff & Kerski, 1995).

4.5.B.15 Depression - Diabetes mellitus

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:

Fluoxetine is effective for reducing the severity of depression in diabetic patients

c) Adult:

1) Fluoxetine was more effective than placebo for management of major depression in patients with comorbid diabetes in an 8-week, randomized, placebo-controlled, double-blind trial. Sixty patients with diabetes who were 21 to 65 years of age were randomized to placebo or fluoxetine 20 milligrams (mg) daily in the morning. Fluoxetine could be increased to a maximum of 40 mg daily depending on side effects and clinical response. The Beck Depression Inventory (BDI) and Hamilton Rating Scale for Depression (HAMD) were used to assess the severity of depression and improvement. Glycemic control was monitored by glycosylated hemoglobin (GHb). Of the 60 patients enrolled, 54 (90%) completed 8 weeks of treatment. Fluoxetine-treated patients demonstrated significantly lower mean posttreatment scores on the BDI and the HAMD compared with placebo-treated patients (BDI, 9.6 versus 13.6, respectively, p=0.03; HAMD, 9.4 versus 14.1, respectively, p=0.01). The percentage of patients with significant clinical improvement measured by the BDI was greater with fluoxetine than placebo (66.7% versus 37%, respectively, p=0.03). Although fluoxetine- treated patients demonstrated a greater reduction in mean GHb levels compared with the placebo group, the difference was not statistically significant (-0.40% versus -0.07%, respectively, p=0.13). Depression remission per HAMD was observed in 43.3% of the fluoxetine group compared with 23.3% of the placebo group, although the difference was not significant (p=0.09). Fluoxetine was generally well tolerated (Lustman et al, 2000).

4.5.B.16 Depression - HIV infection

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:

Depression improved in 78% of women with HIV

c) Adult:

1) In an 8-week, open trial, 14 of 18 women had a clinical response as measured by the Hamilton Rating Scale for Depression (HAM-D) and the Clinical Global Impressions Severity and Improvement scale (CGI). Thirty women began treatment but only 18 completed the trial. Treatment consisted of fluoxetine 20 milligrams (mg) per day or sertraline 50 mg per day if the patient refused fluoxetine. From baseline to week 8, the total HAM-D score (24 to 9; p less than 0.0001) and total Beck Depression Inventory (28 to 13; p less than 0.0001) decreased significantly. Five patients discontinued treatment due to side effects primarily anxiety, overstimulation, or insomnia. The response rate in this study was similar to other studies that included HIV-seropositive men or the 1 study that included HIV-seropositive women (Ferrando et al, 1999).

2) Fluoxetine was safe and effective for treating depression in men who were human immunodeficiency virus (HIV) seropositive and were treated with 1 or more antiretroviral agents primarily zidovudine. All patients (n=47) in this study received weekly supportive group psychotherapy and were randomly assigned to blinded treatment with placebo or fluoxetine 20 milligrams (mg) daily with titration to a maximum dose of 60 mg daily. Thirty-seven (79%) patients completed the 7-week study; withdrawal rates were similar between treatments. Significant reductions in the Hamilton Rating Scale for Depression (HAM-D; p less than 0.05) and Beck Depression Inventory (p less than 0.01) occurred in the fluoxetine compared to the placebo group. A 50% reduction in the HAM-D score occurred in 64% and 23% of patients treated with fluoxetine and placebo, respectively. Adverse effects were frequent in both treatment groups; however, only 1 patient in the placebo group and no patients receiving fluoxetine left the study due to an adverse effect (Zisook et al, 1998).

4.5.B.17 Diabetic neuropathy

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:

The following case report suggests that, like tricyclic antidepressants, fluoxetine may have a role in treating painful diabetic neuropathy, and that it offers a more favorable adverse effect profile for some patients

c) Adult:

1) The case of a 31-year-old woman with autonomic and peripheral neuropathy secondary to insulin-dependent diabetes mellitus and major depression is reported. Previous therapy with trazodone and tricyclic antidepressants had been unsatisfactory due to drug-induced exacerbations of orthostatic hypotension and urinary retention. Fluoxetine treatment was begun using a low dose (5 milligrams) for seven days, then titrated by 5 milligrams/day every three to four days until 20 milligrams/day was reached; after another week, titration continued in the same manner to a daily dose of 40 milligrams. The patient reported decreased pain in her extremities while on 5 milligrams/day and showed continued improvement for three weeks. During this same hospitalization, her depression improved, though not as quickly as her neuropathic symptoms. The patient complained of excessive sweating on the dose of 20 milligrams/day; this adverse effect decreased with confined use of fluoxetine. After seven months without pain on 40 milligrams fluoxetine/day, the patient's pain and depression returned, accompanying deterioration in her disease state. A dosage increase to 60 milligrams/day was quickly followed by pain relief, and later followed by improvement of her depression. More research is needed into the use of fluoxetine for analgesia (Theesen & Marsh, 1989).

4.5.B.18 Dysthymia

a) Overview

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

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:

Small, uncontrolled clinical studies have shown that fluoxetine improves dysthymia in adult and elderly patients. Larger, controlled clinical trials are needed for this indication.

c) Adult:

1) In a study of patients with primary dysthymia, fluoxetine resulted in significant improvement in clinical and social functioning compared to placebo; non-responders also showed improvement with an increase in fluoxetine dose. Patients showing a response at 3 months continued fluoxetine 20 milligrams (mg)/day for an additional 3 months. If a response was NOT evident, the dosage of fluoxetine was increased to 40 mg/day, and placebo-treated patients received fluoxetine 20 mg/day for the

remaining 3 months of the study. At the 6-month evaluation, initial responders were still improved; 50% of non-responders also showed improvement with the higher dose of fluoxetine or after treatment with fluoxetine. Adverse effects were similar in incidence and affected body system between the treatments. This is 1 of the few studies to include an adequate sample (n=140), blinding of treatment assessment, a reasonable duration of treatment, randomization, and a placebo control; however, maintenance of blinding was questionable during the last 3 months of the study, and the sample size was smaller due to exclusion of 37 patients from 1 center who had an exceptional response to fluoxetine. Additional longer, comparative studies are still needed to assess the efficacy of long-term fluoxetine for treating dysthymia (Vanelle et al, 1997).

2) Fluoxetine 20 to 60 milligrams/day has demonstrated efficacy in primary dysthymia (Ravindran et al, 1994). Though this was a non-controlled observation, an overall response rate of 73.1% was reported with subaffective-type dysthymia patients exhibiting a better clinical response to drug therapy than those with character spectrum dysthymia (77% versus 25%, respectively). Full efficacy of fluoxetine treatment for dysthymia may not be seen for a period of 16 weeks (Albert & Ebert, 1996).

3) FLUOXETINE (mean dose, 35.5 milligrams/day) was also effective in a group of elderly patients with dysthymic disorder. Outcome criteria were based on a 50% reduction in Hamilton Rating Scale for Depression (HAM-D) score, final HAM-D score less than 8, and a Clinical Global Impression score of 1 or 2 which was interpreted as very much or much improved. Although this was a relatively small study population (n=20), 60% of patients responded. Further controlled studies are needed to evaluate fluoxetine efficacy for this indication (Nobler et al, 1996).

4.5.B.19 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:

Reduced pain and physical impairment due to fibromyalgia

c) Adult:

1) Fluoxetine reduced pain and improved physical function in women with fibromyalgia. In a randomized, double-blind, placebo- controlled trial, 60 women meeting criteria of the American College of Rheumatology for fibromyalgia were given placebo or fluoxetine in individualized doses for 12 weeks. Subjects were also allowed to continue taking non-steroidal antiinflammatory drugs (NSAIDs) and acetaminophen on their usual schedules. Fluoxetine was started at 20 milligrams/day for the first 2 weeks. If that dose was not tolerated, it was reduced to 20 mg every other day. After the first 2 weeks, the dose could be titrated to a maximum of 80 mg/day by 2-week increments of 10 to 20 mg. The average dose of subjects completing the 12-week study was 55 mg/day. Changes in total scores from baseline to end-of-study on the Fibromyalgia Impact Questionnaire (FIQ) were significantly better for the fluoxetine group than for the placebo group (p=0.005). Pain scores also improved more in the fluoxetine group than in the placebo group (p=0.002). Improvement of 25% or more on total FIQ scores or pain scores were considered clinically meaningful. Total scores were improved by 25% or more in 32% of the fluoxetine group and 15% of the placebo group (p=0.19); pain scores improved by 25% or more in 56% of the fluoxetine group and 15% of the placebo group (p=0.003). There was no significant difference between groups in change in tender-point score. The most common adverse events reported for fluoxetine were headache, insomnia, sedation, and nausea (Arnold et al, 2002).

4.5.B.20 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:

Fluoxetine has shown modest efficacy for treating chronic daily headache
Fluoxetine lacks efficacy for treating migraine
S-fluoxetine is more effective than placebo in the prevention of migraine headache

c) Adult:

1) In a double-blind trial, S-fluoxetine was more effective than placebo in the prophylaxis of migraine. Following a 1-month placebo period (n=49), patients were randomized to receive 40 milligrams (mg) nightly of S-fluoxetine (a dose equivalent to 80 mg of the marketed racemic fluoxetine) or placebo for 3 months. The primary outcome measure was the 28-day frequency of migraine attacks. Patients treated with active drug experienced a 52% (1.7 attacks/28 days) decline in the frequency of attacks and those receiving placebo experienced a 27% (1.1 attacks/28 days) decline in the frequency of attacks. The differences in the frequency of attacks between the 2 treatment groups were statistically significant in month 2 (n=39) and month 4 (n=33) only. An equivalent number of patients discontinued the study due

to adverse events and inadequacy of response in both treatment groups. S-fluoxetine was, therefore, well-tolerated. Due to the decrease in sample size, absolute conclusions of the efficacy of S-fluoxetine in the prophylaxis of migraine must be made with caution (Steiner et al, 1998).

2) Fluoxetine 20 to 40 mg/day was moderately effective in the treatment of chronic daily headache, but was not effective in the treatment of migraine headache. In this study, patients with chronic daily headache (n=64) and migraine headache (n=58) were randomly assigned to fluoxetine or placebo for a three month period. Fluoxetine was initially given as a dose of 20 mg/daily and advanced to 40 mg/daily after one month depending on patient response; the majority of patients required 40 mg. Overall headache status, headache-free days, and investigator judgment were the three determinants of effectiveness. Chronic daily headache sufferers did note significant improvement on the three scales which became apparent after the third month of treatment with fluoxetine. Mood improvement was a major determinant of headache improvement (Saper et al, 1994).

4.5.B.21 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:

Modestly reduced frequency and severity of hot flashes in women with a history of breast cancer

c) Adult:

1) Fluoxetine treatment modestly reduced the frequency and severity of hot flashes in women who could not take hormones because of a history of breast cancer or perceived high risk of breast cancer. In a double-blind, randomized, cross-over trial, 68 women experiencing at least 14 hot flashes per week were given fluoxetine 20 milligrams (mg) per day orally or placebo for 4 weeks and then switched to the opposite treatment for 4 weeks. Hot flash scores (severity times frequency) were reduced at least 75% (in comparison to baseline scores) in 24% of patients taking fluoxetine in the first treatment period and in 11% of those taking placebo. Hot flash scores were increased in 27% of patients receiving fluoxetine and 23% receiving placebo. Crossover data showed a trend for greater improvement in hot flash severity with fluoxetine treatment (p=0.055). Adverse events were similar with the 2 treatments except for more mouth dryness with fluoxetine. Patients reported less trouble sleeping while taking fluoxetine (Loprinzi et al, 2002).

4.5.B.22 Huntington's disease

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:

Fluoxetine did NOT significantly improve total functional capacity (TFC) over 4 months in non-depressed patients with Huntington's Disease (HD).

c) Adult:

1) Thirty patients were randomly assigned to receive placebo or fluoxetine 20 milligrams/day; however, 5 fluoxetine-treated and 2 placebo-treated patients dropped out before the 2 month assessment. Baseline TFC scores were 9.2 and 9.7 (indicating high functional capacity) in the fluoxetine and placebo treatment groups, respectively. At 4 months, the TFC score improved by an average of 0.25 and 0.09 points in the fluoxetine and placebo group, respectively; this is compared to an expected decline of 0.7 over 1 year in most patients with HD. Patients with obsessive behaviors as a component of their disease showed some improvement; however, this must be tested in a controlled clinical trial. The lack of statistically significant improvement in this trial is due to the small sample size which allows only detection of large changes in TFC (Como et al, 1997).

4.5.B.23 Major depressive disorder

FDA Labeled Indication

a) Overview

FDA Approval: Adult, yes; Pediatric, yes ((8 years and older))
Efficacy: Adult, Effective; Pediatric, Effective
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:

Indicated for the treatment of major depressive disorder (Prod Info PROZAC(R) oral pulvule, oral solution, oral tablet, oral delayed-release capsule, 2005)
Effective in placebo-controlled studies using doses from 20 to 80 mg daily (Wernicke et al, 1987;

Rickels et al, 1986; Stark & Hardison, 1985; Fabre & Crismon, 1985)
Similar onset of antidepressant effect to amitriptyline and imipramine (Chouinard, 1985; Cohn & Wilcox, 1985; Bremner, 1984)

c) Adult:

1) SINGLE-AGENT THERAPY

a) A retrospective review of 12 adult patients treated in an outpatient clinic, showed that once-weekly dosing of fluoxetine (90 milligrams (mg) was effective in the treatment of mild to severe depression. All patients were treatment-naive and had an average decrease of 4.6 points on the Hamilton Depression Rating Scale after 12 weeks of therapy (Kabinoff et al, 2002).

b) In a 3-month open label study of 39 outpatients, weekly administration of enteric-coated fluoxetine was effective and well tolerated in the short-term management of depression. Thirty-one patients stabilized on daily fluoxetine were converted to a single weekly dose of 90 milligrams (mg) to 540 mg; one patient required twice-weekly dosing. Seven previously untreated, symptomatic patients were started on fluoxetine 90 mg per week and achieved remission of symptoms before their first monthly appointment. No serious adverse events or hospitalizations were reported. The once-weekly capsule releases 291 micromoles of fluoxetine over 7 days (roughly equivalent to 13 mg released per day). Patients previously receiving fluoxetine 20 mg daily were converted to a 180 mg weekly dosage. At doses similar to usual maintenance doses, all patients remained in remission throughout the study period. The authors suggested that a delayed release, enteric-coated formulation of fluoxetine may provide a convenient alternative in patients requiring long-term treatment for depression (Boungiorno, 2002).

c) Of 106 patients with major depression, who did not respond to sertraline, 67 responded to fluoxetine suggesting that a trial of a second selective serotonin reuptake inhibitor (SSRI) is warranted in unresponsive patients (Thase et al, 1997). Fluoxetine therapy was initiated with 20 milligrams(mg)/day and increased to 60 mg/day as required. At the conclusion of the trial, 36.8%, 40.6%, and 22.6%, respectively, of patients were receiving fluoxetine 20 mg, 40 mg, or 60 mg per day. Scores for the Hamilton Rating Scale for Depression, the primary efficacy measure, showed a 50% decrease which was statistically significant (p less than 0.05). The incidence and severity of common SSRI-induced adverse effects (ie, headache, insomnia, nausea) were NOT higher than expected in patients with prior intolerance to sertraline; however, peripheral edema, myalgia, and pruritus were more common in patients intolerant to sertraline. Randomized, comparative studies are needed to further assess whether a second SSRI is warranted for treating patients who were unresponsive to the first SSRI.

2) COMBINATION THERAPY

a) The combination of clonazepam and fluoxetine was more effective than placebo and fluoxetine for initial treatment of depression. Eighty patients were randomly assigned to receive fluoxetine 20 milligrams (mg) daily plus placebo or fluoxetine 20 mg daily plus clonazepam 0.5 mg at bedtime with an increase to 1 mg at day 4, if needed. Clonazepam and placebo were gradually tapered between days 21 and 33; the dose of fluoxetine could be increased to 40 mg daily at day 42. Scores on the Hamilton depression scale were significantly (p less than 0.001) lower at day 21 for clonazepam and fluoxetine versus placebo and fluoxetine; however, 1 week after discontinuing clonazepam, there was NOT a significant difference between treatment groups. Combination therapy also resulted in more patients with a greater than 50% decrease in the Hamilton depression scale and greater overall improvement on the physician and patient Clinical Global Impression improvement score at day 21. After discontinuing clonazepam, scores on the Hamilton depression scale rose and then decreased to the lowest score by day 56 of treatment. Reasons for using clonazepam augmentation include a decrease in the anxiety and insomnia components of the illness and a possible decrease in the stimulating side effects of fluoxetine. Although combination therapy appeared safe and effective, the presence of confounding factors require careful interpretation (Smith et al, 1998).

b) The efficacy of fluoxetine in treating depression may be enhanced by coadministered pindolol, according to a 6-week randomized, double-blind study (Perez et al, 1997). Overall, 41 of 55 patients (75%) administered fluoxetine 20 milligrams/day with pindolol 7.5 milligrams/day responded to treatment compared with 33 of 56 patients (59%) given fluoxetine and placebo (p=0.04). Drug efficacy measured by decreases in Hamilton Rating Scale for Depression scores and Montgomery-Asberg Depression Rating Scale scores also favored the fluoxetine-pindolol group (p=0.04 and p=0.02, respectively). Patients administered concomitant fluoxetine and pindolol did not experience adverse side effects. The advantage of the combination therapy may relate to pindolol's action in blocking the decrease in serotonergic neural activity caused by selective serotonin reuptake inhibitors (SSRIs), thus enhancing therapeutic effects of the SSRI.

3) MAINTENANCE THERAPY

a) Once-weekly dosing of fluoxetine with the enteric-coated 90- milligram (mg) formulation was effective for maintaining response in patients who had been treated successfully with daily citalopram, paroxetine, or sertraline. In an open-label study, 246 patients who had responded to citalopram 20 to 40 mg/day (n=83), paroxetine 20 mg/day (n=77), or sertraline 50 to 100 mg/day (n=86) were switched to weekly fluoxetine for 12 weeks. Seventy-nine percent of patients successfully completed treatment; 9.3% discontinued treatment because of relapse/lack of efficacy, and 4.9% because of an adverse event. There were no significant increases in depression scores

for any previous-therapy group and there were no significant differences for efficacy among the groups. Statistically significant improvements in general mental health, role limitations due to emotional problems, and vitality were seen for all previous-therapy groups. Treatment-emergent adverse events that occurred in 10% or more of patients included rhinitis, headache, nervousness and insomnia. Diarrhea was the only adverse event showing a difference among previous-therapy groups: 6% each of citalopram group and the sertraline group and 13% of the paroxetine group experienced diarrhea. The incidence of diarrhea in the paroxetine group decreased as time progressed. At the end of the study, 85% of patients preferred the once-weekly fluoxetine treatment to daily treatment with their previous drug (Miner et al, 2002).

b) In a small, double blind, placebo-controlled trial, once weekly fluoxetine, 60 milligrams (mg), was as effective as fluoxetine 20 mg per day or placebo during the continuation phase of major depressive disorder (MDD). Patients with unipolar MDD, who responded to fluoxetine 20 mg daily for 7 weeks, were randomly enrolled into one of three groups: fluoxetine 20 mg daily, fluoxetine 60 mg weekly, or placebo. The fluoxetine groups showed less depressive symptomatology than the placebo group during the 7-week continuation phase, but the difference was not statistically significant. The authors suggest that the placebo response may be due to carry over effects from norfluoxetine following the initial 7 weeks of treatment or due to too short of a continuation phase in this study to determine actual relapse rates. Norfluoxetine serum concentrations for the 60 mg weekly group were approximately 50% of that of found in the fluoxetine 20 mg daily group, leading the authors to suggest that higher weekly doses may be needed (Burke & McArthur-Miller, 2001).

c) A once-weekly formulation of enteric-coated fluoxetine is safe, effective and well tolerated for the long term treatment of depression in patients who responded to 20 milligrams (mg) per day of fluoxetine for acute treatment. Nine hundred thirty-two patients with major depression were treated with fluoxetine 20 mg daily in a thirteen week, open-label phase trial. Patients who responded to acute treatment were randomly assigned to one of three groups in a 25-week, multicenter, placebo-controlled, double-blind, randomized continuation treatment phase. The treatment groups for the continuation phase were as follows: (1) 25 weeks of treatment with 90 mg enteric-coated fluoxetine once weekly (n=190), (2) 25 weeks of treatment with 20 mg fluoxetine daily (n=189), and (3) 25 weeks of placebo (n=122). Patients receiving fluoxetine 90 mg weekly or fluoxetine 20 mg per day showed significantly lower relapse rates than placebo. No significant difference in efficacy was shown between the two groups receiving active drug. The safety profile of the weekly dosing was similar to that of the daily dosing with nervousness and thinking abnormal (ie, impaired concentration or thought process) significantly more frequent in the former group. It was concluded that long-term treatment with once weekly dosing of enteric-coated fluoxetine is effective, safe, and well tolerated for patients responding to 20 mg per day of fluoxetine for acute treatment (Schmidt et al, 2000). The use of fluoxetine 90 milligram (mg) enteric-coated tablets once weekly was associated with increased compliance compared to 20 milligrams of regular release fluoxetine once daily (85.9% versus 79.4%, respectively) in a 12-week, open-label, randomized trial (n=109) (Claxton et al, 2000).

d) Treatment of major depression with fluoxetine for at least 38 weeks has demonstrated efficacy in preventing relapse. Eight hundred and thirty-nine patients with major depression were treated with 20 milligrams (mg) daily of fluoxetine in a 12 to 14 week open-label phase of this trial. Patients experiencing remission (ie, no longer met DSM-III-R criteria for major depression) following this phase were then randomized to one of 4 treatment groups in a 50-week, double-blind, long-term therapy phase. The treatment groups for the long-term phase were as follows: (1) 50 weeks of placebo therapy (n=96), (2) 14 weeks of fluoxetine therapy followed by 36 weeks of placebo (n=97), (3) 38 weeks of fluoxetine followed by 12 weeks of placebo (n=100), and (4) 50 weeks of fluoxetine (n=102). The primary outcome measure was the relapse rate following the 12 week open-label phase of the trial. Patients treated with fluoxetine after the open-label phase of the trial were less likely to experience relapse than those who had received placebo for 50 weeks. This difference, however, was only statistically significant for patients receiving an additional 14 weeks or 38 weeks of fluoxetine treatment. Relapse rates for those treated with a total of 38 weeks with fluoxetine were the lowest. It was, therefore, concluded that optimal therapy to prevent relapse entails 12 initial weeks, followed by at least 26 additional weeks. Due to analysis methods, researchers were uncertain whether therapy with fluoxetine beyond a total of 38 weeks may actually be of greater benefit than demonstrated here in preventing relapse (Reimherr et al, 1998).

d) Pediatric:

1) SINGLE-AGENT THERAPY

a) In an 8-week, placebo-controlled study, fluoxetine was more effective than placebo for treating major depressive disorder in children and adolescents (Emslie et al, 1997a). After a 4-week evaluation phase, patients were randomly assigned to receive placebo or fluoxetine 20 milligrams (mg) daily. Physician assessment using the Clinical Global Impression (CGI) scale and Children's Depression Rating Scale-Revised (CDRS-R) demonstrated statistically significant improvement for fluoxetine compared to placebo; 56% versus 33% of patients treated with fluoxetine and placebo improved on the CGI scale. Drop-outs occurred primarily due to lack of efficacy (19 - placebo, 7 - fluoxetine) but 4 fluoxetine- and 1 placebo-treated patient left the study due to side effects. Fluoxetine produced mania in 3 patients and a severe rash in another. In this study, fluoxetine was effective for the short-term treatment of depression in children; however, confirmation in another

study and long-term evaluation are needed.

2) COMBINATION THERAPY

a) Compared with fluoxetine alone, cognitive-behavioral therapy (CBT) alone, or placebo, fluoxetine combined with CBT improved outcome and reduced suicidal thinking in a randomized controlled trial involving 439 patients between the ages of 12 to 17 years with a primary diagnosis of major depressive disorder. Patients were randomized to fluoxetine 10 to 40 milligrams/day (mg/d), CBT alone, CBT with fluoxetine 10 to 40 mg/d, or placebo for 12 weeks. Outcomes were measured using a Children's Depression Rating Scale-Revised total score and a Clinical Global Impressions improvement score. Compared with placebo, fluoxetine with CBT was statistically significant on the Children's Depression Rating Scale-Revise (p=0.001). Fluoxetine with CBT was superior to fluoxetine alone (p=0.02) and CBT alone (p=0.01) as well. Fluoxetine alone was also superior to CBT alone (p=0.01). Response rates for fluoxetine with CBT were 71% (95% confidence (CI), 62% to 80%); fluoxetine alone, 60.6% (95% CI, 51% to 70%); CBT alone, 43.2% (95% CI 34% to 52%); and placebo, 34.8% (95% CI, 26% to 44%). Fluoxetine alone and fluoxetine with CBT were statistically superior to CBT alone and placebo on the Clinical Global Impressions improvement responder analysis. Suicidal thinking improved significantly in all 4 treatment groups. The greatest reduction occurred with fluoxetine plus CBT (p=0.02 compared to placebo) (Treatment for Adolescents With Depression Study (TADS) Team, 2004).

4.5.B.24 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.B.25 Obesity

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:

Fluoxetine 20 to 80 milligrams/day was effective for promoting weight loss in non-depressed patients, but patients tended to regain weight after fluoxetine was stopped (Levine et al, 1987; Ferguson & Feighner, 1987). The drug has been as effective as benzphetamine (Ferguson & Feighner, 1987). Optimal doses appear to be 60 to 80 milligrams daily.

c) Adult:

1) Patients treated with fluoxetine who completed the trial lost significantly more weight than those in the placebo group. Although at year's end fluoxetine subjects who were classified as binge eaters had lost half the weight lost by the fluoxetine subjects who were not so classified, this difference was not statistically significant. Follow-up data obtained for 15 of the subjects who completed the study showed that, 3 to 6 months later, former fluoxetine subjects had regained significantly more weight than former placebo subjects. Fluoxetine and placebo were compared in a double-blind trial of 45 obese subjects (Marcus et al, 1990). Twenty-one patients completed the year-long program, which included behavior modification instruction (provided primarily during the first 20 weeks) and treatment with placebo or 60 mg of fluoxetine daily. Compliance was assessed by means of pill counts at each of 13 clinic visits and by determination of plasma levels of fluoxetine and norfluoxetine at 3 of the visits. Larger studies are needed to confirm and elucidate the differential effects of fluoxetine on binge- and non-binge-eaters.

2) Therapy with fluoxetine resulted in statistically significant weight loss to week 28; however, at the end of the study period, there was no difference between fluoxetine and placebo. The efficacy of fluoxetine 60 milligrams/day versus placebo in promoting weight loss was evaluated in a 52 week multicenter trial (Goldstein et al, 1994). Study sites that demonstrated the greatest benefit with

fluoxetine also utilized nutrition and behavior counseling.

4.5.B.26 Obsessive-compulsive disorder

FDA Labeled Indication

a) Overview

FDA Approval: Adult, yes; Pediatric, yes ((7 years and older))
Efficacy: Adult, Effective; Pediatric, Effective
Recommendation: Adult, Class IIa; Pediatric, Class IIa
Strength of Evidence: Adult, Category B; Pediatric, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:

Indicated for the treatment of obsessions and compulsions in patients with obsessive-compulsive disorder (OCD), defined as obsessions or compulsions that cause marked distress, are time-consuming, or significantly interfere with social or occupational functioning (Prod Info PROZAC(R) oral pulvule, oral solution, oral tablet, oral delayed-release capsule, 2005).

c) Adult:

1) 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, 1997; Leonard, 1997). 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, 1997). 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, 1997). 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, 1997). 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, 1997).

2) Fluoxetine produced beneficial effects on the time spent obsessing, time spent ritualizing, the SCL-5 obsessive-compulsive disorder subscale, and therapists' global ratings; obsessive thought frequency and compulsive rituals improved slightly, but not to a significant degree. Improvement in overall distress, depression, and anxiety was also observed. In a single-blind trial, 10 patients meeting the DSM-III criteria for obsessive-compulsive disorder were treated with fluoxetine 20 to 80 milligrams daily (Turner et al, 1985). Patients with psychosis, organic brain pathology or primary depression were excluded from the trial.

3) There are at least four cases where combined therapy with clomipramine and fluoxetine was effective in the treatment of obsessive-compulsive disorder where patients were previously unresponsive to singular therapy, in most cases to both agents (Browne et al, 1993). None of the cases mentioned showed evidence of excess serotonin stimulation, despite both agents having potent effects on serotonin.

4) In a report of 72 patients in an ongoing study of over 150 outpatients with obsessive-compulsive disorder, depressed and non-depressed subgroups experienced significant improvements on at least one of two assessments of obsessive-compulsive disorder at 4, 8, and 12 weeks of fluoxetine therapy, compared to baseline (Jenike et al, 1989). Although baseline depression scores were found not to predict the improvements in these scales, overall scores on the depression inventory used did decline significantly at 8 and 12 weeks. The favorable results need to be considered in light of the uncontrolled nature of the study and the fact that 11 patients from an original group of 72 dropped out, primarily due to adverse effects or noncompliance. This study used initial doses of fluoxetine 20 milligrams/day, titrated upward as tolerated to a maximum of 80 milligrams/day; the mean maximal dose was 75 milligrams/day. Doses above 20 milligrams/day were divided (not necessarily evenly) into morning and afternoon allotments.

5) In a one-year open study using 50 patients with obsessive-compulsive disorder unresponsive to, or intolerant of, other antidepressants, 86% of subjects experienced significant improvements on a variety of psychiatric assessment scales. Although the authors stated that subjects had shown no evidence of spontaneous remissions before the trial, they noted that only 23% of fluoxetine-responsive patients who discontinued therapy after the trial relapsed with the same symptoms. The favorable results should be interpreted in light of the fact that fluoxetine doses were rapidly escalated from 20 milligrams/day to 60 to 100 milligrams/day (undivided) over approximately one week, and outcomes were reported only for assessments made after 12 months. Also, 7 patients of an original group of 57 dropped out of the study but were not counted as treatment failures (Fontaine & Chouinard, 1989a).

6) Fluoxetine-treated patients experienced significant improvements (compared to baseline) on a variety of assessments made at 5 monthly intervals after study entry. Weight also decreased significantly for 4 months. An open trial of fluoxetine was performed in 75 outpatients with obsessive-compulsive disorder (Levine et al, 1989). Fluoxetine was titrated from an initial daily dose of 20 milligrams/day to 80 milligrams/day by the end of the second month in most patients. This study may be

criticized for using successively smaller numbers of patients in analyses of results after 2 months, since patients entered the 5-month study at different times. Also, 11 subjects dropped out of the study by the end of their first month, and dropouts continued at a rate of up to 10% per month thereafter.

d) Pediatric:

1) In a retrospective evaluation of 20 children and 18 adolescents with obsessive compulsive disorder (OCD), fluoxetine 1 mg/kg/day (mean dose, 50 mg) effectively improved symptoms of OCD in 74% of patients. Prepubertal and postpubertal subjects responded similarly and a clinical response was maintained over a follow up period averaging 19 months (Geller et al, 1995).

2) In a group of 11 children (ages 10 to 18 years) with obsessive-compulsive symptoms in association with Tourette's syndrome, fluoxetine at a dosage of 20 to 40 milligrams/day was associated with decreased tic severity, and improvement in attention abilities and social functioning (Kurlan et al, 1993). Scores on measures of obsessive-compulsive symptoms, however, showed some improvement, but were not statistically different from placebo.

3) Fluoxetine produced a therapeutic response in 50% of subjects (2 of 4 with primary obsessive compulsive disorder, and 3 of 6 with Tourette's syndrome in addition). Fluoxetine was used for 4 to 20 weeks in an open-label study of 10 children and adolescents with obsessive compulsive disorder (with or without Tourette's syndrome) (Riddle et al, 1990). All responders were receiving 20 mg fluoxetine each day. The subjects ranged in age from 8 to 15 years. Nine subjects were started on a regimen of 20 mg fluoxetine each day; one received 20 mg every other day (reason not stated). One subject's dose was increased after 3 weeks to 40 mg each day.

4.5.B.27 Panic disorder

FDA Labeled Indication

a) Overview

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

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:

Fluoxetine is indicated for the treatment of panic disorder, with or without agoraphobia (Prod Info PROZAC(R) oral pulvule, oral solution, oral tablet, oral delayed-release capsule, 2005)

c) Adult:

1) Fluoxetine (20 to 60 milligrams daily) was shown to be effective in the treatment of panic disorder, with or without agoraphobia, in two 12-week, randomized trials. At study endpoint, the fluoxetine-treated groups had a statistically significantly greater percentage of patients who were free from panic attacks as compared to the placebo groups. Response rates were 42% vs 28% and 62% vs 44% for the fluoxetine and placebo groups, respectively for the first and second studies (Prod Info PROZAC(R) oral pulvule, oral solution, oral tablet, oral delayed-release capsule, 2005).

2) Fluoxetine was useful for treating panic disorder in a 10-week study (Michelson et al, 1998). In a double-blind study, 243 patients with confirmed panic disorder were randomly assigned to placebo, fluoxetine 10 milligrams (mg) daily, or fluoxetine 20 mg daily for 10 weeks with the option for continuing therapy for an additional 24 weeks. Fluoxetine 20 mg compared to placebo resulted in a significant reduction in the Clinical Global Impression improvement scores as assessed by physicians (p=0.02) and patients (p=0.006). Patients treated with fluoxetine 10 mg but not 20 mg daily experienced a significant reduction in total panic attack frequency compared to placebo. Other assessment parameters including the Phobia rating scale score (p=0.01), Hamilton depression scale (p=0.007), Hamilton anxiety scale (p=0.002), Phobic avoidance (p=0.002), anticipatory anxiety (patient-rated, p=0.002), and overall functioning (p=0.08) also showed significant improvement primarily with fluoxetine 20 mg but for some assessments, improvement also occurred with fluoxetine 10 mg. Discontinuation due to adverse effects was similar for all treatment groups. Fluoxetine was effective and tolerated well for treatment of panic disorder.

3) Weekly fluoxetine prevented recurrence of panic attacks in 9 of 10 patients. Ten patients who met DSM-III-R criteria for panic disorder were treated with daily fluoxetine 10 to 40 milligrams/day until control was achieved. Patients were then switched to fluoxetine weekly at the same dose as was used daily with titration to a higher dose if needed. Six of 10 patients required a higher weekly than daily dose (range, 10 to 60 milligrams/week). Only 1 patient had a recurrence of panic disorder 18 months after the switch to weekly therapy. The remaining patients have remained panic attack free for periods of 1 to 26 months. Based on results of this open trial, a controlled clinical trial is needed to further evaluate weekly fluoxetine for panic disorder (Emmanuel et al, 1999).

4) Fluoxetine up to 80 milligrams daily was effective in the treatment of panic attacks in 7 of 16 patients in an open study (Gorman et al, 1987a). Mean doses in the responding patients were 27 mg daily (range, 10 to 70 mg daily). Response was observed after the 6th week of treatment, with the mean time to achieve a complete panic-free state for 4 successive weeks being 10.8 weeks. Side effects were minimal in responding patients; however, 8 of 9 nonresponders developed intolerable side effects (jitteriness, restlessness, diarrhea, and insomnia); these side effects occurred with doses as low as 10 milligrams daily, suggesting idiosyncrasy. Controlled studies are required to allow full evaluation of the efficacy of fluoxetine in panic attacks.

4.5.B.28 Picking own skin

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:

Reduced skin-picking behavior in some subjects

c) Adult:

1) Pathological skin-picking behavior was reduced by fluoxetine treatment in about half of the subjects in a small study. Skin- picking behavior returned after discontinuation of the drug. Fifteen women, of mean age 40.7 years and mean duration of symptoms 25 years, took fluoxetine for 6 weeks, starting at 20 milligrams (mg) per day. Doses were increased, as tolerated, to as high as 60 mg/day in nonresponders. Eight patients showed a response of a 30% or more decrease in their score on the Yale- Brown Obsessive Compulsive Scale. Those 8 were then randomized to continue fluoxetine at their successful dose or to receive placebo, in a double-blind manner, for 6 more weeks. Those taking fluoxetine maintained their response, whereas, those taking placebo all experienced symptom worsening. At follow-up 21 to 30 months later, one patient from the fluoxetine group remained in remission while continuing to take fluoxetine. One discontinued fluoxetine because of sexual side effects and relapsed. Two from that group were lost to follow-up. One patient from the placebo group restarted fluoxetine and remained in remission at 21 months. The other 3 from the placebo group did not resume fluoxetine treatment because of side effects and continued their skin-picking behaviors (Bloch et al, 2001).

4.5.B.29 Postpartum depression

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:

Fluoxetine or 6 counseling sessions produced similar improvement in women with postpartum depression at 4 and 12 weeks. Six to 8 weeks after delivery, 87 women who had a score of 12 or greater on the revised clinical interview schedule and satisfied diagnostic criteria for depression were randomly assigned to receive fluoxetine with 1 or 6 counseling sessions or placebo with 1 or 6 counseling sessions. The investigators and patients were blinded to treatment allocation. Additional benefit was NOT derived from combining fluoxetine with counseling; however, 6 counseling sessions were better than 1. Treatment with fluoxetine or 6 counseling sessions is effective and may be chosen depending on patient preference (Appleby et al, 1997).

4.5.B.30 Posttraumatic stress disorder

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:

Effective in treating PTSD in civilians and combat veterans

c) Adult:

1) Fluoxetine was more effective than placebo in treating posttraumatic stress disorder (PTSD) in a population composed mostly of men (81%), many of whom were exposed to multiple traumas of combat (48%) and/or were victims of war or witnesses of a war event (47%). In a randomized, double- blind, placebo-controlled trial, patients were treated with fluoxetine (n=226), beginning at 20 milligrams (mg) per day and increasing to a maximum of 80 mg/day, or placebo (n=75) for 12 weeks. Mean dose at the end of the study was 57 mg/day. Fluoxetine-treated patients showed significantly greater improvement in the total score of the Treatment Outcome PTSD scale (TOP-8) in comparison to placebo-treated patients (fluoxetine, -10.3; placebo, -8; p=0.006). Improvement was significant beginning at 6 weeks. Response rates (a 50% or greater decrease in the TOP-8 total score and a Clinical Global Impressions-Severity of Illness scale (CGI- S) score of 1 or 2) were 60% for the fluoxetine group and 44% for the placebo group (p=0.02). Significantly greater improvements compared with placebo treatment were seen in those with combat-related trauma (p less than 0.01) and those with no dissociative symptoms (p less than 0.001). In contrast to other studies that have reported little effect of fluoxetine in combat veterans, the patients in this study were comparatively young and had recently experienced trauma. Dissociative symptoms at baseline may be a predictor of a high placebo effect. Adverse effects were

similar for fluoxetine and placebo (Martenyi et al, 2002).
2) Fluoxetine was more effective than placebo for treating post-traumatic stress disorder (PTSD) (Connor et al, 1999). In a 12-week, double-blind study, 54 patients were randomly assigned to placebo or fluoxetine 10 milligrams (mg) daily with titration to 60 mg daily, if needed. Seventeen patients withdrew from treatment of whom 11 and 6 were in the placebo and fluoxetine group, respectively. For the primary efficacy measure, the Duke Global Rating (Duke) for PTSD, significantly more patients reached a score of 1 (no symptoms) during treatment with fluoxetine than placebo (59% versus 19%; p less than 0.0005). The Davidson Trauma Scale (DTS) total scores were also significantly lower in patients treated with fluoxetine compared to placebo. The onset of beneficial effects was observed at 2 weeks on the Duke scale and at 4 weeks on the DTS. This study included only civilians, primarily women, who fulfilled DSM-IV criteria for PTSD.

4.5.B.31 Premature ejaculation

a) Overview

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

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:

Fluoxetine was useful in the treatment of premature ejaculation by increasing time to ejaculation

c) Adult:

1) Treatment with either 20 milligram (mg) daily or 90 mg weekly fluoxetine effectively increased ejaculatory latency time in men with premature ejaculation. In a prospective, randomized study, patients (n=80) with premature ejaculation received fluoxetine 90 mg once weekly or fluoxetine 20 mg once daily for 3 months. Mean latency time to ejaculation increased in both treatment groups, however, there were no significant differences between groups. From baseline to 4 weeks after the end of treatment, mean ejaculatory latency time increased from 0.48 minute to 3.57 minutes and from 0.50 minute to 3.37 minutes in patients given 90 mg and 20 mg fluoxetine, respectively (p less than 0.01, both values). Partner sexual satisfaction was 27% in the 90 mg treatment group and 26% in the 20 mg treatment group. Adverse events were similar between groups, including, headache, nausea, and insomnia, (Manasia et al, 2003).
2) Latency time to ejaculation increased from slightly less than 1 minute to nearly 10 minutes during 8-weeks open-label treatment of 11 men with fluoxetine 40 milligrams (mg) daily (maximum 60 mg), with confirmation in a placebo-controlled trial of 17 men (Lee et al, 1996a; Kara et al, 1996a). Significant subjective changes included increased sexual desire, partner satisfaction, and decreased anxiety concerning premature ejaculation (Lee et al, 1996a).

4.5.B.32 Premenstrual dysphoric disorder

FDA Labeled Indication

a) Overview

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

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:

Indicated for the treatment of premenstrual dysphoric disorder (PMDD) (Prod Info SARAFEM(R) Oral Capsule, 2005)

c) Adult:

1) Fluoxetine was significantly superior to placebo in reducing symptoms of tension, irritability, and dysphoria, as measured by visual-analogue scales. Benefit was noted as early as the first menstrual cycle. The authors concluded that fluoxetine administered once daily at a dosage of 20 milligrams was optimum in providing therapeutic efficacy and a side effect profile similar to the placebo group. Fluoxetine treatment was studied in a randomized, double-blind, placebo-controlled trial involving a large group of women (180 women completed the study) with PREMENSTRUAL DYSPHORIA, or premenstrual syndrome (Steiner et al, 1995). The study included women who had at least a one-year history of five or more symptoms of premenstrual dysphoria defined as being severe enough to impair activities of daily living. After a washout period of two menstrual cycles, patients were randomized to receive placebo, fluoxetine 20 milligrams/daily, or fluoxetine 60 milligrams/daily for six menstrual cycles. Further analysis of this study showed that fluoxetine was superior to placebo in relieving physical symptoms (including specifically bloating, breast tenderness) other than headache (Steiner et al, 2001). Fluoxetine 60 mg was not better than fluoxetine 20 mg. Further study is needed to define whether fluoxetine is required on a daily basis throughout the menstrual cycle.
2) Patients treated with fluoxetine had significantly lower overall premenstrual scores for affective but not somatic symptoms. The effect of fluoxetine was examined in 10 women with premenstrual syndrome (PMS) or late luteal phase dysphoric disorder in an open-label trial (Rickels et al, 1990). After initial evaluations and a one-month placebo period, patients were to take fluoxetine (20 mg/day) for two

months. Patients recorded the daily severity of 17 affective and somatic symptoms of PMS. The means of the premenstrual total scores (sum for the 7 worst days of days 20 to 28) and postmenstrual total scores (sum for days 6 to 12) for the second month of fluoxetine therapy were compared to scores for the same patients during the placebo period.

4.5.B.33 Raynaud's phenomenon

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:

Decreased attack frequency and severity in patients with primary Raynaud's phenomenon
More effective in women than in men

c) Adult:

1) Fluoxetine reduced the severity and frequency of attacks of Raynaud's phenomenon and was more effective than nifedipine. After a 2-week washout period, patients with primary (n=26) or secondary (n=27) Raynaud's phenomenon were given fluoxetine 20 milligrams (mg) daily or nifedipine 40 mg daily for 6 weeks. After another 2-week washout period, patients were crossed over to the alternate treatment for 6 weeks. Attack severity was significantly reduced by fluoxetine (p=0.0002) but not by nifedipine (p=0.14). Likewise, attack frequency was significantly reduced by fluoxetine (p=0.003) and not by nifedipine (p=0.22). Subgroup analysis showed significant reductions in attack severity and frequency with fluoxetine in females (p less than 0.0002 and p=0.0004, respectively), whereas the reduction in males was not statistically significant. Reductions in attack severity with fluoxetine were statistically significant in patients with primary Raynaud's phenomenon (p=0.009) and in those with secondary Raynaud's phenomenon (p=0.01). Reductions in attack frequency were significant for patients with primary Raynaud's phenomenon (p=0.03) but not for those with secondary Raynaud's phenomenon . Reductions with nifedipine were not statistically significant for those subgroups (Coleiro et al, 2001a).

4.5.B.34 Schizophrenia; Adjunct

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:

Fluoxetine improved positive symptom scores in one study and negative symptom scores in another
Fluoxetine reduced the effectiveness of olanzapine treatment
Fluoxetine did not reduce olanzapaine-induced weight gain

c) Adult:

1) Addition of fluoxetine to olanzapine treatment of first- episode schizophrenia did not reduce OLANZAPINE-INDUCED WEIGHT GAIN, and, furthermore, fluoxetine reduced the effectiveness of olanzapine on positive symptoms and disorganized behavior. In a randomized, double-blind, placebo-controlled trial, 30 patients with first-episode DSM-IV schizophrenia were given olanzapine 10 milligrams (mg) per day and either fluoxetine 20 mg/day (n=15) or placebo (n=15) for 8 weeks. Mean weight gain in the 11 completers in the fluoxetine group was 7.9 kilograms (kg) and in the 13 completers of the placebo group 6 kg (p=0.44). Patients in the placebo group had significantly greater reductions in scores on the positive and disorganized subscales of the psychometric instruments used (p=0.001 and p=0.02, respectively). Scores on the negative symptom subscale or the Hamilton depression scale were not significantly different for the 2 groups. Two patients (both in the fluoxetine group) withdrew from the study because of lack of response and 2 from each group because of psychotic exacerbation (Poyurovsky et al, 2002).

2) Fluoxetine-treated patients showed statistically significant improvement of negative symptoms as measured by change on the Scale for the Assessment of Negative Symptoms at the end point (12 weeks) compared to the baseline value (p less than 0.001). Furthermore, fluoxetine decreased depressive symptoms as measured by the Hamilton Rating Scale for Depression and Anxiety (HAMD) (p less than 0.05). The effect of adjunctive fluoxetine on negative schizophrenic symptoms was evaluated in 34 inpatients with chronic schizophrenia. Fluoxetine 20 milligrams/day or placebo was administered for 12 weeks in a randomized, double-blind study. Adverse effects were more common with fluoxetine than placebo; they included nausea, headache, nervousness, anxiety, and insomnia. However, these effects were mild and transient (Spina et al, 1994).

4.5.B.35 Seasonal affective disorder

a) Overview

FDA Approval: Adult, no; Pediatric, no

Efficacy: Adult, Evidence is inconclusive
Recommendation: Adult, Class IIb
Strength of Evidence: Adult, Category B
See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:
In a short-term, small study, fluoxetine was effective in the treatment of seasonal affective disorder

c) Adult:
1) Fluoxetine was comparable to bright light therapy in the treatment of seasonal affective disorder/winter type. Forty patients with seasonal affective disorder/winter type were randomized to receive 5 weeks of treatment with fluoxetine 20 milligrams (mg) once in the morning (n=20) or bright light (3000 lux) therapy (n=20) in a parallel design, single-blind study. Those receiving bright light therapy did so for either 2 hours in the morning (n=12), 2 hours in the evening (n=5), or 1 hour in the morning and 1 hour in the evening (n=3). Responders were those experiencing reductions in both the Hamilton Depression Rating Scale scores and Hamilton Depression Rating Scale supplement scores from baseline. Thirteen (65%) patients were responders in the fluoxetine treated group, and 14 (70%) were responders in the bright light group; differences were not statistically significant. Five (25%) of those in the fluoxetine group and 10 (50%) of those in the bright light group met criteria for remission, differences were not statistically significant. Both treatments were found to be very well tolerated. Although fluoxetine was relatively effective in the treatment of seasonal affective disorder, further studies involving a larger patient population are necessary to establish significance (Ruhrmann et al, 1998).

4.5.B.36 Severe major depression with psychotic features
See Drug Consult reference: PSYCHOTIC DEPRESSION - DRUG THERAPY

4.5.B.37 Slow channel syndrome
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:
Improved symptoms of slow-channel myasthenic syndrome in two female patients

c) Adult:
1) Two female patients with slow-channel myasthenic syndrome reported improved muscle strength and endurance following fluoxetine treatment. The first patient, a 22-year-old woman carrying the epsilon-T264P slow- channel mutation received fluoxetine treatment at an initial dose of 40 milligrams (mg) daily, titrated over 18 months to 120 mg/day. She was confined to a wheelchair, required nocturnal respiratory support and had a Neuropathy Impairment Score (NIS) of 78/176. The second patient, a 34-year-old woman carrying the epsilon-L269F slow-channel mutation received fluoxetine 80 mg daily and had a NIS of 42/176. After 3 years of fluoxetine therapy, both patients reported ongoing improvements in muscle strength, endurance, and daily activities. The NIS scores were reduced by 77% and 81% for the first and second patient, respectively (Harper et al, 2003).

4.5.B.38 Social phobia
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 1 trial, FLUOXETINE, comprehensive cognitive behavioral group therapy (CCBGT) and their combination significantly improved symptoms of social phobia compared with placebo; however, fluoxetine plus CCBGT was not superior to fluoxetine monotherapy and symptoms remained in many patients after 14 weeks of treatment
Another trial found no significant difference between placebo and fluoxetine related to improvement of social phobia
Fluoxetine may be effective in ameliorating social phobic symptoms during clozapine treatment in schizophrenic patients

c) Adult:
1) A randomized, double-blind trial suggests that FLUOXETINE or comprehensive cognitive behavioral group therapy (CCBGT) may improve symptoms of GENERALIZED SOCIAL PHOBIA (GSP), and that combining fluoxetine with CCBGT was NOT significantly better than either monotherapy. The 14-week trial enrolled subjects with GSP according to DSM-IV criteria (n=295, intent-to-treat; n=211, completers). Randomization was to 5 groups treated with fluoxetine (n=57), CCBGT (n=60), fluoxetine and CCBGT (n=59), CCBGT and placebo (n=59), or placebo (n=60). Fluoxetine was initiated as a daily dose of 10

milligrams (mg), followed by 20 mg at day 8, 30 mg at day 15, and 40 mg at day 29; increases could be made to 50 or 60 mg/day, if tolerated and therapeutically warranted (doses at final visit averaged 43.6 mg). At the end of 14 weeks, response rates on the Clinical Global Impressions scale by group (based on ITT data) were 50.9% for fluoxetine, 51.7% for CCBGT, 54.2% for fluoxetine/CCBGT, 50.8% for CCBGT/placebo, and 31.7% for placebo (p less than 0.05, pair-wise each active treatment versus placebo; p=0.09 overall active treatment vs placebo). According to both the Brief Social Phobia Scale and the Social Phobia and Anxiety Inventory, all active treatments conferred significantly better results than did placebo (p less than 0.05). In linear mixed-effects models analysis, all active treatments were superior to placebo, although there were no significant differences between one active treatment group and another (also no significant differences between combination therapy and monotherapy). All treatments were well tolerated. The investigators noted that substantial GSP symptoms remained after 14 weeks of treatment, and that longer-term may be necessary (Davidson et al, 2004).

2) A 14-week course of oral FLUOXETINE (n=30) failed to provide greater improvement in symptoms of SOCIAL PHOBIA than placebo (n=30), based on a randomized, double-blind trial. During a placebo run-in period, potential enrollees were excluded if they scored less than 50 on the Liebowitz Social Anxiety Scale (LSAS) or if their LSAS score dropped by more than 20% during the 2 weeks of placebo treatment. All subjects had a primary diagnosis of generalized social phobia (DSM-IV) over a duration of at least 6 months. Fluoxetine dosing started at 20 milligrams (mg)/day, which could be reduced to 10 mg/day if an adverse event occurred. After 8 weeks at the 10- or 20-mg/day level, fluoxetine could be increased every 2 weeks in 20 mg/day increments to a maximum of 60 mg/day. Mean daily doses of fluoxetine were 34.23, 46.92, and 50.00 mg at weeks 10, 12, and 14, respectively (mode was 40 mg and 60 mg at weeks 12 and 14). After 14 weeks of treatment, both the fluoxetine and placebo group showed a significant improvement from baseline on the LSAS (mean change: fluoxetine, 22.6, p less than 0.001; placebo, 23.4, p less than 0.001). No significant difference on the LSAS was found between fluoxetine- and placebo-treated subjects (p=0.901). On the Clinical Global Impressions - Improvement scale, proportions rated as 'much improved' or 'very much improved' were 40% and 30% for the fluoxetine and placebo groups, respectively (p=0.417). Hamilton Rating Scale for Depression (HAM-D) scores showed no significant changes between baseline and post-treatment for either fluoxetine or control. Although there were significant changes from baseline on many secondary outcome measures, no significant between-group differences were found, except for a rating of bodily pain. The short form health survey (SF-36) showed a significantly greater decrease in bodily pain after treatment with fluoxetine compared with placebo (p=0.05). Drop-outs for adverse side effects were 1 and 3 for the fluoxetine and placebo groups, respectively. Fluoxetine-related adverse events were headache (53%), insomnia (47%), asthenia (30%), and nervousness (30%); placebo-related adverse reactions included headache (40%), insomnia (30%), nervousness (23%), and myalgia (20%) (Kobak et al, 2002).

3) Fluoxetine was effective for ameliorating social phobia that emerged during clozapine treatment. Twelve patients (5 women and 7 men, aged 19 to 28 years) with paranoid schizophrenia based on DSM-III-R criteria who developed social phobia 9 to 20 weeks after beginning clozapine were included in the study. The mean daily dose of clozapine and fluoxetine was 325 milligrams (mg) (range, 250 to 400 mg) and 35.83 mg, respectively, at 12 weeks. Patients were evaluated using the Scale for the Assessment of Negative Symptoms (SANS), Scale for the Assessment of Positive Symptoms (SAPS), the Brief Psychiatric Rating Scale (BPRS), the Liebowitz Social Phobia Scale (LSPS), the Frankfurter Beschwerde Fragebogen Scale (FBF), and the Brief Psychiatric Rating Scale. Following 8 weeks of treatment with fluoxetine, no significant differences were observed in the mean BPRS and SAPS scores while a significant decrease was found in SANS anhedonia (p less than 0.05) and avolition (p less than 0.05). After 8 weeks of fluoxetine treatment, 8 of 12 patients demonstrated amelioration of social phobic symptoms of 35% or greater on the LSPS total score, and 3 patients showed a greater than 50% reduction. Four of 12 patients demonstrated less than 25% reduction in LSPS total score. The LSPS mean anxiety/fear subscore (range of scale 0 to 72) and mean withdrawal subscore (range of scale 0 to 72) were reduced from 38.5 and 44.7, respectively, to 24.81 and 35.67, respectively, following 12 weeks of fluoxetine treatment (p less than 0.05) (Pallanti et al, 1999).

4.5.B.39 Tinnitus

a) Overview

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

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:

Relieved intractable tinnitus in 3 patients
See Drug Consult reference: DRUG THERAPY OF TINNITUS

c) Adult:

1) In 3 patients, fluoxetine 10 milligrams daily abolished tinnitus within 1 week. All 3 patients had high-tone sensorineural hearing loss with intractable tinnitus which interfered with sleep. Vitamins and stress relief produced no improvement so fluoxetine was tried. Further study of fluoxetine for this indication is warranted (Shemen, 1998).

4.5.B.40 Trichotillomania

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:

Fluoxetine has been effective in several case reports; however, it was ineffective in a small clinical trial which evaluated fluoxetine for treating trichotillomania. Larger, placebo-controlled clinical trials are needed.

c) Adult:

1) Fluoxetine up to 80 mg/day was NOT effective in a group of patients with trichotillomania. In this placebo-controlled trial, 23 adult patients were treated for a period of 12 weeks. No significant differences were noted between fluoxetine and placebo (Streichenwein & Thornby, 1995).

2) Case reports of trichotillomania and other forms of self-injurious behaviors have noted some benefit with fluoxetine therapy (Ricketts et al, 1993; Sheika et al, 1993; Sovner et al, 1993). These behaviors are often associated with depression or obsessive-compulsive disorder which may account for the efficacy of fluoxetine.

4.5.B.41 Vasovagal syncope; Prophylaxis

a) Overview

FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Ineffective; Pediatric, Ineffective
Recommendation: Adult, Class III; Pediatric, Class III
Strength of Evidence: Adult, Category B; Pediatric, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:

In a prospective, randomized study, fluoxetine was not superior to propranolol or placebo in the prophylaxis of vasovagal syncope (VVS) in patients, aged 15 to 70 years, with a history of untreated VVS (Theodorakis et al, 2006)

c) Adult:

1) Results of a prospective, randomized study showed that fluoxetine was not superior to propranolol or placebo in preventing the recurrence of vasovagal syncope (VVS) in patients with untreated VVS. Patients (n=96; mean age 42 years; range, 15 to 70 years) who had experienced at least 5 syncopes in their lifetime, not less than 2 syncopal attacks during the prior year, and whose last syncopal attack occurred at least 1 month prior to study enrollment were randomized to receive either oral fluoxetine (n=32), oral propranolol (n=32), or placebo (n=32) for 6 months. The fluoxetine dose was 20 milligrams (mg) per day and the propranolol dose ranged from 10 to 40 mg three times daily, depending on the subject's resting heart rate and tolerance of treatment. The primary endpoint was the time to the first recurrence of syncope or presyncope. Secondary endpoints included the number of patients with recurrence of syncope/presyncope and total vasovagal episodes (sum of syncopal and presyncopal episodes), and patient's well-being. Excluding 2 patients who refused follow-up, no difference was noted between the 3 groups with regards to the occurrence of syncopal, presyncopal, and total vasovagal episodes during the 6-month follow-up period (p greater than 0.05). Overall, a syncopal or presyncopal episode occurred in 38% (n=36/94) of the patients, with rates of 22% (n=7/32) in the fluoxetine group, 41% (n=13/31) in the placebo group, and 51% (n=16/31) in the propranolol group. Additionally, no difference was noted between the 3 groups when syncopal and presyncopal episodes were assessed separately. However, an on-treatment analysis that further excluded 18 patients who discontinued therapy revealed significantly longer mean time to a syncopal or presyncopal episode for the fluoxetine group (5.4 +/- 0.3 months) compared to the placebo group (4.2 +/- 0.5 months; p=0.05) and the propranolol group (4.1 +/- 0.4 months; p=0.046). Although the difference in mean times to a syncopal episode between the 3 groups was not statistically significant, the mean time to a presyncopal episode was significantly longer for the fluoxetine group (5.5 +/- 0.2 months) compared to the placebo group (4.6 +/- 0.4 months; p=0.048) and the propranolol group (4.5 +/- 0.4 months; p=0.008). Additionally, after 6 months of treatment, improvements in well-being scores (assessed by patient-filled questionnaires) were observed only for the fluoxetine group (p less than 0.01) (Theodorakis et al, 2006).

d) Pediatric:

1) Results of a prospective, randomized study showed that fluoxetine was not superior to propranolol or placebo in preventing the recurrence of vasovagal syncope (VVS) in patients with untreated VVS. Patients (n=96; mean age 42 years; range, 15 to 70 years) who had experienced at least 5 syncopes in their lifetime, not less than 2 syncopal attacks during the prior year, and whose last syncopal attack occurred at least 1 month prior to study enrollment were randomized to receive either oral fluoxetine (n=32), oral propranolol (n=32), or placebo (n=32) for 6 months. The fluoxetine dose was 20 milligrams (mg) per day and the propranolol dose ranged from 10 to 40 mg three times daily, depending on the subject's resting heart rate and tolerance of treatment. The primary endpoint was the time to the first recurrence of syncope or presyncope. Secondary endpoints included the number of patients with recurrence of syncope/presyncope and total vasovagal episodes (sum of syncopal and presyncopal

episodes), and patient's well-being. Excluding 2 patients who refused follow-up, no difference was noted between the 3 groups with regards to the occurrence of syncopal, presyncopal, and total vasovagal episodes during the 6-month follow-up period (p greater than 0.05). Overall, a syncopal or presyncopal episode occurred in 38% (n=36/94) of the patients, with rates of 22% (n=7/32) in the fluoxetine group, 41% (n=13/31) in the placebo group, and 51% (n=16/31) in the propranolol group. Additionally, no difference was noted between the 3 groups when syncopal and presyncopal episodes were assessed separately. However, an on-treatment analysis that further excluded 18 patients who discontinued therapy revealed significantly longer mean time to a syncopal or presyncopal episode for the fluoxetine group (5.4 +/- 0.3 months) compared to the placebo group (4.2 +/- 0.5 months; p=0.05) and the propranolol group (4.1 +/- 0.4 months; p=0.046). Although the difference in mean times to a syncopal episode between the 3 groups was not statistically significant, the mean time to a presyncopal episode was significantly longer for the fluoxetine group (5.5 +/- 0.2 months) compared to the placebo group (4.6 +/- 0.4 months; p=0.048) and the propranolol group (4.5 +/- 0.4 months; p=0.008). Additionally, after 6 months of treatment, improvements in well-being scores (assessed by patient-filled questionnaires) were observed only for the fluoxetine group (p less than 0.01) (Theodorakis et al, 2006).

4.6 Comparative Efficacy / Evaluation With Other Therapies

Amineptine

Amisulpride

Amitriptyline

Aprepitant

Bupropion

Clomipramine

Desipramine

Dothiepin

Doxepin

Fluvoxamine

Imipramine

Maprotiline

Mianserin

Milnacipran

Mirtazapine

Moclobemide

Nefazodone

Nifedipine

Nortriptyline

Olanzapine/Fluoxetine Hydrochloride

Paroxetine

Phenelzine

Protriptyline

Reboxetine

Sertraline

St John's Wort

Trazodone

Venlafaxine

4.6.A Amineptine

4.6.A.1 Depression

a) A multicenter study of 169 patients compared the efficacy and the tolerability of amineptine 200 milligrams (mg)/day and fluoxetine 20 mg/day for 90 days in major depressive episodes. The patients were selected according to the Diagnostic and Statistical Manual, third edition revised, (DSM-III-R) criteria of major depressive disorders. Use of tranquilizers was permitted during the study. The efficacy for each drug began as soon as day 7 and lasted throughout the study (p less than 0.01). Clinical evaluation using Montgomery and Asberg Depression Rating Scales (MADRS), Humeur Angoisse Ralentissement Danger scale (HARDS) , Widlocher Retardation Rating Scale and Hopkins Symptoms Check-List (HSCL) showed significant improvement (p less than 0.01 on day 7 for fluoxetine; p less than 0.05 on day 7 and less than 0.01 on day 21 for amineptine). It appeared that the effect of amineptine began earlier than fluoxetine, but in general no statistical differences were noted between the two drugs at any time of the study. The tolerability was judged to be good. The most common adverse effects in the amineptine group included excitement and insomnia, whereas tachycardia, nausea and vomiting were most frequently reported in the fluoxetine group (Dalery et al, 1992).

4.6.B Amisulpride

4.6.B.1 Dysthymia

a) The efficacy and safety of low doses of amisulpride (50 milligrams (mg) daily) and of fluoxetine (20 mg daily) were evaluated in a randomized, double-blind, parallel-group comparison. One hundred forty-two patients with dysthymia received amisulpride and 139 received fluoxetine. No statistically significant difference between the two groups was found in the number of responders at study-end according to the Montgomery and Asberg Depressive Rating Scale. In addition, amisulpride was well tolerated (Smeraldi et al, 1996).

b) Another double-blind, randomized trial reported that amisulpride 50 milligrams (mg) daily (139 patients) was at least as effective as fluoxetine 20 mg daily (129 patients) in medium-term treatment (three months) of dysthymia, in spite of 72 withdrawals (Biondi et al, 1996). These preliminary results should be confirmed in further trials.

4.6.C Amitriptyline

Depression

Diabetic neuropathy - Pain

Headache

Mixed anxiety and depressive disorder

Musculoskeletal pain

4.6.C.1 Depression

a) SUMMARY: In clinical studies (n=64, n=44, n=51, n=130), fluoxetine (20 to 80 mg/day) showed comparable antidepressant efficacy to amitriptyline (50 to 300 mg/day). The study periods were 5 to 6

weeks. Fluoxetine has been reported to be better tolerated than amitriptyline with weight gain occurring in amitriptyline-treated patients and weight loss occurring in fluoxetine-treated patients (Chouinard, 1985a; Feighner, 1985; Young et al, 1987; Laakmann et al, 1988; Fawcett et al, 1989); (Altamura et al, 1989). In addition, anticholinergic effects associated with amitriptyline have been bothersome (Altamura et al, 1989).
b) Amitriptyline and fluoxetine provided similar efficacy in elderly patients with Alzheimer's Disease and major depression (Taragano et al, 1997). Thirty-seven patients were randomly assigned to receive amitriptyline 25 milligrams (mg) or fluoxetine 10 mg daily for 6 weeks. At 6 weeks, scores on the Hamilton Rating Scale for Depression decreased from 25.9 to 16.5 (p less than 0.0001); the Mini-Mental State Exam also decreased by 2.4 points. In the amitriptyline group, 58% of patients left the study due to adverse effects which included confusion, disorientation, and constipation. In the fluoxetine group, 22% of patients dropped out due to nausea and loose stools. Limitations of this study are the small size, lack of a placebo-control, and differences in the side effect profile which may have prevented effective blinding. While both agents are effective, fluoxetine was tolerated better than amitriptyline.
c) In 51 outpatients with primary major depressive disorder, amitriptyline and fluoxetine showed comparable antidepressant efficacy with amitriptyline showing some possible superiority over fluoxetine with respect to Hamilton Psychiatric Rating Scale for Depression (HAM-D) anxiety/somatization and sleep disturbance factors. Fluoxetine had a significantly better efficacy/side effect index and significantly fewer autonomic adverse effects than amitriptyline. However, there was a trend for fluoxetine to have greater effects than amitriptyline on HAM-D cognitive disturbance factors. Patients received fluoxetine 20 to 80 mg/day or amitriptyline 75 to 300 mg/day (Chouinard, 1985a). Similar results were reported in another study (n=40) (Fawcett et al, 1989).
d) Fluoxetine 20 mg/day and amitriptyline 75 mg/day were effective in treating 28 elderly patients with major depressive episodes. This was a 5-week randomized, double-blind study. The difference in response to biological symptoms such as early morning awakening, weight loss, sexual dysfunction, guilt and suicidal thoughts was not statistically significant between treatment groups. However, amitriptyline provided a significantly better response than fluoxetine on anxious symptoms. More severe side effects, mainly anticholinergic, were seen with amitriptyline and weight gain was only seen in amitriptyline-treated patients (Altamura et al, 1989).

4.6.C.2 Diabetic neuropathy - Pain

a) Treatment with amitriptyline and desipramine showed no significant difference in pain relief, in either depressed or non-depressed patients with diabetic neuropathy and fluoxetine was no better than placebo in this patient population. There was no significant difference in any groups relative to adverse effects (Max et al, 1992). Thirty-eight patients received either amitriptyline 12.5 to 150 mg (mean 105 mg) once daily or desipramine 12.5 to 150 mg (mean 111 mg) once daily and 46 patients received either fluoxetine 20 to 40 mg (mean 40 mg) once daily or placebo (benztropine 0.125 to 1.5 mg) once daily. Pain intensity was rated by patient daily diary and global rating scales and mood was assessed by a psychiatrist at the beginning and end of each six-week treatment period. This was a randomized, double-blind, two-period crossover study.

4.6.C.3 Headache

a) In a small, unblinded, 12-week study, patients found that both fluoxetine and amitriptyline were beneficial for chronic tension-type headache and episodic tension-type headache while neither was very effective for migraine headache (Oguzhanoglu et al, 1999). Patients with a variety of headaches were assigned to receive either amitriptyline titrated up to 50 milligrams (mg) nightly or fluoxetine 20 mg every morning. In the group with migraine headaches, neither the amitriptyline group (n=8) nor the fluoxetine group (n=7) experienced a decrease in number of headaches or pain intensity. Fluoxetine reduced duration of pain as compared to baseline at 4, 8, and 12 weeks (p=0.01, p=0.0146, p=0.013, respectively). In patients with chronic tension-type headache, amitriptyline-treated patients (n=5) experienced reduced numbers of days of pain per month at 4, 8, and 12 weeks (p=0.0187, p=0.03, p=0.009, respectively). Fluoxetine-treated patients (n=8) experienced reduced days of pain only at 4 and 8 weeks (p=0.0157, p=0.004, respectively). Neither drug was very effective against pain intensity. In the episodic tension-type headache, amitriptyline patients (n=9) experienced a decrease in the number of days with pain at 4 and 8 weeks only (p=0.0012, p=0.0002, respectively) while fluoxetine patients (n=10) experienced this at 4, 8, and 12 weeks (p=0.0018, p=0.0148, p=0.0179, respectively). Reduction in pain intensity occurred only with fluoxetine during weeks 4 and 8 (p=0.0156, p=0.0313, respectively).

4.6.C.4 Mixed anxiety and depressive disorder

a) Fluoxetine and amitriptyline had comparable effectiveness in patients with depression and associated anxiety (Versiani et al, 1999). Patients (n=157) were randomly assigned to blinded treatment with fluoxetine 20 milligrams (mg) per day or amitriptyline 50 mg per day titrated to a maximum dose of 250 mg if needed; all patients received capsules in the morning (fluoxetine) and evening (amitriptyline). No statistically significant differences were detected between treatments for efficacy measures including the Hamilton Rating Scale for Depression (HAM-D), the HAM for Anxiety (HAM-A), the Raskin-Covi Depression and Anxiety Scale, the Clinical Global Impression-Improvement, and the Patient Global Impression. The only difference between treatments was a single factor, the HAM-D sleep factor which favored amitriptyline (p less than 0.001). The response rate for both treatments was 74%. Greater than 80% of patients completed the study. Fluoxetine is comparable to amitriptyline for treating patients with anxious depression.

4.6.C.5 Musculoskeletal pain

a) Fluoxetine was superior (p less than 0.001) to amitriptyline and placebo in decreasing pain intensity and providing pain relief in 59 patients with rheumatic pain conditions. Amitriptyline was also superior (p less than 0.05) to placebo in decreasing pain intensity and providing pain relief. Rheumatic pain conditions consisted of low back pain, fibromyalgia, osteoarthritis, and rheumatoid arthritis. Patients received fluoxetine 20 mg/day, amitriptyline 25 mg/day or placebo once daily for 4 weeks (Rani et al, 1996).

4.6.D Aprepitant

4.6.D.1 Depression

a) In a large dose-finding study (n=approximately 800) involving patients with major depression and anxiety, neither aprepitant (10 to 300 milligrams (mg) once daily) nor fluoxetine (20 mg once daily) were superior to placebo (Krishnan, 2002). Lack of benefit in this study has shed doubt on the efficacy of aprepitant in depression. However, poorly controlled patient selection may have contributed to negative results. Post hoc analysis of this study did suggest a trend toward benefit of aprepitant in severely depressed patients (Lieb et al, 2002; Krishnan, 2002), and a further confirmatory study in a well-defined population is required to confirm the efficacy of aprepitant and/or its usefulness in certain depressed subgroups.

4.6.E Bupropion

4.6.E.1 Depression

a) Bupropion and fluoxetine were found to be equally effective for the treatment of DSM-III-R major depressive disorder, with no significant difference in the incidence of adverse effects. Weekly assessments of therapeutic response (HAM-A, HAM-D, CGI) and presence of adverse effects were carried over a 6-week period. Mean daily dosage was 382 milligrams for bupropion and 38 milligrams for fluoxetine (Feighner et al, 1991).

4.6.E.2 Adverse Effects

a) Fluoxetine was more frequently associated with sexual dysfunction than was sustained release (SR) bupropion or placebo in patients being treated for moderate to severe depression. In a double-blind, double-dummy, 8-week trial, patients experiencing an episode of recurrent major depression were randomized to receive bupropion SR 150 to 400 milligrams (mg) per day (n=150), fluoxetine 20 to 60 mg/day (n=154), or placebo (n=152). Bupropion and fluoxetine showed similar efficacy for the treatment of depressive symptoms. However, significantly more patients receiving fluoxetine experienced orgasm dysfunction (p less than 0.001) and sexual arousal disorder (p less than 0.05) than did patients receiving bupropion or placebo. The difference between fluoxetine and bupropion was maintained when only patients with remission of depression were analyzed. There were no significant differences between bupropion and placebo for either orgasm dysfunction or sexual arousal disorder at any treatment week. Relative to baseline values, sexual desire disorder decreased in the bupropion group but was unchanged in the placebo and fluoxetine groups over the 8-week study. Of the patients who were satisfied with their sexual functioning at baseline, more in the fluoxetine group than in the bupropion group became dissatisfied during treatment (p less than 0.05) (Coleman et al, 2001).

4.6.F Clomipramine

4.6.F.1 Obsessive-compulsive disorder

a) Treatment with fluoxetine (FLX) was compared with treatment with clomipramine (CMI) in two groups of patients with obsessive compulsive disorder (OCD) using two different experimental designs. In the first group of 11 patients with OCD studied using a randomized, double-blind, crossover design, treatment with FLX (20 to 80 milligrams/d) for 10 weeks was found to produce therapeutic effects similar to that obtained with CMI (50 to 250 milligrams/d) for 10 weeks. There were significantly fewer total side effects reported during FLX than CMI treatment. Drug tapering and placebo substitution in the 4-week crossover interval phase led to substantial relapses in OCD symptoms and depression. In addition, response to the second drug took as long as response to the first drug, despite a putative common mechanism of action of serotonin uptake inhibition. A second group of 21 patients with OCD that had been previously stabilized on CMI with at least partial benefit were crossed over to FLX in double blind fashion. After 10 weeks of FLX, most patients manifested behavioral rating scores of OCD and depressive symptoms that were comparable with pre-crossover ratings completed during CMI treatment. A significant exacerbation in OCD and depression ratings as well as a similar lag in therapeutic efficacy were also noted in this second cohort of patients with OCD. Platelet serotonin concentrations were reduced 95% during both CMI and FLX treatment periods. These results suggest that FLX may represent a viable alternative to CMI in the treatment of OCD, although more studies with larger sample sizes are needed (Pigott et al, 1990).

b) Clomipramine (CMI) and fluoxetine (FLX) were shown to be equally effective in the treatment of 120 patients with DSM-III major unipolar depressive disorder over a 6-week period. Adverse effects were more frequent with CMI. Those that did occur with FLX tended to disappear during the course of the study (Noguera et al, 1991).

4.6.G Desipramine

4.6.G.1 Depression

a) Fluoxetine and desipramine had similar efficacy in a double-blind, randomized, 6-week study (n=55). The 46 patients completing the study (desipramine = 20, fluoxetine = 26) showed improvement in Hamilton Depression rating and Clinical Global Impression Scales vs placebo with no statistically significant differences between drugs. Fewer side effects of lesser intensity were noted with fluoxetine (Remick et al, 1993).

b) For the initial treatment of depression, desipramine and fluoxetine are equivalent in terms of overall treatment costs, efficacy, and quality of life. In a randomized, controlled trial, patients with newly diagnosed depression (n=536) were prescribed either fluoxetine or a tricyclic antidepressant (imipramine or desipramine) and assessed at 1, 3, and 6 months for both efficacy of the antidepressant regimen as measured by the Hamilton Depression Rating Scale and the Hopkins Symptom Checklist and quality of life. Drug cost and total health care costs were also measured. Clinical efficacy and quality of life were similar between the two groups; however, patients treated with fluoxetine had fewer adverse effects, were less likely to require a change in their medication, and had less outpatients visits. Although drug costs were higher, total treatment costs were slightly lower for the fluoxetine group; however, this difference was not statistically significant (Simon et al, 1996a).

4.6.H Dothiepin

1) Efficacy

a) Dothiepin and fluoxetine were shown to have similar limited effects on psychomotor and driving performance in a double-blind, placebo controlled, crossover, 3 week study involving 18 healthy volunteers (Ramaekers et al, 1995). At the doses used in this study, neither dothiepin nor fluoxetine would be expected to impair driving performance. Placebo, fluoxetine 20 mg, and dothiepin 75 mg (increased to 150 mg on day 8) were administered for 22 days. Sustained attention was reduced by 6.7% on day 1 by dothiepin and by 7.4% (day 1), 6.7% (day 8), and 6.5% (day 22) by fluoxetine. Critical fusion frequency was significantly reduced by day 22 by 1.13 Hz (dothiepin) and 1.24 Hz (fluoxetine). There was no significant effect with either drug in two tests of actual highway driving. Similar incidence of side effects was reported for each drug.

b) Dothiepin and fluoxetine were shown to have similar limited effects on psychomotor and driving performance in a double-blind, placebo controlled, crossover, 3 week study involving 18 healthy volunteers (Ramaekers et al, 1995a). At the doses used in this study, neither dothiepin nor fluoxetine would be expected to impair driving performance. Placebo, fluoxetine 20 mg, and dothiepin 75 mg (increased to 150 mg on day 8) were administered for 22 days. Sustained attention was reduced by 6.7% on day 1 by dothiepin and by 7.4% (day 1), 6.7% (day 8), and 6.5% (day 22) by fluoxetine. Critical fusion frequency was significantly reduced by day 22 by 1.13 Hz (dothiepin) and 1.24 Hz (fluoxetine). There was no significant effect with either drug in two tests of actual highway driving. Similar incidence of side effects was reported for each drug.

4.6.I Doxepin

4.6.I.1 Depression

a) Doxepin and fluoxetine had similar efficacy in a comparative study involving 80 depressed patients (61 outpatients, 19 inpatients) diagnosed as having major depressive disorder. The patients received either fluoxetine 20 to 60 milligrams/day (mean, 28.9 mg/day) or doxepin 100 to 200 milligrams/day (mean, 146.8 mg/day). Both treatment groups showed improvement over time, with no difference between fluoxetine and doxepin at study termination. The most common side effects of fluoxetine (headache, nausea, and insomnia) were in contrast to the pronounced anticholinergic side effects of doxepin (dry mouth, fatigue, constipation). Moreover, the significant weight gain associated with doxepin therapy was not seen with fluoxetine treatment (Remick et al, 1989).

b) Fluoxetine 20 to 80 milligrams daily (once daily or divided twice a day) and doxepin 50 to 200 milligrams daily (once daily or divided twice a day or three times a day) had comparable efficacy in the treatment of depression in geriatric patients (at least 64 years of age). Each drug was administered in increasing doses over the first two weeks of the study, with maintenance doses (up to 80 mg daily of fluoxetine and 200 mg daily of doxepin) being determined by the third week; this maintenance dose was given for three more weeks (total, six weeks). Both drugs were considered equally effective using the following parameters: Hamilton Psychiatric Rating Scale for Depression (HAM-D), Raskin Severity of Depression Scale, Covi Anxiety Scale, Clinical Global Impressions severity and improvement, Patient Global Improvement, and SCL-58 scales. Both drugs produced significant improvement compared to baseline scores. Fluoxetine was associated with a lower degree of drowsiness/sedation, dry mouth, constipation and vision disturbances. However, nervousness/anxiety, insomnia, sweating, dyspepsia, and nausea occurred to a greater degree with fluoxetine. Body weight decreased with fluoxetine and increased with doxepin (Feighner & Cohn, 1985).

c) In one study comparing fluoxetine and doxepin, both drugs were effective in major depressive disorder in geriatric patients, with a lower incidence of side effects being observed with fluoxetine (Feighner & Cohn, 1985). Weight loss occurred with fluoxetine, as compared to weight gain with doxepin, which was statistically significant. Heart rate was shown to increase in doxepin-treated patients as compared to decreases in fluoxetine-treated patients; this was also a statistically significant difference. Significant improvement in depressive symptoms was further demonstrated in a group (n=33) of geropsychiatric patients. Although this study only followed patients for a period of one month, significant side effects such as nausea, weight loss,

and agitation were not noted. Doses of fluoxetine used were 20 mg every other day to 20 mg daily (Orengo et al, 1996).

4.6.J Fluvoxamine

4.6.J.1 Depression

a) In a randomized, double-blind study (n=100), fluvoxamine and fluoxetine demonstrated comparable efficacy and side effects in out-patients with major depression. After randomization, patients were treated initially with fluvoxamine 50 milligrams (mg) daily adjusted to a maximum of 150 mg daily or fluoxetine 20 mg daily adjusted to a maximum of 80 mg daily. Throughout the study, significant differences in efficacy were NOT detected on several depression scales including the Hamilton depression scale and clinical global impressions scale. Adverse effects were common with both drugs but the severity was mild in the majority of patients. Even though this study included 100 patients, it may NOT have detected subtle differences between the 2 treatments (Rapaport et al, 1996).

4.6.K Imipramine

4.6.K.1 Depression

a) SUMMARY: Fluoxetine has been as effective as imipramine in the treatment of depression, while producing a lower incidence of side effects. Overall cost of therapy, clinical efficacy, and patient quality of life have been shown to be equivalent after six months of treatment.

b) In a double-blind, randomized, parallel group study, fluoxetine was better tolerated although not more effective than imipramine in the treatment of major depression with atypical features. A total of 154 patients (age 18 to 65 years) who met DSM-IV criteria for major depression for at least 1 month and also met the Columbia criteria for atypical depression were randomized to receive fluoxetine, imipramine, or placebo for 10 weeks. Fluoxetine was administered as 20 milligrams (mg) daily for 4 weeks, 40 mg daily for week 5, and 60 mg daily for the remaining weeks. Imipramine was administered as 50 mg daily for the first week, increasing by 50 mg/day each week until a maximum of 300 mg daily was reached. Mean daily doses at the end of the study were 51.4 mg/day for fluoxetine and 204.9 mg/day for imipramine. Fluoxetine and imipramine did not differ from one another based on the Clinical Global Impression (CGI) scale improvement scores following 10 weeks of treatment. Fluoxetine and imipramine were significantly more effective than placebo in the intention-to-treat (p less than 0.007 and 0.003, respectively) and completer groups (p less than 0.03 and 0.001, respectively). Imipramine-treated patients demonstrated a significantly higher dropout rate than fluoxetine-treated patients (p=0.04). In the intention-to-treat group, depression outcome measures including the 17-item and 28-item Hamilton Depression Rating Scale and Patient Global Improvement demonstrated no differences between fluoxetine and imipramine and a consistent clinical benefit of both treatment groups compared with placebo. Adverse effects significantly more common for imipramine than for fluoxetine included dry mouth (81% versus 28%, respectively), somnolence (42% versus 24%, respectively), and dizziness (44% versus 25%, respectively); cough and back pain occurred at a significantly higher incidence in fluoxetine- versus imipramine-treated patients (McGrath et al, 2000).

c) For the initial treatment of depression, imipramine and fluoxetine are equivalent in terms of overall treatment costs, efficacy, and quality of life. In a randomized, controlled trial, patients with newly diagnosed depression (n=536) were prescribed either fluoxetine or a tricyclic antidepressant (imipramine or desipramine) and assessed at 1, 3, and 6 months for both efficacy of the antidepressant regimen as measured by the Hamilton Depression Rating Scale and the Hopkins Symptom Checklist and quality of life. Drug cost and total health care costs were also measured. Clinical efficacy and quality of life were similar between the two groups; however, patients treated with fluoxetine had fewer adverse effects, were less likely to require a change in their medication, and had less outpatients visits. Although drug costs were higher, total treatment costs were slightly lower for the fluoxetine group; however, this difference was not statistically significant (Simon et al, 1996).

d) Controlled studies have demonstrated that oral fluoxetine in doses of 40 to 80 milligrams daily is as effective as imipramine 150 to 250 milligrams daily in the treatment of major depression (Cohn & Wilcox, 1985; Stark & Hardison, 1985; Levine et al, 1987a). Fluoxetine was as effective as imipramine doses of 150 to 300 milligrams/day (Byerly et al, 1988). However, in one report (Bremner, 1984a), fluoxetine was reported superior to imipramine in several depression scales in a 5-week controlled study involving 40 depressed outpatients. In all studies, the incidence of side effects (anticholinergic effects, dizziness, drowsiness, dry mouth, cardiovascular effects) was less with fluoxetine as compared with imipramine; fluoxetine was associated with a greater incidence of anxiety or nervousness, insomnia, and excessive sweating. In another study, excessive sweating (as well as nausea) was higher with fluoxetine than imipramine (Stark & Hardison, 1985). Of significance, weight loss has occurred during fluoxetine therapy, as compared to generally no change in body weight or increases in weight with imipramine. The onset of antidepressant action of each drug has been similar, generally within one week.

e) Imipramine and fluoxetine had similar efficacy in multicenter, double-blind, placebo-controlled, outpatient studies comparing the treatment of major depressive disorder (Stark & Hardison, 1985). Five hundred forty patients were randomly assigned to receive either fluoxetine 60 to 80 milligrams daily, imipramine 150 to 300 milligrams daily (the majority of patients), or placebo. Patients were treated for up to 6 weeks in double-blind fashion. Imipramine and fluoxetine were both superior to placebo on all measures (Hamilton Psychiatric Rating Scale for Depression total, Raskin Severity of Depression Scale, Clinical Global

Impressions Severity of Illness Scale, Global Improvement and secondary symptom measures). Fluoxetine and imipramine were similarly effective on all general measures of improvement. Anorexia and nausea occurred to a significantly higher degree in fluoxetine-treated patients; constipation, dizziness, drowsiness, dry mouth, somatosensory disturbances, and excessive sweating were reported more frequently with imipramine.

f) The efficacy and safety of fluoxetine and imipramine was compared in 40 depressed outpatients in a double-blind, 5-week parallel trial (Bremner, 1984a). Fluoxetine was given in doses increasing from 20 to 40 milligrams daily, then to 60 milligrams daily, during the first week; imipramine doses were increased from 75 to 100 milligrams daily, then to 125 milligrams daily. During the second and third weeks, the maintenance dose of each drug was determined, with fluoxetine being given in doses up to 80 milligrams daily and imipramine up to 300 milligrams daily. During the fourth and fifth weeks of the study, the maintenance dose was achieved; the maintenance dose for most fluoxetine patients was 60 milligrams daily, and 175 or 200 milligrams daily for imipramine. Fluoxetine was reported superior to imipramine in the total Hamilton Psychiatric Rating Scale for Depression, as well as the HAM-D scales for anxiety/somatization, retardation and sleep disturbance. Fluoxetine was also reported more beneficial than imipramine in the Raskin Severity of Depression Scale and Covi Anxiety Scale. However, for the HAM-D total score, and the Raskin and Covi scales, fluoxetine was statistically superior to imipramine only during the last week of the study (week 5). The Clinical Global Impressions demonstrated the superiority of fluoxetine over imipramine for severity of depression but not global improvement. Weight loss (average, 3.8 pounds) occurred with fluoxetine during treatment, with an increase in weight being seen with imipramine (average, 0.7 pounds). Heart rate increased significantly with imipramine, as compared to slight decreases with fluoxetine. Blood pressure decreased with fluoxetine as compared with increases with imipramine, and fluoxetine was associated with a lesser degree of gastrointestinal disturbances, dizziness, and drowsiness. Dry mouth occurred in one of 20 fluoxetine patients and in 9 of 20 imipramine-treated patients, with nervousness occurring in three fluoxetine-treated patients and in two imipramine-treated patients.

4.6.L Maprotiline

4.6.L.1 Cerebral hemiplegia - Cerebrovascular accident

a) A randomized, placebo-controlled trial analyzed the effects of maprotiline and fluoxetine on the motor/functional capacities of poststroke patients undergoing physical therapy. Fifty-two severely disabled hemiplegic subjects after unilateral ischemic stroke in the territory of the middle cerebral artery were randomly assigned to three treatment groups - placebo, maprotiline (150 mg/day), or fluoxetine (20 mg/day) - during 3 months of physical therapy. The greatest improvement in walking and activity of daily living capacity was observed in the fluoxetine treatment group and the lowest in the maprotiline group. Furthermore, fluoxetine yielded a significantly larger number of patients with good recovery compared to maprotiline or placebo. These effects of the drugs were not related to their efficacy in treating depressive symptoms (Dam et al, 1996). Further investigation is needed to assess the efficacy of fluoxetine in facilitating recovery in stroke survivors undergoing physical therapy.

4.6.M Mianserin

4.6.M.1 Depression

a) Both mianserin- and fluoxetine-treated groups showed significant improvement in depressive symptoms at 3 and 6 weeks in a comparative study of the treatment of elderly depressed patients (Pia et al, 1992). Forty patients were randomly assigned to receive fluoxetine 20 milligrams/day or mianserin 40 milligrams/day. Fluoxetine showed a greater effect on Hamilton Rating Scale for Depression subgroup analyses. Mianserin was associated with a greater number of side effects requiring discontinuation of therapy.

b) In a placebo-controlled, double-blind trial in depressed outpatients, clinical improvement occurred in significantly more of the patients receiving fluoxetine (55%) than in those receiving placebo (23%); there was no significant difference between the results for mianserin (50%) and the results for fluoxetine or placebo. Although the authors counted subjects who withdrew within 2 weeks of the start of the 6-week trial as treatment failure, the results may still be considered equivocal due to the high overall dropout rates (46% for fluoxetine, 48% for mainserin, and 43% for placebo). The incidence of side effects was high, 92%, 88%, and 44% for fluoxetine, mianserin, and placebo, respectively (Muijen et al, 1988).

4.6.N Milnacipran

4.6.N.1 Depression

a) Several comparative trials (mainly unpublished) have indicated no significant difference in efficacy between milnacipran 50 to 150 mg twice daily and fluvoxamine 100 mg twice daily or fluoxetine 20 mg once daily in major depression (Guelfi et al, 1998; Anon, 1997). One study reported the superiority of fluoxetine 20 mg once daily (statistically significant for most parameters) over milnacipran 100 mg once daily in major depressive outpatients (Ansseau et al, 1994); however, this study suffered from methodological problems, the most significant being once-daily dosing of milnacipran, which may not achieve therapeutic levels.

b) Meta-analyses of studies comparing milnacipran and fluoxetine/fluvoxamine have been performed by the manufacturer; greater improvements (eg, Hamilton, Montgomery-Asberg) were described for milnacipran,

which were usually statistically significant (Lopez-Ibor et al, 1996; Anon, 1997; Elwood, 1997). However, only a few trials were selected for analysis, and not all patients in these trials were evaluated; the superiority of milnacipran was demonstrated only after results were subjected to multiple reanalysis (Anon, 1997).
c) Comparisons with other similar agents (eg, sertraline) are lacking.

4.6.O Mirtazapine

4.6.O.1 Depression

a) In a multicenter, double-blind, 6-week study, mirtazapine was as effective as fluoxetine but mirtazapine may have had an earlier onset of action (Wheatley et al, 1998). Patients with major depression were randomly selected to receive mirtazapine titrated up to 15 to 60 milligrams (mg) daily (n=66) or fluoxetine titrated up to 20 to 40 mg daily (n=67). The major endpoint was improvement on the 17-item Hamilton Rating Scale for Depression (17-HAM-D). The mean daily dosage was mirtazapine 39.8 mg/day and fluoxetine 23.8 mg/day. Both groups had improved 17-HAM-D scores throughout the study. Mirtazapine-treated patients had significantly better scores than the fluoxetine group on days 21 (p =0.16) and 28 (p=0.009). However, the magnitude of change between the 2 groups was not significantly different at the end of the study. At the endpoint, 23.3% of mirtazapine-treated and 25.4% of fluoxetine-treated patients had 17-HAM-D scores less than or equal to 7. The incidence of adverse events was low in both groups at 10% or less.

4.6.P Moclobemide

4.6.P.1 Depression

a) Moclobemide and fluoxetine were at least equally effective in the short-term treatment of depression with dysthymia. In a 6 week, double-blind study, patients were randomized to receive either moclobemide 150 milligrams (mg) twice daily (n=21) or fluoxetine 20 mg daily (n=21) for 6 weeks. At 6 weeks, the Hamilton depression rating scale (HDRS) scores showed similar decreases from baseline on both drugs. However, more patients achieved a greater than 50% decrease in the HDRS score on moclobemide (71%) than on fluoxetine (38%)(p less than 0.05). The clinical global impression scale also trended towards a better response with moclobemide but the difference was not significant. A larger study with a placebo group is needed to provide evidence of the possible superiority of moclobemide over fluoxetine (Duarte et al, 1996).
b) A study suggested a tendency for patients with atypical depression (using the MADRS and GCI scores) to respond more favorably to moclobemide than to fluoxetine (Lonnqvist et al, 1994). This needs to be substantiated by other studies. In one study, elderly patients with major depression associated with cognitive impairment or dementia showed significant improvement in orientation and memory recall ability with moclobemide compared with placebo (Fitton et al, 1992).

4.6.Q Nefazodone

Depression - Parkinson's disease

Depression - Sleep disorder

4.6.Q.1 Depression - Parkinson's disease

a) Nefazodone was more effective than fluoxetine in reducing extrapyramidal symptoms in patients with Parkinson's disease and comorbid depression, while both therapies were equally effective as antidepressants. In a prospective, randomized, single-blind study, depressed patients with Parkinson's disease (n=16) received nefazodone (100 to 300 milligrams (mg)/day; final mean dose 200 mg/day) or fluoxetine (20 to 50 mg/day; final mean dose, 25 mg/day) for 3 months. Antiparkinsonian medications remained stable from 4 weeks prior to initiation of nefazodone or fluoxetine therapy and throughout the study. A neurologist made blinded assessments and a psychiatrist made non-blinded assessments at baseline, and on days 15, 30, 60 and 90. The total Unified Parkinson Disease Rating Scale (UPDRS) score and the UPDRS part III score improved significantly over time in nefazodone- treated patients (time effect: p=0.004 and p=0.003, respectively). Fluoxetine-treated patients did not show a significant improvement in these scores over time. From baseline to endpoint, the nefazodone group showed a mean difference in total UPDRS scores of -12 as compared with 1.1 for the fluoxetine group. Scores for the Beck Depression Inventory and Clinical Global Impressions-Severity of Illness Scale improved significantly from baseline to endpoint in both treatment groups, with no significant difference between groups. Three patients in the nefazodone group discontinued treatment due to increased tremor or diarrhea. Other adverse events associated with either treatment were asthenia, anxiety, orthostatic dizziness, and constipation. Larger, well-controlled studies are needed to support the preferred use of nefazodone for the treatment of depression and comorbid Parkinson's disease (Avila et al, 2003).

4.6.Q.2 Depression - Sleep disorder

a) Nefazodone and fluoxetine were similarly effective for treating depression; however, nefazodone produced greater improvement in sleep disturbances than fluoxetine (Gillin et al, 1997). Patients (n=44) with

depression confirmed by the Hamilton Rating Scale for Depression (HAM-D) were randomly assigned to receive nefazodone 100 milligrams (mg) twice daily increased to 200 mg twice daily or fluoxetine 20 mg/day; the double dummy technique was used to maintain blinding. Nefazodone decreased the percentage of awake and movement time and the number of awakenings without altering rapid eye movement (REM) sleep or REM latency; whereas, fluoxetine decreased sleep efficiency, REM sleep, and increased the number of awakenings per night. While results of this study suggest that nefazodone improves sleep in depressed patients, larger, placebo controlled studies are needed to confirm the present findings.

4.6.R Nifedipine

4.6.R.1 Raynaud's phenomenon

a) Fluoxetine reduced the severity and frequency of attacks of Raynaud's phenomenon and was more effective than nifedipine. After a 2-week washout period, patients with primary (n=26) or secondary (n=27) Raynaud's phenomenon were given fluoxetine 20 milligrams (mg) daily or nifedipine 40 mg daily for 6 weeks. After another 2-week washout period, patients were crossed over to the alternate treatment for 6 weeks. Attack severity was significantly reduced by fluoxetine (p=0.0002) but not by nifedipine (p=0.14). Likewise, attack frequency was significantly reduced by fluoxetine (p=0.003) and not by nifedipine (p=0.22). Subgroup analysis showed significant reductions in attack severity and frequency with fluoxetine in females (p less than 0.0002 and p=0.0004, respectively), whereas the reduction in males was not statistically significant. Reductions in attack severity with fluoxetine were statistically significant in patients with primary Raynaud's phenomenon (p=0.009) and in those with secondary Raynaud's phenomenon (p=0.01). Reductions in attack frequency were significant for patients with primary Raynaud's phenomenon (p=003) but not for those with secondary Raynaud's phenomenon . Reductions with nifedipine were not statistically significant for those subgroups (Coleiro et al, 2001).

4.6.S Nortriptyline

Cerebrovascular accident - Depression

Depression

4.6.S.1 Cerebrovascular accident - Depression

a) Nortriptyline was superior to fluoxetine in the treatment of post-stroke depression; neither had an effect on improving recovery in depressed or non- depressed patients. Depressed patients who had suffered a stroke in the last 6 months randomly received either nortriptyline (n=16) or fluoxetine (n=23) for 12 weeks. Some patients also entered a 12-week crossover phase to placebo (n=17). Non-depressed stroke patients randomly received 12 weeks of nortriptyline (n=15), fluoxetine (n=17), or placebo (n=16). Initial nortriptyline doses of 25 milligrams (mg) were titrated to 100 mg over 6 weeks and fluoxetine 10 mg was titrated to 40 mg over 9 weeks. Outcome measures included the Hamilton Rating Scale for Depression (HAM-D) and the recovery of activities of daily living as measured by the Functional Independence Measures. After 12 weeks, the depressed patients in the nortriptyline group had a significantly lower mean HAM-D score as compared to those in the fluoxetine or placebo groups (p less than 0.05). The successful treatment rate of depression was 63% for nortriptyline, 9% for fluoxetine, and 24% for placebo. All patients showed significant (p less than 0.006) improvements in the Functional Independence measures with no differences seen between the depressed or non-depressed patients (Robinson et al, 2000).

4.6.S.2 Depression

a) In a double-blind, randomized, comparative study involving 156 patients, nortriptyline and fluoxetine were found to be equally efficacious in the treatment of acute major depression of moderate severity. Patients received either nortriptyline 100 mg/day or fluoxetine 40 mg/day in 2 divided doses for a total of 5 weeks. By the end of 5 weeks, the percentages of patients much or very much improved were 71% for nortriptyline and 65% for fluoxetine. The average total scores on the Hamilton Rating Scale for Depression, for patients in both treatment groups, declined by approximately 50%. Analysis of the side effect profiles revealed statistically significant differences for only 2 symptoms; nausea was more common among patients treated with fluoxetine, while dry mouth was more frequently associated with nortriptyline (Fabre et al, 1991).

4.6.T Olanzapine/Fluoxetine Hydrochloride

4.6.T.1 Depression - Schizophrenia

a) Results of an 8-week, double-blind trial demonstrated that patients receiving both olanzapine and fluoxetine in combination demonstrated greater improvement in Montgomery-Asberg Depression Rating Scale (MADRS) and Clinical Global Impression (CGI) total scores than patients receiving either medication alone. Twenty-eight patients with nonpsychotic treatment-refractory depression received olanzapine (5 to 20 milligrams/day) and/or fluoxetine (20 to 60 milligrams/day). In addition, there were no significant differences in adverse events among the 3 different treatment groups (Keck et al, 2000).

4.6.U Paroxetine

4.6.U.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, 2001).

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.V Phenelzine

4.6.V.1 Obsessive-compulsive disorder

a) In a small study (n=54), fluoxetine was superior (p less than 0.05) to phenelzine and placebo based on the Yale-Brown Obsessive Compulsive scale but not 3 other rating scales. Changes in score from baseline to week 10 were generally less than 1 point on the National Institute of Mental Health Global Obsessive Compulsive scale, the Clinical Global Impression scale, and the obsessive compulsive scale. Patients were randomly assigned to receive placebo, fluoxetine adjusted to a maximum of 80 milligrams (mg) daily, or phenelzine adjusted to a maximum of 60 mg daily. No serious adverse effects occurred in any of the treatment groups. The small sample size and relatively small changes limit the power of this study to detect differences between treatments.

4.6.W Protriptyline

4.6.W.1 Obstructive sleep apnea

a) Fluoxetine was better tolerated and equally effective as protriptyline in the treatment of obstructive sleep apnea. Six of 12 subjects with obstructive sleep apnea had a good response to either protriptyline (10 mg) or fluoxetine (20 mg) per day. The proportion of time spent in REM sleep and the number of apneas or hypopneas during NREM sleep were significantly reduced in both treatment groups. There was however, no significant improvement in the number of arterial oxygen desaturation events, the level of arterial oxygen desaturation, or the number of arousals with either treatment for the group as a whole (Hanzel et al, 1991).

4.6.X Reboxetine

4.6.X.1 Depression

a) SUMMARY: Reboxetine appears to be at least as effective and well-tolerated as fluoxetine.

b) In an 8-week double-blind comparison, oral REBOXETINE (4 milligrams (mg) twice daily; n=79) and oral FLUOXETINE (20 mg once daily; n=89) were equally efficacious and well tolerated in the treatment of patients with acute major depressive disorder (DSM-III-R). Decreases in scores on the Hamilton Rating Scale for Depression (HAM-D) were similar between groups (19.2 and 16.8 points, respectively, reboxetine and fluoxetine); the percentages for responders (at least 50% decrease in HAM-D score) and for those achieving remission (HAM-D score of 10 or less) were not significantly different in the 2 groups. No significant differences occurred between reboxetine- and fluoxetine-treated patients with respect to improvement in ratings on the Clinical Global Impression scale, the Montgomery-Asberg Depression Rating Scale, and the Social Adaptation Self-evaluation Scale. Most adverse effects were mild or moderate, with at least 1 adverse event occurring in 67.1% and 67.4%, respectively, of the reboxetine and fluoxetine groups. The authors suggested that reboxetine was more effective than fluoxetine in patients with the most severe depression based on a subgroup analysis involving those rated most severely ill at baseline (Massana et al, 1999).

c) In a placebo-controlled comparative trial employing a 21-item self- rating scale, the Social Adaptation Self-evaluation Scale (SASS), reboxetine was superior to placebo (p less than 0.05) and fluoxetine (p less than 0.05). Using the Hamilton Depression rating scale (HAM-D), both active treatments were superior to placebo in efficacy, but little difference in efficacy was observed between the 2 active treatments. Total

HAM-D scores at last assessment demonstrated average improvements of 13.3, 13.4 and 8.6 points, respectively, with reboxetine, fluoxetine, and placebo. Patients (n=302) were randomized to treatment with reboxetine 8 milligrams (mg) per day (n=103), fluoxetine 20 mg/day (n=100), or placebo (n=99) for an 8-week study period, with dosage increases to 10 mg/day reboxetine or 40 mg/day fluoxetine possible after 4 weeks of treatment. The mean total SASS scores were significantly higher for patients treated with either active treatment than those treated with placebo and significantly higher for reboxetine-treated patients than for the fluoxetine-treated group. An analysis of individual SASS items (point-biserial correlation analysis), reboxetine treatment demonstrated a significant correlation to improvement in individual item score for 20 of the 21 items compared with placebo; fluoxetine demonstrated significant correlation for 12 items compared with placebo. In direct comparison of SASS scores for groups treated with reboxetine and fluoxetine, 9 of the 21 items were significantly correlated with reboxetine, but none were significantly correlated with fluoxetine. A subset of patients classified as "in remission" (HAM-D total score of 10 or lower) at last assessment, 14 SASS items were significantly associated with reboxetine treatment. Both active treatments positively affected social motivation and behavior, but reboxetine also demonstrated efficacy in improving negative self- perception and motivation towards action (Dubini et al, 1997; Dubini et al, 1997a).

4.6.Y Sertraline

Depression

Obsessive-compulsive disorder

Weight gain

4.6.Y.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) An eight-week, double-blind, randomized study evaluated the efficacy and safety of fluoxetine vs sertraline in the treatment of major depression (DSM-III-R). One-hundred and eight out-patients with major depression entered into the study, but only 88 (48 sertraline and 40 fluoxetine) were evaluable. The final mean daily dose of fluoxetine was 28 milligrams (mg) and for sertraline 72 mg. Both treatment groups showed a statistically significant improvement from baseline at one week, and this was maintained until the end of treatment. No statistically significant differences were observed between the two treatment groups on the primary efficacy variables measured by Hamilton Rating Scale for Depression and Anxiety (HAMD), Clinical Global Impression Scale (CGI), Montgomery Asberg Depression Rating Scale (MADRS), Leeds Sleep Score scale and Zung Anxiety Rating Scale. The incidence of adverse events was similar: 39.3% for fluoxetine and 40.4% for sertraline. Most common were gastrointestinal (nausea and abdominal pain) and central nervous system (irritability, headache, somnolence, anorexia, agitation, anxiety and insomnia) effects. Sertraline was better tolerated than fluoxetine overall; 9.6% of sertraline-treated patients discontinued treatment, compared with 19.6% in the fluoxetine-treated group (Aguaglia et al, 1993). Investigation in a larger population is warranted to definitively establish the comparative efficacy and safety of the two drugs (Aguaglia et al, 1993).

4.6.Y.2 Obsessive-compulsive disorder

a) Both fluoxetine and sertraline were effective and well tolerated in the treatment of patients with obsessive- compulsive disorder (OCD). Patients received either sertraline, 50 to 200 milligrams (mg) per day (mean 139.5 +/- 58.5 mg; N=76), or fluoxetine, 20 to 80 mg/day (mean 56.7 +/- 23.0 mg; N=72), in a double-blind manner for 24 weeks. Group assignment was random and resulted in matched patient populations. Safety and efficacy measures were taken at the end of study weeks 1, 2, 4, 6, 8, 12, 16, 20, and 24 weeks or at the last assessment period if patients failed to complete the study. Primary efficacy measures included the Yale-Brown Obsessive- Compulsive Scale (Y-BOCS), the National Institute of Mental Health Global Obsessive-Compulsive Rating (NIHM-OC), and the Clinical Global Impression Severity and Improvement

scales (CGI-S and CGI-I). Secondary measures included the Hamilton Rating Scale for Depression (HAM-D 21 item version) and the Clinical Anxiety Scale (CAS). By the end of the 24 week study, both medications were effective and there were no significant treatment differences between the two groups. All primary and secondary measures showed similar amounts of improvement. The time-course of improvement was also similar for both groups, with sertraline showing a statistically significant greater improvement, on some measures (Y-BOCS change score and global severity of illness score) during some of the early assessments (weeks 4, 8, 12), however this study was not sufficiently powered to reliably detect differences between the drug treatments during this time period. Adverse drug effects were described as mild to moderate for both drugs with no significant difference in incidence reported for sertraline or fluoxetine (Bergeron et al, 2002).

4.6.Y.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.Z St John's Wort

4.6.Z.1 Depression

a) St. John's Wort and fluoxetine significantly decreased symptoms of depression, with no difference found between groups in a randomized, double-blind, multicenter trial. Seventy patients diagnosed with mild to moderate depression by International Classification of Diseases (ICD)-10 criteria and having a Hamilton Rating Scale for Depression (HAMD) score between 16 and 24 were given either a Hypericum preparation (Calmigen(R)) 150 milligrams (mg) twice daily (n=35) or fluoxetine (Prozac(R)) 20 mg twice daily (n=35) for 6 weeks. The Hypericum perforatum extract contained 0.45 to 0.495 mg hypericin per 150 mg. Mean HAMD scores decreased significantly (p less than 0.001) for both groups: by 50% for the St. John's Wort group and 58% for the fluoxetine group. The changes for the 2 groups were not significantly different. Response rates (responder = a subject with 50% or greater decrease in HAMD score) were 55% for St. John's Wort and 66% for fluoxetine (p=0.41). Two patients in each group dropped out because of adverse effects: anxiety and nausea in the St. John's wort group and headache/dry mouth and nausea/diarrhea in the fluoxetine group (Behnke et al, 2002).

4.6.AA Trazodone

Depression

Mania

4.6.AA.1 Depression

a) Fluoxetine was as effective as trazodone in the treatment of major depression in a 6-week, double-blind, outpatient study involving 43 patients (Debus et al, 1988). The mean final doses of oral trazodone and fluoxetine in the responding patients were 284 and 29 mg daily, respectively. In nonresponders, the corresponding doses were 327 and 33 mg, respectively. HAM-D scores were lower at weeks 1 and 2 with fluoxetine when compared to trazodone and sleep was improved to a greater degree with trazodone. Adverse effects occurred to a similar degree with each agent with the exception of weight loss (more frequent with fluoxetine) and dizziness (more frequent with trazodone).

b) A six-week, double-blind trial compared fluoxetine (21 patients) with trazodone (19 patients) in the treatment of major depression (Perry et al, 1989). Although trazodone appeared to provide significantly greater improvement in HAM-D and Clinical Global Impressions scores at 3 weeks, the differences were not statistically significant at 4, 5, and 6 weeks. The authors surmise that the early difference may have been due to: an insufficient fluoxetine dose early in the trial (mean daily doses of fluoxetine and trazodone during week 3 were 21 mg and 241 mg, respectively), which was mitigated by larger subsequent increases in fluoxetine doses compared to trazodone doses; a slower onset of antidepressant action for fluoxetine, compared to trazodone; or a higher incidence of depressive illness lasting longer than one year in the

fluoxetine group (67%) than in the trazodone group (37%, reported incorrectly as 35%). Although the authors cite the statistically significant fluoxetine-associated weight loss seen in this trial (mean 1.98 lb/patient) as a clinically significant advantage for this agent, trazodone was also associated with weight loss in this study (mean 0.13 lb/patient), and the weight losses exhibited by the treatment groups were not significantly different.

4.6.AA.2 Mania

a) In literature reports of drug-induced mania caused by fluoxetine or trazadone, fluoxetine-treated patients manifested symptoms of mania more slowly than trazodone-treated patients (Terao, 1993). Mean time to onset of mania in fluoxetine-treated patients was significantly longer than trazodone-treated patients; 59 days (range = 10 to 154 days) versus 16 days (range =4 to 70 days) respectively.

4.6.AB Venlafaxine

Depression

Mixed anxiety and depressive disorder

4.6.AB.1 Depression

a) Analysis of pooled data from 8 randomized, double-blind studies (n=2045) showed a remission rate of depression of 45% with venlafaxine treatment, 35% with serotonin reuptake inhibitors (SSRIs), and 25% with placebo. Remission was defined as a total score of 7 or less on the 17-item Hamilton Rating Scale for Depression. Venlafaxine was significantly (p less than 0.001) more effective than SSRIs from 2 weeks onward and from placebo from 3 weeks onward. The end-of-therapy remission rate with SSRIs was significantly better than that with placebo (p=0.001). The odds ratio for remission was 1.5, in favor of venlafaxine over SSRIs (Thase et al, 2001).

b) Venlafaxine and fluoxetine had similar efficacy in the treatment of major depression in an 8 week, double-blind study. One-hundred and ninety-six patients were randomized to receive venlafaxine 37.5 milligrams (mg) twice daily, and 186 patients were randomized to receive fluoxetine 20 mg daily. If patients did not demonstrate an adequate response to therapy, venlafaxine was increased to 75 mg twice daily and fluoxetine to 20 mg twice daily. Primary outcome measures were scores on the Hamilton Rating Scale for Depression (HAM-D), the Montgomery-Asberg Depression Rating Scale (MADRS), the Clinical Global Impressions Severity of Illness Score (CGI-S), and the Clinical Global Impressions Improvement Score (CGI-I). In both treatment groups, HAM-D and MADRS scores improved significantly after 8 weeks of therapy. CGI-I scores were also improved, 80.6% of patients scored 1 (very much improved) or 2 (much improved) with venlafaxine and 83.9% with fluoxetine. Remission rates were equivalent in both groups, 60.2%, as determined by scores of 8 or less on the HAM-D scale. The only significant difference between treatment groups was the number of patients that required a dosage increase, fluoxetine (n=54) and venlafaxine (n=43). After treatment with higher doses, the number of patients scoring 1 on the CGI-I were significantly greater in the venlafaxine group than the fluoxetine group. The frequency of adverse events associated with both medications were comparable. Overall, there were very few differences in efficacy and tolerability between venlafaxine and fluoxetine (Cost e Silva, 1998).

c) Venlafaxine was effective in the treatment of major depression in an 8-week, open-label, comparative trial with fluoxetine. At the initiation of the study, 55 patients received venlafaxine 37.5 milligrams (mg) twice daily; 55 received fluoxetine 20 mg daily. If after 15 days of treatment response was inadequate, doses were increased to venlafaxine 75 mg twice daily and fluoxetine 40 mg daily. Both medications were significantly effective in treating major depression, as determined by improvements in patient scores on the Hamilton Depression Rating Scale (HAM-D), Montgomery-Asberg Depression Rating Scale (MADRS), and the Clinical Global Impressions Scale (CGI). There were no significant differences between the 2 medications. A trend towards greater improvement existed in patients requiring higher doses of venlafaxine than fluoxetine. Patients treated with venlafaxine were significantly more likely to experience constipation, dizziness, dry mouth, and vomiting (Diaz-Martinez et al, 1998).

d) Venlafaxine 200 mg/day for 4 weeks tended to be more effective than fluoxetine 40 mg/day in the treatment of 68 inpatients with major depression; however, the difference was not statistically significant by the end of the 6-week study period (Holliday & Benfield, 1995). Patients were assessed using the Hamilton Depression Rating Scale, Montgomery-Asberg Depression Rating Scale, and the Clinical Global Impressions scale. The incidence of adverse effects was similar for both groups.

4.6.AB.2 Mixed anxiety and depressive disorder

a) Extended release (XR) venlafaxine was more effective than placebo for improving the symptoms of depression and anxiety in patients with major depressive disorder and comorbid generalized anxiety disorder (GAD). However, time to response was greater in patients with comorbidity than in patients with major depressive disorder only. Fluoxetine, on the other hand, was not significantly better than placebo in patients with comorbidity. From the data of all the patients meeting DSM-IV criteria for major depressive disorder in a double-blind, randomized trial (n=368), results from the subset of patients who had comorbid

GAD (n=92) were analyzed separately and compared to results of the noncomorbid patients. Patients took once-daily doses of venlafaxine XR 75 milligrams (mg), fluoxetine 20 mg, or placebo for 12 weeks. Doses could be increased to a maximum of 225 mg for venlafaxine and 60 mg for fluoxetine. According to the criteria of more than 50% reduction (from baseline) in the Hamilton-Depression (HAM-D) and Hamilton-Anxiety (HAM-A) scores, improvement with venlafaxine was significantly greater (p less than 0.05) than with placebo by 12 weeks of treatment. There was a similar trend with fluoxetine, but at no time was fluoxetine statistically superior to placebo. About one third of patients with comorbidity showed response at 4 weeks; however, overall, there was no evident trend for a placebo- drug difference until after the eighth week of treatment. Among patients without comorbidity, the placebo-venlafaxine difference was evident as early as week 2. By week 12, response rate was 66% on HAM-D and 59% on HAM-A for those taking venlafaxine, 52% and 45% for those taking fluoxetine, and 36% and 24% for those taking placebo (Silverstone & Salinas, 2001).

4.6.AB.3 Adverse Effects

a) During a randomized, double-blind trial of elderly patients with major depression, the rate of study discontinuation as a result of adverse events was significantly greater for patients receiving venlafaxine (27%) compared with patients receiving placebo (9%; p=0.0017) but there were no significant differences when the fluoxetine group (19%) was compared with the placebo group (p=0.0666) or when fluoxetine was compared to venlafaxine (p=0.1838). Elderly patients (mean age, 71 years) with major depression were randomized to venlafaxine immediate-release (n=104), fluoxetine (n=100), or placebo (n=96) for 8 weeks. The dose of venlafaxine was titrated from 37.5 to 225 milligrams (mg) per day, and fluoxetine doses were titrated from 20 to 60 mg per day over a 29-day period. The most frequently reported adverse events in the venlafaxine and fluoxetine groups were nausea (45% and 23%, respectively) and headache (26% and 18%, respectively). The adverse events most frequently reported in the placebo group were headache (22%) and dry mouth (15%) (Schatzberg & Roose, 2006).

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