

DRUGDEX-EV 2389

MICROMEDEX

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FLUOXETINE

[Overview](#)
[Dosing Information](#)
[Pharmacokinetics](#)
[Cautions](#)
[Clinical Applications](#)
[References](#)

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 [2]

b) [Major depressive disorder](#)

1) initial, 20 mg ORALLY once daily in the morning [2]

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 the last daily dose of 20 mg [2]

c) [Obsessive-compulsive disorder](#)

1) initial, 20 mg ORALLY once daily in the morning [2]

2) maintenance, 20 to 60 mg ORALLY daily (single or divided doses) after several weeks if inadequate response; maximum dose 80 mg daily [2]

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 [2]

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 [52]

2) Pediatric

a) safety and effectiveness in pediatric patients younger than age 8 yr (**major depressive disorder**) and younger than age 7 yr (**obsessive-compulsive disorder**) have not been established [2]

1) Major depressive disorder

a) 8 years and older, 10 to 20 mg ORALLY once daily [2]

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 to 60 mg daily [2]

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 to 30 mg daily [2]

3) Contraindications**a) Fluoxetine Hydrochloride**

1) concomitant use of monoamine oxidase inhibitors (MAOIs), **pimozide**, or **thioridazine** [107][108]

2) hypersensitivity to **fluoxetine** or any components of the product [108][108]

3) use of **thioridazine** or MAOIs within 5 weeks after **fluoxetine** discontinuation [107][108]

4) use of **fluoxetine** within 14 days of MAOI discontinuation [107][108]

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

9)) Suicide

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)) 345.79 [145][344]

b)) pKa

1)) 9.5 [791]

c)) Solubility

1)) Soluble in water at 14 mg/mL [145][344].

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 C (59 and 86 degrees F); protect from light [344].

b)) Tablet

1)) Store at controlled room temperature, 25 degrees C (77 degrees F), with excursions permitted between 15 and 30 degrees C (59 and 86 degrees F) [145].

1.3) Adult Dosage**1.3.1) Normal Dosage****1.3.1.A) Fluoxetine****1.3.1.A.1) Cataplexy - Narcolepsy**

See Drug Consult reference: [NARCOLEPSY AND CATAPLEXY - DRUG THERAPY](#)

1.3.1.B) Fluoxetine Hydrochloride**1.3.1.B.1) Oral route****1.3.1.B.1.a) Bulimia nervosa**

1)) The recommended dose for [bulimia nervosa](#) is 60 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 [2].

2)) Continued fluoxetine treatment (60 mg/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 [3].

1.3.1.B.1.b) Major depressive disorder

1)) The recommended starting dose of fluoxetine in patients with major depressive disorder is 20 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) [2].

2)) Once weekly dosing of 90-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 [2][19].

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

[24]

3)) Results of a randomized double-blind study demonstrated that continuation phase treatments of major depressive disorder (MDD) with fluoxetine 20 mg/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) [25]. 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 mg 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 mg daily [26][27][28][29][30]. Many of the early clinical trials used protocols that required titration of the [fluoxetine](#) dose from 20 mg/day to 80 mg/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 mg, 40 mg and 60 mg without titration [31]. 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 mg, 20 mg, and 40 mg, it was found that endpoint and weekly analyses of outcome variables resulted in a flat dose-response curve and superiority of all doses compared with placebo [31]. There were differences seen on individual measures: the 5-mg dose was superior in improving the HAM-D Sleep Disturbance factor; the 20-mg dose was superior on the CGI severity scale; and the 40-mg 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 mg/day [32]; these patients were randomized to further treatment with 20 mg/day or 60 mg/day on a double-blind basis. Although the 60-mg 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](#) [33].

5)) Beneficial effects have been observed in patients receiving [fluoxetine](#) 5 mg/day for depression or [panic disorder](#) [34]. However, the majority of patients treated for depression respond to [fluoxetine](#) 20 to 30 mg/day [35]; (Fabre & Putnam, 1987). The dosage range for [fluoxetine](#) is 20 to 80 mg/day [36]. The effectiveness of [fluoxetine](#) 40, 60, or 80 mg is similar whether doses are administered once or twice daily [37].

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](#) [21].

1.3.1.B.1.c) [Obsessive-compulsive disorder](#)

1)) The recommended starting dose of [fluoxetine](#) in patients with [obsessive-compulsive disorder](#) (OCD) is 20 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) [2].

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 [2].

1.3.1.B.1.d] Panic disorder

1)) The recommended starting dose of [fluoxetine](#) for the treatment of [panic disorder](#) is 10 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 [2].

2)) [Fluoxetine](#) in doses up to 80 mg daily was reported effective in the treatment of panic attacks in 7 of 16 patients in an open study [51]. Mean doses in the responding patients were 27 mg daily (range, 10 to 70 mg daily).

1.3.1.B.1.e] Premenstrual dysphoric disorder

1)) The starting dose of [fluoxetine](#) ([Sarafem\(R\)](#)) in patients with [premenstrual dysphoric disorder](#) (PMDD) is 20 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 with 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 [52].

1.3.1.B.2] Tinnitus

See Drug Consult reference: DRUG THERAPY OF TINNITUS

1.3.1.B.3] Maximum Dose

a)) The maximum dose of [fluoxetine](#) is 80 mg per day [2][52].

1.3.2] Dosage in Renal Failure**A) [Fluoxetine](#) Hydrochloride**

1)) Dosage adjustments for [renal impairment](#) are not routinely necessary [2][52].

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 [104][105].

1.3.3] Dosage in Hepatic Insufficiency**A) [Fluoxetine](#) Hydrochloride**

1)) [Fluoxetine](#) is metabolized in the liver [105] 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](#) [2][52].

2)) A significant reduction in plasma clearance and an increase in the elimination half-life of fluoxetine were observed in stable alcoholic cirrhosis patients. The formation of norfluoxetine was also decreased, and its clearance reduced, in these patients compared with normal volunteers [106]. 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 [2].

1.3.5] Dosage Adjustment During Dialysis

A) Fluoxetine Hydrochloride

1)) Fluoxetine 20 mg 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 [2][52].

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 [104].

1.4] Pediatric Dosage

1.4.1] Normal Dosage

1.4.1.A] Fluoxetine

1.4.1.A.1] Anorexia nervosa

See Drug Consult reference: ANOREXIA NERVOSA - DRUG THERAPY

1.4.1.B] Fluoxetine Hydrochloride

1.4.1.B.1] Oral route

1.4.1.B.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 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 [2].

1.4.1.B.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 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 [2].

2)) For lower weight children (7 years and older), the recommended starting dose of [fluoxetine](#) in the treatment of [obsessive-compulsive disorder](#) is 10 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 [2].

1.4.2] Dosage in Renal Failure**A) [Fluoxetine](#) Hydrochloride**

1)) Dosage adjustments for [renal impairment](#) are not routinely necessary [2].

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](#) [2].

1.4.4] Dosage Adjustment During Dialysis**A) [Fluoxetine](#) Hydrochloride**

1)) [Fluoxetine](#) 20 mg 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](#) [2].

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 [10][795][12].

2) Peak Response

a)) Depression, regular release: 4 weeks [796].

b)) [Obsessive compulsive disorder](#), regular release: 5 weeks or longer [796].

2.2] Drug Concentration Levels

A)) Time to Peak Concentration

1)) Oral, regular release: 6 to 8 hours [800][801][802][803].

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 [10]. Corresponding plasma concentrations in patients receiving [fluoxetine](#) 80 mg daily were 698 ng/mL and 421 ng/mL (norfluoxetine), respectively [804].

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 [796].

2.3] ADME

2.3.1] Absorption

A)) Bioavailability

1)) Oral, regular release: 100% [801].

2)) The enteric-coated weekly formulation, pulvules, tablets, and oral solution are bioequivalent [796].

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 [796].

B)) Effects of Food

1)) clinically insignificant [801].

a)) The absorption of [fluoxetine](#) is delayed but not decreased in the presence of food [801].

2.3.2] Distribution

A)) Distribution Sites

1)) Protein Binding

a)) 94.5% [796][801][802].

1j) Fluoxetine is bound to albumin and alpha-1-glycoprotein; protein binding is NOT altered in patients with renal failure [796][801][802].

Bj) Distribution Kinetics

1j) Volume of Distribution

a) 1000 to 7200 L [802].

1j) 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 [802].

2.3.3] Metabolism

Aj) Metabolism Sites and Kinetics

1j) Liver, extensive [796][802].

a) Fluoxetine is metabolized primarily via N-demethylation to the active metabolite, norfluoxetine [801][802]. Glucuronide conjugates are also found but in small quantities [801].

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) [806].

Bj) Metabolites

1j) Norfluoxetine, active [802][807].

a) Norfluoxetine has similar pharmacologic activity to the parent compound [801].

2j) Glucuronide metabolites [801].

2.3.4] Excretion

Aj) Kidney

1j) Renal Excretion (%)

a) 60% [801].

2j) Only 2.5 to 5.0% of an oral dose is recovered as unchanged drug; 10% is excreted as free norfluoxetine [801][802]. Conjugated metabolites, fluoxetine glucuronide and norfluoxetine glucuronide, represent 5.2% and 9.5% of a dose, respectively [801].

Bj) Other

1j) OTHER EXCRETION

a) Feces, 12% [801].

2.3.5] Elimination Half-life

A) Parent Compound

1) ELIMINATION HALF-LIFE

a) 4 to 6 days, chronic administration [811][796][801].

1) Following acute administration, the elimination half-life of fluoxetine is 1 to 3 days [796][811].

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 [806].

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 [802].

B) Metabolites

1) Norfluoxetine, 4 to 16 days [796][801][812].

2.3.6] Extracorporeal Elimination

A) Hemodialysis

1) Dialyzable: No[802]

a) Fluoxetine and norfluoxetine are not removed to a significant degree by hemodialysis [802].

3.0] Cautions

[Contraindications](#)

[Precautions](#)

[Adverse Reactions](#)

[Teratogenicity/Effects in Pregnancy/Breastfeeding](#)

[Drug Interactions](#)

3.0.A] Black Box WARNING

Fluoxetine Hydrochloride

Oral (Capsule; Capsule, Delayed Release; Solution)

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) [107][108].

Oral (Tablet)

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.

Pooled analyses of short-term (4 to 16 weeks) placebo-controlled 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 [109].

3.1] Contraindications

A) Fluoxetine Hydrochloride

- 1) concomitant use of monoamine oxidase inhibitors (MAOIs), [pimozide](#), or [thioridazine](#) [107][108]
- 2) hypersensitivity to [fluoxetine](#) or any components of the product [108][108]
- 3) use of [thioridazine](#) or MAOIs within 5 weeks after [fluoxetine](#) discontinuation [107][108]
- 4) use of [fluoxetine](#) within 14 days of MAOI discontinuation [107][108]

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 and other psychiatric disorders during the first few months of therapy or following changes in dosage [107][108]

- 2)) abrupt withdrawal; serious discontinuation symptoms have been reported; gradual reduction in dose recommended [107]
- 3)) acute [narrow angle glaucoma](#) or increased intraocular pressure; mydriasis has been reported [107]
- 4)) [allergic reactions](#), including [anaphylaxis](#), [angioedema](#), and [urticaria](#) have been reported; in the case of rash, or other possibly allergic symptoms for which an alternative etiology cannot be identified, discontinue therapy [107][108]
- 5)) [bipolar disorder](#); increased risk of precipitation of a mixed/[manic episode](#) with antidepressant treatment only [107][108]
- 6)) concomitant use of NSAIDs, [aspirin](#), [warfarin](#), or other drugs that affect coagulation; abnormal bleeding, particularly the gastrointestinal tract, may occur; monitoring recommended [107]
- 7)) concomitant serotonergic drug use (serotonin precursors (tryptophan), SSRIs, serotonin-norepinephrine reuptake inhibitors); risk of [serotonin syndrome](#), use is not recommended[107][108]
- 8)) [diabetes](#), history of; increased risk of [hypoglycemia](#) [107][108]
- 9)) pulmonary events, including fibrosis, have been rarely reported [107][108]
- 10)) seizures, history of [107][108]
- 11)) [serotonin syndrome](#) and neuroleptic malignant syndrome-like reactions ([serotonin syndrome](#) in its most severe form), have been reported with [fluoxetine](#) therapy alone or in combination with other serotonergic drugs; monitoring recommended [107][108]
- 12)) skin reactions, including serious cutaneous systemic illnesses (eg [leukocytoclastic vasculitis](#), [erythema multiforme](#), and lupus-like syndrome) with fatalities have been reported rarely; in the case of rash, or other possibly allergic symptoms for which an alternative etiology cannot be identified, discontinue therapy [107][108]
- 13)) volume-depleted, elderly, or concurrent diuretic therapy; [hyponatremia](#) and syndrome of [inappropriate antidiuretic hormone secretion](#) (SIADH) has occurred with [fluoxetine](#) [107][108]

3.3] Adverse Reactions

3.3.1] Cardiovascular Effects

3.3.1.A] [Fluoxetine](#) Hydrochloride

3.3.1.A.1] [Bradycardia](#)

- a)) One paper reported a case of bradycardia in an elderly woman treated with 20 mg [fluoxetine](#) per day [142]. 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 [143].

3.3.1.A.2] [Chest pain](#)

- a)) Incidence: at least 1%[145]
- b)) In all United States clinical trials in patients (n=10,782) treated for conditions other than [Premenstrual Dysphoric Disorder](#), chest pain was reported in at least 1 in 100 patients [145].

3.3.1.A.3] Electrocardiogram abnormal

a) Cardiovascular side effects reported during treatment with fluoxetine included QT prolongation [129]; (Prod Info Sarafem(R), 2001)[130][131][132]. 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 [133].

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 [134].

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 [133].

3.3.1.A.4] 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) [144].

3.3.1.A.5] 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 [135].

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 [136].

3.3.1.A.6] 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 [140].
- 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 [141].
- c) Cardiovascular side effects reported during treatment with [fluoxetine](#) included QT prolongation [129];(Prod Info [Sarafem](#)(R), 2001)[130][131][132].

3.3.1.A.7] 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 [137].
- 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 [138].

3.3.1.A.8] 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 [139].

3.3.2] Dermatologic Effects

3.3.2.A] [Fluoxetine](#) Hydrochloride

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 [200].

3.3.2.A.2] Diaphoresis

a) Excessive sweating has been reported in association with [fluoxetine](#) in up to 30% of patients [147][132][187][37]. Sweating appeared in fewer patients treated with [fluoxetine](#) than [imipramine](#); however, [fluoxetine](#) was associated with a higher incidence of sweating than placebo [147][132][180].

3.3.2.A.3] Hypersensitivity angiitis

a) [Leukocytoclastic vasculitis](#) was reported in 1 patient in premarketing trials of [fluoxetine](#) for indications other than [premenstrual dysphoric disorder](#). Another patient developed a severe desquamating syndrome that was considered to be [vasculitis](#) or [erythema multiforme](#). Neither case was definitively diagnosed [145].

3.3.2.A.4] Rash

a) Incidence: 7%[129]

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 [145][132]. One case of [erythema multiforme](#) was also reported [129].

3.3.3] Endocrine/Metabolic Effects

3.3.3.A] [Fluoxetine Hydrochloride](#)

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 [167].

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 [167].

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 [168].

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 [166].

3.3.3.A.3] Hypoglycemia

a) Hypoglycemia has been associated with fluoxetine use [145][161].
 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 [169].

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 [124].

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 [171].

b) Hyponatremia secondary to SIADH has been reported in patients taking therapeutic doses of fluoxetine [172][173][174][175].

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 [176].

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 [177].

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 [178].

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 [179].

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 bupirone 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 bupirone, olanzapine, and fluoxetine, the man's symptoms resolved over several days. Bupirone 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 and an increased incidence or severity of antidepressant-related adverse events [170].

3.3.3.A.7] Weight change finding

- a)] In 2 placebo-controlled clinical trials, the incidence of clinically significant weight gain (7% or greater) was 8%, 6% and 1% in patients who received fluoxetine tablets 20 mg/day, 60 mg/day, and placebo, respectively [145]
- b)] In 2 placebo-controlled clinical trials, the incidence of clinically significant weight loss (7% or greater) was 7%, 12% and 3% in patients who received fluoxetine tablets 20 mg/day, 60 mg/day, and placebo, respectively [145]
- c)] Weight gain has not occurred with fluoxetine therapy; stabilization of weight or weight loss has occurred in most controlled studies [180][147][131][181][182].
- d)] 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 [183].

3.3.4] Gastrointestinal Effects

3.3.4.A] Fluoxetine Hydrochloride

3.3.4.A.1] Diarrhea

- a)] Incidence: 10% to 38%[132][192]
- b)] Diarrhea has occurred 10% of patients in one study [132], and in 38% of patients receiving therapeutic doses of fluoxetine for panic attacks in another study [192].

3.3.4.A.2] Gastrointestinal hemorrhage

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

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 [184]. 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 [185].

3.3.4.A.4] Loss of appetite

- a) Incidence: 3.5% to 15%[145][187][132][129]
- b) In placebo-controlled trials of female patients with **Premenstrual Dysphoric Disorder** (PMDD), anorexia was reported in 3.8% of patients taking **fluoxetine** 20 mg/daily continuously (n=104) and in 3.5% of patients taking 20 mg/day intermittently (n=86) [145].
- c) In 2 placebo-controlled clinical trials, the incidence of anorexia was 4%, 13% and 2% in patients who received **fluoxetine** tablets 20 mg/day continuously or intermittently pooled, 60 mg/day continuously, and placebo pooled, respectfully for **premenstrual dysphoric disorder** [145].
- d) 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 [187][132][129]. **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 [188].

3.3.4.A.5] Nausea

- a) Incidence: 20% to 30%[189][132][147][180][187][191]
- b) The most common side effect of **fluoxetine** therapy is nausea, which may occur in 25% to 30% of patients [132][147][180][187][191].
- c) The SSRIs produce nausea in 20% to 25% of patients. 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 [189].

3.3.4.A.6] Nausea and vomiting

- a) Incidence: 20% to 25%[189]
- 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 [189].

3.3.4.A.7] 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](#) [190].

3.3.4.A.8] 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 [186].

3.3.4.A.9] Xerostomia

- a) Dry mouth occurred in 14% of patients [132].
- b) Dryness of the mouth generally occurs to a lesser degree with [fluoxetine](#) than with [imipramine](#) [180][147], [doxepin](#) [187] and [amitriptyline](#) [131][191].

3.3.5] Hematologic Effects

3.3.5.A] Fluoxetine Hydrochloride

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 480×10^6 cells/L, [platelets](#) 34×10^9 /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 [127].

3.3.5.A.2] Bleeding

- a) Summary

1j) 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 [124].

b) Incidence: up to 1%[123]

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 [123].

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 [125].

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 [126].

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 [128].

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 [193][194][132][195].
- b) Elevations in [total bilirubin](#), [direct bilirubin](#), AST/SGOT, [ALT/SGPT](#), total [alkaline phosphatase](#), and gamma-glutamyltransferase were documented [193].
- 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 [196].

3.3.7] Immunologic Effects

3.3.7.A] [Fluoxetine Hydrochloride](#)

3.3.7.A.1] Systemic lupus erythematosus-related syndrome

- a) Incidence: rare[145]
- b) In patients who have developed rash while receiving [fluoxetine](#) therapy, systemic adverse reactions such as lupus-like syndrome have been reported rarely. Although rare, these events may be serious, involving other organ systems (eg, lungs, kidneys, or liver) and potential death [145].

3.3.8] Musculoskeletal Effects

3.3.8.A] [Fluoxetine Hydrochloride](#)

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) [202].
- 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 [203].

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 [201].

3.3.9] Neurologic Effects

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

3.3.9.B.1] Asthenia

a) Incidence: 9% to 21%[129]

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 [129]. Asthenia has occurred to a greater degree with imipramine than with fluoxetine [147].

3.3.9.B.2] Dizziness

a) Incidence: 2% to 11%[145]

b) In placebo-controlled trials of female patients with Premenstrual Dysphoric Disorder (PMDD), dizziness was reported in 7% of patients taking fluoxetine 20 mg/day continuously (n=104) and in 2% of patients taking fluoxetine 20 mg/day intermittently (n=86) compared with 3% of patients taking placebo (pooled, n=196) [145].

c) In placebo-controlled trials of female patients (18 to 45 yr) with depression, obsessive compulsive disorder and bulimia, dizziness was reported in 11% of patients taking fluoxetine up to 80 mg daily (n=1145) compared with 5% of patients taking placebo (n=553) [145].

3.3.9.B.3] 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 [150];(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 [151].

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 [152].

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 [153].

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 [154].

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 [155].

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) [156].

3.3.9.B.4] 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 [148][149].

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 time line correlates well with the half-life of fluoxetine and other possible causes of memory loss were ruled out [148].

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 [149].

3.3.9.B.5] Impaired psychomotor performance

a) Summary

1) [Fluoxetine](#) therapy may have an effect on psychomotor function [159][160]. 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 [159].

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 [159].

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 [160].

3.3.9.B.6] Insomnia

a) Incidence: 9% to 26%[145]

b) In placebo-controlled trials of female patients with depression, [obsessive compulsive disorder](#) and [bulimia](#), insomnia was reported in 24% of patients taking [fluoxetine](#) up to 80 mg daily (n=1145) compared with 11% of patients taking placebo (n=553) [145].

c) In placebo-controlled trials of female patients with [Premenstrual Dysphoric Disorder](#) (PMDD), insomnia was reported in 9% of patients taking [fluoxetine](#) 20 mg/daily continuously (n=104) and in 10% of patients taking 20 mg/day intermittently (n=86) compared with 7% of patients taking placebo (pooled, n=196) [145].

d) In 2 placebo-controlled clinical trials, the incidence of insomnia was 9%, 26% and 7% in patients who received [fluoxetine](#) tablets 20 mg/day continuously or intermittently pooled, 60 mg/day continuously, and placebo pooled, respectively for [premenstrual dysphoric disorder](#) [145].

3.3.9.B.7] 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](#) [157].

3.3.9.B.8] Paresthesia

- a) Incidence: at least 1%[145]
- b) In all United States clinical trials in patients (n=10,782) treated for conditions other than [Premenstrual Dysphoric Disorder](#), paresthesia was reported in at least 1 in 100 patients [145].
- c) 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 [158].

3.3.9.B.9] 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) [146].

3.3.9.B.10] Seizure**a) Summary**

- 1) In all United States [fluoxetine](#) studies the incidence of seizure was 0.2% (n=10,782) [145][161]. 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 [132].
- 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 [162].
- 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 [163]. Previously, seizures have been observed in 12 of 6000 patients receiving [fluoxetine](#) during premarketing trials [129].

d) Two patients currently taking [lithium](#) and [fluoxetine](#) in therapeutic doses for depression and [suicidal ideation](#) experienced seizures following ingestion of LSD [164].

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 [165].

3.3.9.B.11] Somnolence

a) Incidence: 13%[145]

b) In placebo-controlled trials of female patients with depression, [obsessive compulsive disorder](#) and [bulimia](#), somnolence was reported in 13% of patients taking [fluoxetine](#) up to 80 mg daily (n=1145) compared with 6% of patients taking placebo (n=553) [145].

3.3.9.B.12] Tremor

a) Incidence: 12%[145]

b) In placebo-controlled trials of female patients with depression, [obsessive compulsive disorder](#) and [bulimia](#), tremor was reported in 12% of patients taking [fluoxetine](#) up to 80 mg daily (n=1145) compared with 1% of patients taking placebo (n=553) [145].

3.3.10] Ophthalmic Effects

3.3.10.A] [Fluoxetine](#) Hydrochloride

3.3.10.A.1] Mydriasis

a) Mydriasis has been reported in patients taking [fluoxetine](#). Caution should be used when [fluoxetine](#) is prescribed to individuals with raised intraocular pressure or individuals at risk for acute [narrow-angle glaucoma](#) [107].

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 [197].

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 [132][129][198][192]. These disturbances tend to occur early in treatment. Approximately 3% of patients in clinical trials have noted changes in vision [129].

3.3.12] Psychiatric Effects

3.3.12.A] [Fluoxetine](#) Hydrochloride

3.3.12.A.1] Anxiety

- a) Incidence: 3% to 9%[145]
- b) Anxiety has been reported with [fluoxetine](#) therapy [132][223][180][147][191][37] In 2 placebo-controlled clinical trials, the incidence of anxiety was 3%, 9% and 4% in patients who received [fluoxetine](#) tablets 20 mg/day continuously or intermittently pooled, 60 mg/day continuously, and placebo pooled, respectfully for [premenstrual dysphoric disorder](#) [145].

3.3.12.A.2] Depression, worsening

- a) Incidence: rare[222]
- b) While evidence exists from placebo-controlled, maintenance trials in adults with depression to substantiate a delay in the recurrence of depression with antidepressant use, clinical worsening of depression has been reported in patients receiving antidepressant therapy, particularly during the initial few months of treatment and during dose adjustments. It may persist until significant remission occurs. All patients treated with antidepressants for any indication should be monitored for signs of clinical worsening [145].
- c) 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 [222].

3.3.12.A.3] Feeling nervous

- a) Incidence: 3% to 14%[145]
- b) In placebo-controlled trials of female patients with [Premenstrual Dysphoric Disorder](#) (PMDD), nervousness was reported in 7% of patients taking [fluoxetine](#) 20 mg/day continuously (n=104) and 3% of patients taking [fluoxetine](#) 20 mg/day g intermittently (n=86) compared with 3% of patients taking placebo (pooled, n=196) [145].
- c) In placebo-controlled trials of female patients with depression, [obsessive compulsive disorder](#) and [bulimia](#), nervousness was reported in 14% of patients taking [fluoxetine](#) up to 80 mg daily (n=1145) compared with 10% of patients taking placebo (n=553) [145].
- d) In 2 placebo-controlled clinical trials, the incidence of nervousness was 5%, 9% and 3% in patients who received [fluoxetine](#) tablets 20 mg/day continuously or intermittently pooled, 60 mg/day continuously, and placebo pooled, respectfully for [premenstrual dysphoric disorder](#) [145].

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 [205].
- 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 [206].

3.3.12.A.5] [Hypomania](#)

a) Incidence: rare[129]

b) In United States placebo-controlled trials, 0.7% of 10,872 fluoxetine-treated patients reported mania or [hypomania](#) [145][129].

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 [208].

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 [207].

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 [207][37]. In United States placebo-controlled trials, 0.7% of 10,872 fluoxetine-treated patients reported mania or [hypomania](#) [129].

b) Incidence: rare[129]

c) In United States placebo-controlled trials, 0.7% of 10,872 fluoxetine-treated patients reported mania or [hypomania](#) [129].

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 [208].

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 [207].

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 [209].

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 [210].

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 [211].

3.3.12.A.9] Suicidal thoughts

a) Adults

1) No clinically significant differences in the risk of suicide and suicide attempts were observed across antidepressant agents and antidepressant classes in a 9-year, population-based cohort study consisting 287,543 adults. Based on the health care utilization data, the overall combined event rates of suicide death or hospitalization due to self harm ranged from 4.41 to 9.09 per 1000 person years. Among patients who received fluoxetine (n=22,207; 10,872 person-years), suicide occurred at an event rate of 0.92/1000 person-years (95% confidence interval (CI), 0.44 to 1.69) and suicide attempts occurred at a rate of 6.35/1000 person-years (95% CI, 4.94 to 8.03). Based on data among treatment-naïve patients alone (no antidepressant use in the past 3 years; n=10,953; 5728 person-years), suicide occurred at a rate of 1.05/1000 person-years (95% CI, 0.38 to 2.28) and suicide attempts occurred at a rate of 4.89/1000 person-years (95% CI, 3.25 to 7.06). Most events were reported within the first 6 months after start of therapy [204].

2) The risk of suicidality varied among 11 antidepressant drugs studied in greater than 77,000 adults with major depressive disorder or other psychiatric disorders in pooled analysis of placebo-controlled trials. However, for almost all drugs studied, there was a tendency toward increased suicidality in younger patients. The risk difference (drug versus placebo in the number of cases of suicidality per 1000 patients treated) was 14 additional cases in patients less than 18 years of age, 5 additional cases in patients 18 to 24 years, 1 fewer case in patients 25 to 64 years, and 6 fewer cases in patients 65 years and older. No suicides occurred in the pediatric trials. Suicides did occur in the adult trials; however, the number of suicides was insufficient to determine causality [145].

3) 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)) [212].

4) 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 [213]. 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](#).

5) [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 [214].

6) 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](#) [215][216]. 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 [216].

7) 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 [217][218].

8) 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 [219].

9) 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 [220].

b) Pediatrics

1) A causal role for antidepressants in inducing suicidality has been established in pediatric patients. While [fluoxetine](#) is not approved for use in children [145], 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 [221].

2j) The risk of suicidality varied among 11 antidepressant drugs studied in greater than 77,000 adults with [major depressive disorder](#) or other psychiatric disorders in pooled analysis of placebo-controlled trials. However, for almost all drugs studied, there was a tendency toward increased suicidality in younger patients. The risk difference (drug versus placebo in the number of cases of suicidality per 1000 patients treated) was 14 additional cases in patients less than 18 years of age, 5 additional cases in patients 18 to 24 years, 1 fewer case in patients 25 to 64 years, and 6 fewer cases in patients 65 years and older. No suicides occurred in the pediatric trials. Suicides did occur in the adult trials; however, the number of suicides was insufficient to determine causality [145].

c) Management

1j) 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 [222].

2j) Patients should be observed for these symptoms especially during the initial few months of therapy, and at times of dosage increases or decreases [145].

3.3.12.A.10] Suicide

a) No clinically significant differences in the risk of suicide and suicide attempts were observed across antidepressant agents and antidepressant classes in a 9-year, population-based cohort study consisting 287,543 adults. Based on the health care utilization data, the overall combined event rates of suicide death or hospitalization due to self harm ranged from 4.41 to 9.09 per 1000 person years. Among patients who received [fluoxetine](#) (n=22,207; 10,872 person-years), suicide occurred at an event rate of 0.92/1000 person-years (95% confidence interval (CI), 0.44 to 1.69) and suicide attempts occurred at a rate of 6.35/1000 person-years (95% CI, 4.94 to 8.03). Based on data among treatment-naïve patients alone (no antidepressant use in the past 3 years; n=10,953; 5728 person-years), suicide occurred at a rate of 1.05/1000 person-years (95% CI, 0.38 to 2.28) and suicide attempts occurred at a rate of 4.89/1000 person-years (95% CI, 3.25 to 7.06). Most events were reported within the first 6 months after start of therapy [204].

b) Suicide has been reported in adult patients receiving antidepressant therapy in clinical trials including [fluoxetine](#); however, the number of suicides was insufficient to determine causality. No suicides were reported in the pediatric trials with [fluoxetine](#) [145].

3.3.14] Reproductive Effects

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

3.3.14.B.1] Fibrocystic breast changes

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 [224].

3.3.14.B.2] Sexual dysfunction

a) Summary

1) The overall incidence of sexual dysfunction is unknown. Sexual dysfunction may persist after discontinuation of fluoxetine [107]. Both anorgasmia and delayed orgasm have been reported in both males and females receiving fluoxetine [225][226][156]. Paradoxically, there is at least one case report of a woman experiencing multiple orgasms and repeated yawning [227], as well as improvement of sexual response in a few cases of elderly men [228][229]. 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 [230][231]. 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 [232]. Other accounts range from 7.8% to 75% [233][234][235][236]. 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 [237].

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 [238]. Positive results were also obtained in a double-blind placebo controlled study on 17 patients [239].

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 [231].

d) In 3 case reports of elderly men [229] 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 [228].

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 [180]. 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 [225].

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 [227].

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) [156].

3.3.15] Respiratory Effects

3.3.15.A] [Fluoxetine](#) Hydrochloride

3.3.15.A.1] [Extrinsic allergic alveolitis](#)

a) 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](#) [199].

3.3.15.A.2] [Pharyngitis](#)

a) Incidence: 6% to 10%[145]

b) In placebo-controlled trials of female patients with [Premenstrual Dysphoric Disorder](#) (PMDD), [pharyngitis](#) was reported in 10% of patients taking [fluoxetine](#) 20 mg/day continuously (n=104) and in 6% of patients taking 20 mg/day intermittently (n=86) compared with 5% of patients taking placebo (pooled, n=196) [145].

c) In placebo-controlled trials of female patients with depression, [obsessive compulsive disorder](#) and [bulimia](#), [pharyngitis](#) was reported in 6% of patients taking [fluoxetine](#) up to 80 mg daily (n=1145) compared with 5% of patients taking placebo (n=553) [145].

3.3.15.A.3] [Rhinitis](#)

a) Incidence: 16% to 23%[145]

b) In placebo-controlled trials of female patients with [Premenstrual Dysphoric Disorder](#) (PMDD), [rhinitis](#) was reported in 23% of patients taking [fluoxetine](#) 20 mg/day continuously (n=104) and in 16% of patients taking [fluoxetine](#) 20 mg/day intermittently (n=86) compared with 15% of patients taking placebo (pooled, n=196) [145].

3.3.15.A.4] Yawning

a) In placebo-controlled trials of female patients with depression, [obsessive compulsive disorder](#) and [bulimia](#), yawning was reported in 5% of patients taking [fluoxetine](#) up to 80 mg daily (n=1145) compared with less than 0.5% of patients taking placebo (n=553) [145].

3.3.16] Other

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

3.3.16.B.1] Drug withdrawal

a) A discontinuation syndrome of dizziness, lightheadedness, insomnia, fatigue, anxiety, agitation, nausea, headache, and sensory disturbances has been described after abrupt discontinuation of fluoxetine therapy [245].

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 [246].

3.3.16.B.2] Influenza-like symptoms

a) Incidence: 3% to 12%[145]

b) In placebo-controlled trials of female patients with Premenstrual Dysphoric Disorder (PMDD), flu syndrome was reported in 12% of patients taking fluoxetine 20 mg/day continuously (n=104) and in 3% of patients taking fluoxetine 20 mg/day intermittently (n=86) compared with 7% of patients taking placebo (pooled, n=196) [145].

c) In placebo-controlled trials of female patients with depression, obsessive compulsive disorder and bulimia, flu syndrome was reported in 7% of patients taking fluoxetine up to 80 mg daily (n=1145) compared with 3% of patients taking placebo (n=553) [145].

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 [240].

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](#) [241].

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 [242].

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 [243].

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 [clonazepam](#) 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 [244].

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 and an increased incidence or severity of antidepressant-related adverse events [170].

3.4] [Teratogenicity/Effects in Pregnancy/Breastfeeding](#)

A) [Teratogenicity/Effects in Pregnancy](#)

1) U.S. Food and Drug Administration's Pregnancy Category: Category C (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

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 SSRIs, but the exposed infants were more likely to require treatment in a special or intensive care unit [774]. 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](#) [773]. A study of prospectively collected data suggests antenatal use of SSRI antidepressants is associated with QTc interval prolongation in exposed neonates [771]. 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 [772]. 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 [145][344]; however, one small study indicated no long-term effects on cognitive ability

were demonstrated. The same study did show evidence of an increased risk for social-behavioral abnormalities at 2 to 6 years of age in children exposed to SSRIs or SNRIs in utero who developed [neonatal abstinence syndrome](#) (NAS) at birth [778]. 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](#) [781][783]. In pregnant patients diagnosed with [obsessive compulsive disorder](#), [fluoxetine](#) is recommended when [behavioral therapy](#) has proven inadequate [784][785].

5) Literature Reports

a) A nested case-controlled study showed that [fluoxetine](#), [sertraline](#), [citalopram](#), [fluvoxamine](#), or combined use of 2 or more SSRIs during pregnancy did not correspond with a significantly increased risk of [spontaneous abortion](#). However, [paroxetine](#) or [venlafaxine](#) use alone did increase the [spontaneous abortion](#) risk. Data collected from the Quebec Pregnancy Registry between January 1998 and December 2003 on women who filled at least 1 antidepressant prescription during pregnancy and had a clinically detected [spontaneous abortion](#) by the twentieth week of gestation (n=284) showed an increased risk of [spontaneous abortion](#) (adjusted odds ratio (OR), 1.68; 95% confidence interval (CI), 1.38 to 2.06) when compared with randomly selected registry controls (4 matched controls per case) without antidepressant use. Tracked antidepressant categories included SSRIs, tricyclic antidepressants, serotonin-norepinephrine reuptake inhibitors, combined use of 2 or more antidepressant classes, or others. [Paroxetine](#) use (adjusted OR 1.75; 95% CI, 1.31 to 2.34) or [venlafaxine](#) use (adjusted OR 2.11; 95% CI, 1.34 to 3.3) alone were independently associated with a higher risk of [spontaneous abortion](#). The highest daily doses of [paroxetine](#) or [venlafaxine](#) during pregnancy were associated with the greatest [spontaneous abortion](#) risk; of the women taking [paroxetine](#) (n=84) or [venlafaxine](#) (n=33) who spontaneously aborted, an adjusted analysis showed 25.5% averaged daily doses of more than 25 mg of [paroxetine](#) and 50% averaged daily doses greater than 150 mg of [venlafaxine](#). [770].

b) 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 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, temperature instability, feeding difficulty, vomiting, [hypoglycemia](#), hypotonia, hypertonia, hyperreflexia, tremor, jitteriness, irritability, and constant crying; a clinical scenario reflective of [serotonin syndrome](#) in some cases. 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 [145][344].

c) A study of prospectively collected data suggests antenatal use of 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 msec (the widely used upper limit cited by authorities in both pediatric cardiology and neonatology). A pediatric cardiologist blinded to drug exposure, interpreted all ECGs using standard statistical analyses. ECG recordings revealed markedly prolonged mean QTc intervals in exposed neonates compared to unexposed neonates (mean, 409 +/- 42 msec vs 392 +/- 29 msec; p=0.02). The mean uncorrected QT interval was 7.5% longer among exposed neonates (mean, 280 +/- 31 msec vs 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 [771].

d) 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; 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](#) [772].

e) A case-control study found that the use of SSRIs after 20 weeks of gestation was associated with an increased risk of [persistent pulmonary hypertension of the newborn](#) (PPHN). [Fluoxetine](#), [paroxetine](#), and [sertraline](#) were the specific SSRIs studied to carry this increased risk. A total of 377 women who had infants with PPHN were matched to 836 women and their infants. Assessment of exposure was determined by telephone interview within 6 months of birth. After adjusting for other covariates, SSRI use after 20 weeks of gestation was associated with an odds ratio of 6.1 (95% confidence interval, 2.2 to 16.8; $p=0.001$) of delivering an infant with PPHN relative to no use during the pregnancy. SSRI use before 20 weeks of gestation and non-SSRI antidepressant 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% [773].

f) A population-based study of 1782 pregnant women exposed to SSRIs found no increased risk of adverse perinatal outcome except for treatment in the neonatal intensive or special care unit, particularly with third-trimester exposure. Using 1996 to 2001 data derived from a government project involving 4 birth or medication registries in Finland, women who had at least one purchase (a 3-month's 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 (+/- 7) years. There were more than twice as many smokers and 6 times as many pregnancies induced by artificial reproductive techniques in the SSRI group compared to controls (p less than 0.001), and mean length of gestation and birth weight were lower (p less than 0.001) in the SSRI group. Malformations, however, were not more common in the SSRI group ($p=0.4$). Purchases of SSRIs ([citalopram](#), [fluoxetine](#), [paroxetine](#), [sertraline](#), and [fluvoxamine](#)) were more common in the first trimester than later in pregnancy, with 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% confidence interval, 1.1 to 2.2) [774].

g) 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 2 groups. However, Apgar scores at 15 minutes were lower in the fluoxetine group [775].

h) In one study assessing the direct effects of fluoxetine on infant outcome at birth [776], 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 [777].

i) In a prospective, single-blind, cohort study, full-term infants who developed neonatal abstinence syndrome (NAS) at birth had similar cognitive abilities compared with full term infants without NAS at birth when reevaluated at 2 to 6 years of age. However, infants with NAS at birth were at an increased risk for social-behavioral abnormalities at 2 to 6 years of age. The study was designed to assess the long-term neurodevelopment of children exposed in utero to fluoxetine, paroxetine, citalopram, sertraline, fluvoxamine, or venlafaxine. Children with NAS at birth (n=30; Finnegan score of 4 or greater) were compared to children without NAS (n=52; Finnegan score 0 to 3); both groups were similar in mean cognitive ability (106.9 +/- 14 versus 100.5 +/- 14.6, respectively; p=0.12) and developmental scores (98.9 +/- 11.4 versus 95.7 +/- 9.9, respectively; p=0.21). Cognitive ability was based on scores from the Wechsler Preschool and Primary Scale of Intelligence II, the Stanford-Binet Intelligence Scales, or the Bayley Scale of Infant Development II. The NAS infants had an increased risk of social-behavior abnormalities (odds ratio (OR) 3.03, 95% CI, 1.07 to 8.6, p=0.04) based on the Denver Developmental Screening Test II (DDST-II) and NAS after birth was associated with advanced maternal age (OR 1.12, 95% CI, 1 to 1.25, p=0.04). In addition, there was a trend towards small head circumference in the NAS group when compared with the children without NAS (n=6 (20%) versus n=3 (6%), respectively; p=0.068) [778].

j) Based on analyses of independently collected data 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 [779][777][780][781]. 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 [779].

k) An increased risk for CNS serotonergic symptoms was observed during the first 4 days of life in infants of mothers taking SSRIs during the third trimester of pregnancy. In a controlled, prospective study, women taking 20 to 40 mg/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 2 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; 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 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 [782].

B) Breastfeeding

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

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 breastmilk and the oral dose available to the infant has been estimated at 15 to 20 mcg/kg/day for **fluoxetine** [788], and 40 mcg/kg/day for **fluoxetine** plus norfluoxetine [791]. The American Academy of Pediatrics considers antidepressants to be drugs worthy of concern in the nursing infant [786]. 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 SSRIs via breastmilk 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 [787][788][789].

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** [790].

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 [791].

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 [791].

e) The manufacturer reports a maternal plasma concentration of 295 nanograms (ng)/mL for [fluoxetine](#) plus norfluoxetine, with a corresponding breastmilk concentration of 70.4 ng/mL. No adverse effects in the nursing infant were reported. In another case, a nursing infant's plasma drug levels were 340 ng/mL of [fluoxetine](#) and 208 ng/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 [145][344].

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 breastmilk. 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. Postexposure levels were measured at 4 to 12 weeks later. Mean maternal plasma concentrations of [fluoxetine](#) were 125 nanograms (ng)/mL, and norfluoxetine were 142 ng/mL. All but one infant had plasma [fluoxetine](#) levels below 1 ng/mL, and the mean infant plasma concentration of norfluoxetine was 3.2 ng/mL. Mean maternal pre- and post-fluoxetine 5-HT levels were 157 ng/mL and 23 ng/mL, respectively. The mean infant pre- and postexposure 5-HT concentrations were 217 ng/mL and 230 ng/mL, respectively. Bayley 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 [787].

5) Drug Levels in Breastmilk

a) Parent Drug

1) Milk to Maternal Plasma Ratio

a) 0.21-1.51 [789][814]

b) Active Metabolites

1) NORFLUOXETINE [813]

3.5] Drug Interactions

3.5.1] Drug-Drug Combinations

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 selective serotonin reuptake inhibitors 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. Monitor patient for signs of increased bleeding when [fluoxetine](#) is administered with [abciximab](#) concomitantly[344].

3) Severity: major

4) Onset: unspecified

5) Substantiation: probable

6) Clinical Management: When [abciximab](#) and [fluoxetine](#) are given concurrently, monitor patient for signs of increased bleeding[344].

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[382][383][384]. [Fluoxetine](#) has been shown to prolong the QTc interval at the recommended therapeutic dose [385].

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: Caution is recommended with the concomitant use of NSAIDs and SSRIs due to an increased risk of [gastrointestinal bleeding](#)[688][689]. Bleeding events have included [epistaxis](#), ecchymosis, [hematoma](#), [petechiae](#), and life-threatening hemorrhages [692][693][694][695].

3) Severity: major

4) Onset: unspecified

5) Substantiation: probable

6) Clinical Management: Use caution when prescribing NSAIDs to patients who take SSRIs. Concomitant use of NSAIDs and SSRIs may cause an increased risk of bleeding[688][689]. 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 (GI) bleeding and this effect is potentiated by concurrent use of NSAIDs or low-dose [aspirin](#). Hospitalizations for [upper GI 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 (CI), 2.7 to 4.7). Combined use of an SSRI and NSAIDs or low-dose [aspirin](#) increased the risk to 12.2 (95% CI, 7.1 to 19.5) and 5.2 (95% CI, 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 [690].

b) Coadministration of ketorolac with psychoactive drugs (such as [fluoxetine](#)) has been associated with hallucinations in some patients [691].

3.5.1.D] Acemetacin

1) Interaction Effect: an increased risk of bleeding

- 2) Summary: Caution is recommended with the concomitant use of NSAIDs and SSRIs due to an increased risk of [gastrointestinal bleeding](#) [688][689]. Bleeding events have included [epistaxis](#), ecchymosis, [hematoma](#), [petechiae](#), and life-threatening hemorrhages [692][693][694][695].
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: probable
- 6) Clinical Management: Use caution when prescribing NSAIDs to patients who take SSRIs. Concomitant use of NSAIDs and SSRIs may cause an increased risk of bleeding [688][689]. 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 (GI) bleeding and this effect is potentiated by concurrent use of NSAIDs or low-dose [aspirin](#). Hospitalizations for [upper GI 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 (CI), 2.7 to 4.7). Combined use of an SSRI and NSAIDs or low-dose [aspirin](#) increased the risk to 12.2 (95% CI, 7.1 to 19.5) and 5.2 (95% CI, 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 [690].

b) Coadministration of ketorolac with psychoactive drugs (such as [fluoxetine](#)) has been associated with hallucinations in some patients [691].

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 [586][587][124]. 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](#) [124].
- 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 [124].
- 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 [584]. In addition, both [fluoxetine](#) and [warfarin](#) are tightly bound to albumin. In combination, the possibility for protein-binding displacement of either drug is present [585].

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 [586].

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 [587].

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](#) [588][589].

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 [590].

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[417]. [Fluoxetine](#) has demonstrated QT prolongation at therapeutic doses [418].
- 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: Caution is recommended with the concomitant use of NSAIDs and SSRIs due to an increased risk of [gastrointestinal bleeding](#)[688][689]. Bleeding events have included [epistaxis](#), ecchymosis, [hematoma](#), [petechiae](#), and life-threatening hemorrhages [692][693][694][695].
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: probable
- 6) Clinical Management: Use caution when prescribing NSAIDs to patients who take SSRIs. Concomitant use of NSAIDs and SSRIs may cause an increased risk of bleeding[688][689]. 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 (GI) bleeding and this effect is potentiated by concurrent use of NSAIDs or low-dose [aspirin](#). Hospitalizations for [upper GI 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 (CI), 2.7 to 4.7). Combined use of an SSRI and NSAIDs or low-dose [aspirin](#) increased the risk to 12.2 (95% CI, 7.1 to 19.5) and 5.2 (95% CI, 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 [690].

b) Coadministration of ketorolac with psychoactive drugs (such as [fluoxetine](#)) has been associated with hallucinations in some patients [691].

3.5.1.H] Almotriptan

- 1) Interaction Effect: an increased risk of [serotonin syndrome](#)
- 2) Summary: Concomitant use of triptans and selective serotonin reuptake inhibitors (SSRI's) has been associated with [serotonin syndrome](#), some of which life-threatening[435]. 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](#) [259].
- 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 (C_{max}). 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, T_{max} 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 [434].

3.5.1.1) 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[744][745]. The mechanism of this interaction is thought to be inhibition by **fluoxetine** of the cytochrome P450A4 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 [741]. 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 [742]. 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 [743].

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[382][383][384]. [Fluoxetine](#) has been shown to prolong the QTc interval at the recommended therapeutic dose [385].
- 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[388]. 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 [389], [quetiapine](#) [390], sertindole [391], sultopride [392], and zotepine [393].
- 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[680][681]. 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 [682]. In addition,

concurrent use of [fluoxetine](#) and TCAs such as [desipramine](#), [nortriptyline](#), and [imipramine](#) has resulted in significant increases in TCA concentrations [683][683][684][685][686][687].

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 [674].

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 [675].

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 [676].

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 [677].

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 [678].

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 [679].

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[680][681]. 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 [682]. In addition, concurrent use of fluoxetine and TCAs such as desipramine, nortriptyline, and imipramine has resulted in significant increases in TCA concentrations [683][683][684][685][686][687].

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 [674].

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 [675].

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 [676].

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 [677].

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 [678].

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 [679].

3.5.1.N] 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[586][587][124]. 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](#) [124].

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[124].

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 [584]. In addition, both [fluoxetine](#) and [warfarin](#) are tightly bound to albumin. In combination, the possibility for protein-binding displacement of either drug is present [585].

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 [586].

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 [587].

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](#) [588][589].

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 [590].

3.5.1.O] 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[586][587][124]. 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](#) [124].

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[124].

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 [584]. In addition, both [fluoxetine](#) and [warfarin](#) are tightly bound to albumin. In combination, the possibility for protein-binding displacement of either drug is present [585].

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 [586].

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 [587].

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](#) [588][589].

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 [590].

3.5.1.P] 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[586][587][124]. 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](#) [124].

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[124].

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 [584]. In addition, both [fluoxetine](#) and [warfarin](#) are tightly bound to albumin. In combination, the possibility for protein-binding displacement of either drug is present [585].

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 [586].

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 [587].

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](#) [588][589].

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 [590].

3.5.1.Q) Apazone

1)) Interaction Effect: an increased risk of bleeding

2)) Summary: Caution is recommended with the concomitant use of NSAIDs and SSRIs due to an increased risk of [gastrointestinal bleeding](#)[688][689]. Bleeding events have included [epistaxis](#), ecchymosis, [hematoma](#), [petechiae](#), and life-threatening hemorrhages [692][693][694][695].

3)) Severity: major

4)) Onset: unspecified

5)) Substantiation: probable

6)) Clinical Management: Use caution when prescribing NSAIDs to patients who take SSRIs. Concomitant use of NSAIDs and SSRIs may cause an increased risk of bleeding[688][689]. 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 (GI) bleeding and this effect is potentiated by concurrent use of NSAIDs or low-dose [aspirin](#). Hospitalizations for [upper GI 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 (CI), 2.7 to 4.7). Combined use of an SSRI and NSAIDs or low-dose [aspirin](#) increased the risk to 12.2 (95% CI, 7.1 to 19.5) and 5.2 (95% CI, 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 [690].

b)) Coadministration of ketorolac with psychoactive drugs (such as [fluoxetine](#)) has been associated with hallucinations in some patients [691].

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[446]. [Fluoxetine](#) has been shown to prolong the QTc interval at the recommended therapeutic dose [447].
- 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[586][587][124]. 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](#) [124].
- 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[124].
- 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 [584]. In addition, both [fluoxetine](#) and [warfarin](#) are tightly bound to albumin. In combination, the possibility for protein-binding displacement of either drug is present [585].

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 [586].

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 [587].

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](#) [588][589].

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 [590].

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. If [aripiprazole](#) is coadministered with [fluoxetine](#), reduce the [aripiprazole](#) dose to one-half of its normal dose. For use of [aripiprazole](#) in poor CYP2D6 metabolizers, the [aripiprazole](#) dose should be reduced to one-half of its normal dose and adjusted as necessary to achieve a favorable clinical response. If coadministration includes a CYP3A4 and a CYP2D6 inhibitor, reduce the [aripiprazole](#) dose to one-quarter of its normal dose. If therapy with [fluoxetine](#) and/or the CYP3A4 inhibitor are discontinued, the dose of [aripiprazole](#) should then be increased[536][537].

3) Severity: moderate

4) Onset: delayed

5) Substantiation: theoretical

6) Clinical Management: Coadministration of [aripiprazole](#) and a CYP2D6 inhibitor, such as [fluoxetine](#), may result in increased [aripiprazole](#) plasma levels. Reduce the [aripiprazole](#) dose to one-half of its normal dose when these agents are coadministered. For use of [aripiprazole](#) in poor CYP2D6 metabolizers, the [aripiprazole](#) dose should be reduced to one-half of its normal dose and adjusted as necessary to achieve a favorable clinical response. If coadministration includes a CYP3A4 inhibitor and a CYP2D6 inhibitor, reduce the [aripiprazole](#) dose to one-quarter of its normal dose. If therapy with [fluoxetine](#) and/or the CYP3A4 inhibitor are discontinued, the dose of [aripiprazole](#) should then be increased[536][537].

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[672][673]. 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](#) [672].
- 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 [670].

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 [671].

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 selective serotonin reuptake inhibitors 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. Monitor patient for signs of increased bleeding when [fluoxetine](#) is administered with [aspirin](#) concomitantly[344].
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: probable
- 6) Clinical Management: When [fluoxetine](#) and [aspirin](#) are given concurrently, monitor patient for signs of increased bleeding[344].
- 7) Probable Mechanism: unknown

3.5.1.W] Aspirin

- 1) Interaction Effect: an increased risk of bleeding

2) Summary: Caution is recommended with the concomitant use of NSAIDs and SSRIs due to an increased risk of [gastrointestinal bleeding](#)[688][689]. Bleeding events have included [epistaxis](#), ecchymosis, [hematoma](#), [petechiae](#), and life-threatening hemorrhages [692][693][694][695].

3) Severity: major

4) Onset: unspecified

5) Substantiation: probable

6) Clinical Management: Use caution when prescribing NSAIDs to patients who take SSRIs. Concomitant use of NSAIDs and SSRIs may cause an increased risk of bleeding[688][689]. 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 (GI) bleeding and this effect is potentiated by concurrent use of NSAIDs or low-dose [aspirin](#). Hospitalizations for [upper GI 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 (CI), 2.7 to 4.7). Combined use of an SSRI and NSAIDs or low-dose [aspirin](#) increased the risk to 12.2 (95% CI, 7.1 to 19.5) and 5.2 (95% CI, 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 [690].

b) Coadministration of ketorolac with psychoactive drugs (such as [fluoxetine](#)) has been associated with hallucinations in some patients [691].

3.5.1.X] [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[254]. 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](#) [255]. In addition, [fluoxetine](#) has been shown to prolong the QTc interval at the recommended therapeutic dose [256].

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 [253]. 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.Y] [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[340].

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.Z] 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[382][383][384]. [Fluoxetine](#) has been shown to prolong the QTc interval at the recommended therapeutic dose [385].

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.AA] Benoxaprofen

1) Interaction Effect: an increased risk of bleeding

2) Summary: Caution is recommended with the concomitant use of NSAIDs and SSRIs due to an increased risk of [gastrointestinal bleeding](#)[688][689]. Bleeding events have included [epistaxis](#), [ecchymosis](#), [hematoma](#), [petechiae](#), and life-threatening hemorrhages [692][693][694][695].

3) Severity: major

4) Onset: unspecified

5) Substantiation: probable

6) Clinical Management: Use caution when prescribing NSAIDs to patients who take SSRIs. Concomitant use of NSAIDs and SSRIs may cause an increased risk of bleeding[688][689]. 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 (GI) bleeding and this effect is potentiated by concurrent use of NSAIDs or low-dose [aspirin](#). Hospitalizations for [upper GI 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 (CI), 2.7 to 4.7). Combined use of an SSRI and NSAIDs or low-dose [aspirin](#) increased the risk to 12.2 (95% CI, 7.1 to 19.5) and 5.2 (95% CI, 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 [690].

b)) Coadministration of ketorolac with psychoactive drugs (such as [fluoxetine](#)) has been associated with hallucinations in some patients [691].

3.5.1.AB] [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[351][352]. Even though no formal drug interaction studies have been done, the coadministration of [bepridil](#) and [fluoxetine](#) is contraindicated [352].

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.AC] [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[586][587][124]. 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](#) [124].

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[124].

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 [584]. In addition, both [fluoxetine](#) and [warfarin](#) are tightly bound to albumin. In combination, the possibility for protein-binding displacement of either drug is present [585].

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 [586].

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 [587].

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](#) [588][589].

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 [590].

3.5.1.AD] [Bretylum](#)

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[382] [383][384]. [Fluoxetine](#) has been shown to prolong the QTc interval at the recommended therapeutic dose [385].

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.AE] [Bromfenac](#)

- 1) Interaction Effect: an increased risk of bleeding
- 2) Summary: Caution is recommended with the concomitant use of NSAIDs and SSRIs due to an increased risk of [gastrointestinal bleeding](#)[688][689]. Bleeding events have included [epistaxis](#), ecchymosis, [hematoma](#), [petechiae](#), and life-threatening hemorrhages [692][693][694][695].
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: probable
- 6) Clinical Management: Use caution when prescribing NSAIDs to patients who take SSRIs. Concomitant use of NSAIDs and SSRIs may cause an increased risk of bleeding[688][689]. 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 (GI) bleeding and this effect is potentiated by concurrent use of NSAIDs or low-dose [aspirin](#). Hospitalizations for [upper GI 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 (CI), 2.7 to 4.7). Combined use of an SSRI and NSAIDs or low-dose [aspirin](#) increased the risk to 12.2 (95% CI, 7.1 to 19.5) and 5.2 (95% CI, 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 [690].

b) Coadministration of ketorolac with psychoactive drugs (such as [fluoxetine](#)) has been associated with hallucinations in some patients [691].

3.5.1.AF] Bufexamac

- 1) Interaction Effect: an increased risk of bleeding
- 2) Summary: Caution is recommended with the concomitant use of NSAIDs and SSRIs due to an increased risk of [gastrointestinal bleeding](#)[688][689]. Bleeding events have included [epistaxis](#), ecchymosis, [hematoma](#), [petechiae](#), and life-threatening hemorrhages [692][693][694][695].
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: probable
- 6) Clinical Management: Use caution when prescribing NSAIDs to patients who take SSRIs. Concomitant use of NSAIDs and SSRIs may cause an increased risk of bleeding[688][689]. 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 (GI) bleeding and this effect is potentiated by concurrent use of NSAIDs or low-dose [aspirin](#). Hospitalizations for [upper GI 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 (CI), 2.7 to 4.7). Combined use of an SSRI and NSAIDs or low-dose [aspirin](#) increased the risk to 12.2 (95% CI, 7.1 to 19.5) and 5.2 (95% CI, 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 [690].

b)) Coadministration of ketorolac with psychoactive drugs (such as [fluoxetine](#)) has been associated with hallucinations in some patients [691].

3.5.1.AG| [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](#)[420][421]. 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 [419].

3.5.1.AH| [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](#)[457][458][459]. 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 [460].
- 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 [453][454][455].

b)) Three cases of potentiation of the antidepressant effects of [fluoxetine](#) by [buspirone](#) have been reported [456]. 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](#) [242].

3.5.1.AI] Cannabis

1)) Interaction Effect: manic symptoms

2)) Summary: One case of mania following use of marijuana with [fluoxetine](#) therapy has been reported[298]. 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 [297].

3.5.1.AJ] Carbamazepine

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

2j) 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[265][266][267]. Conversely, no changes in steady state carbamazepine levels have been reported with the addition of fluoxetine [268]. Symptoms of serotonin syndrome (hypertension, hyperthermia, myoclonus, mental status changes) have also been reported with this combination [269].

3j) Severity: moderate

4j) Onset: delayed

5j) Substantiation: probable

6j) 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.

7j) Probable Mechanism: decreased carbamazepine metabolism

8j) Literature Reports

a) An interaction between fluoxetine and carbamazepine was reported in six normal volunteers [260]. 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 [261]. 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 [262].

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 dextimide, 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 [263].

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 [264].

3.5.1.AK] Carprofen

- 1) Interaction Effect: an increased risk of bleeding
- 2) Summary: Caution is recommended with the concomitant use of NSAIDs and SSRIs due to an increased risk of [gastrointestinal bleeding](#)[688][689]. Bleeding events have included [epistaxis](#), ecchymosis, [hematoma](#), [petechiae](#), and life-threatening hemorrhages [692][693][694][695].
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: probable
- 6) Clinical Management: Use caution when prescribing NSAIDs to patients who take SSRIs. Concomitant use of NSAIDs and SSRIs may cause an increased risk of bleeding[688][689]. 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 (GI) bleeding and this effect is potentiated by concurrent use of NSAIDs or low-dose [aspirin](#). Hospitalizations for [upper GI 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 (CI), 2.7 to 4.7). Combined use of an SSRI and NSAIDs or low-dose [aspirin](#) increased the risk to 12.2 (95% CI, 7.1 to 19.5) and 5.2 (95% CI, 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 [690].

b) Coadministration of ketorolac with psychoactive drugs (such as [fluoxetine](#)) has been associated with hallucinations in some patients [691].

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[586][587][124]. 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](#) [124].
- 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[124].
- 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 [584]. In addition, both [fluoxetine](#) and [warfarin](#) are tightly bound to albumin. In combination, the possibility for protein-binding displacement of either drug is present [585].

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 [586].

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 [587].

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](#) [588][589].

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 [590].

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[525][526]. 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 [524].

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[275][276]. 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[397][398][399] . 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 [400].
- 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 elective serotonin reuptake inhibitors 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. Monitor patient for signs of increased bleeding when [fluoxetine](#) is administered with [cilostazol](#) concomitantly[344].
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: probable
- 6) Clinical Management: When [cilostazol](#) and [fluoxetine](#) are given concurrently, monitor patient for signs of increased bleeding[344].
- 7) Probable Mechanism: unknown

3.5.1.AQ| Citalopram

- 1) Interaction Effect: increased risk of [serotonin syndrome](#) ([hypertension](#), [hyperthermia](#), myoclonus, mental status changes)
- 2) Summary: Concurrent use of an SSRI together with another SSRI may result in [serotonin syndrome](#), which may be life-threatening, and is not recommended. 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[448][449][450][451]. If symptoms of [serotonin syndrome](#) occur, drug discontinuation is recommended [452][344]. Symptoms of [serotonin syndrome](#) include neuromuscular abnormalities (including hyperreflexia, 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 [248].
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Coadministration of an SSRI with another SSRI may result in a life-threatening condition called [serotonin syndrome](#) and is not recommended[448][449][450][451]. If these agents are used together, monitor closely for symptoms of [serotonin syndrome](#), especially during treatment initiation and dose increases, and discontinue therapy if symptoms occur [452][344]. Symptoms of [serotonin syndrome](#) include neuromuscular abnormalities (including hyperreflexia, 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 [248].
- 7) Probable Mechanism: additive serotonergic effect

3.5.1.AR| Citalopram

- 1) Interaction Effect: increased [citalopram](#) exposure and risk of QT interval prolongation
- 2) Summary: In a [pharmacokinetic study](#) in patients who received [citalopram](#) 40 mg/day for 21 days, combined administration with [cimetidine](#) (a potent CYP2C19 inhibitor) 400 mg/day for 8 days resulted in an increase in [citalopram](#) AUC and Cmax of 43% and 39%, respectively. Although the interaction between [citalopram](#) (a CYP2C19 substrate) and [fluoxetine](#) (another CYP2C19 inhibitor) has not been

specifically studied, concomitant use may result in increased [citalopram](#) exposure and an increased risk of QT prolongation. If coadministration of [citalopram](#) with [fluoxetine](#) is required, do not exceed [citalopram](#) doses of 20 mg/day[757].

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: The concomitant use of [citalopram](#) with [fluoxetine](#) may result in increased [citalopram](#) exposure and risk of QT prolongation. If coadministration of [citalopram](#) with [fluoxetine](#) is required, do not exceed [citalopram](#) doses of 20 mg/day[757].

7) Probable Mechanism: inhibition of CYP2C19-mediated [citalopram](#) metabolism by [fluoxetine](#)

3.5.1.AS] [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](#)[708].

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](#) [707].

3.5.1.AT] [Clobazam](#)

1) Interaction Effect: increased [fluoxetine](#) plasma concentrations

2) Summary: The concomitant use of [fluoxetine](#), a CYP2D6 substrate[336], and clobazam, a CYP2D6 inhibitor, may increase [fluoxetine](#) plasma concentrations. Dose reduction of [fluoxetine](#) may be required when coadministered with clobazam [595].

3) Severity: moderate

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: The concomitant use of clobazam with [fluoxetine](#) may cause increased [fluoxetine](#) plasma concentrations. If administered concomitantly, a dose reduction of [fluoxetine](#) may be warranted[595].

7) Probable Mechanism: inhibition of CYP2D6-mediated [fluoxetine](#) metabolism by clobazam

3.5.1.AU] [Clometacin](#)

1) Interaction Effect: an increased risk of bleeding

2) Summary: Caution is recommended with the concomitant use of NSAIDs and SSRIs due to an increased risk of [gastrointestinal bleeding](#)[688][689]. Bleeding events have included [epistaxis](#), ecchymosis, [hematoma](#), [petechiae](#), and life-threatening hemorrhages [692][693][694][695].

3) Severity: major

- 4) Onset: unspecified
- 5) Substantiation: probable
- 6) Clinical Management: Use caution when prescribing NSAIDs to patients who take SSRIs. Concomitant use of NSAIDs and SSRIs may cause an increased risk of bleeding[688][689]. 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 (GI) bleeding and this effect is potentiated by concurrent use of NSAIDs or low-dose [aspirin](#). Hospitalizations for [upper GI 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 (CI), 2.7 to 4.7). Combined use of an SSRI and NSAIDs or low-dose [aspirin](#) increased the risk to 12.2 (95% CI, 7.1 to 19.5) and 5.2 (95% CI, 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 [690].

b) Coadministration of ketorolac with psychoactive drugs (such as [fluoxetine](#)) has been associated with hallucinations in some patients [691].

3.5.1.AV] Clonixin

- 1) Interaction Effect: an increased risk of bleeding
- 2) Summary: Caution is recommended with the concomitant use of NSAIDs and SSRIs due to an increased risk of [gastrointestinal bleeding](#)[688][689]. Bleeding events have included [epistaxis](#), ecchymosis, [hematoma](#), [petechiae](#), and life-threatening hemorrhages [692][693][694][695].
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: probable
- 6) Clinical Management: Use caution when prescribing NSAIDs to patients who take SSRIs. Concomitant use of NSAIDs and SSRIs may cause an increased risk of bleeding[688][689]. 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 (GI) bleeding and this effect is potentiated by concurrent use of NSAIDs or low-dose [aspirin](#). Hospitalizations for [upper GI 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 (CI), 2.7 to 4.7). Combined use of an SSRI and NSAIDs or low-dose [aspirin](#) increased the risk to 12.2 (95% CI, 7.1 to 19.5) and 5.2 (95% CI, 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 [690].

b) Coadministration of ketorolac with psychoactive drugs (such as [fluoxetine](#)) has been associated with hallucinations in some patients [691].

3.5.1.AW] [Clopidogrel](#)

- 1) Interaction Effect: contradictory effects of a reduction in clinical efficacy of [clopidogrel](#) and also an increased risk of bleeding
- 2) Summary: [Clopidogrel](#), a prodrug, is metabolized to its active metabolite by CYP2C19. Although the interaction between [clopidogrel](#) and [fluoxetine](#) has not been studied, coadministration of [omeprazole](#), a CYP2C19 inhibitor like [fluoxetine](#), with [clopidogrel](#) resulted in reduced [clopidogrel](#) active metabolite concentrations and reduced [platelet](#) inhibition. A similar interaction would be expected between [clopidogrel](#) and other CYP2C19 inhibitors[335]. Additionally, the release of serotonin by [platelets](#) is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of some 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 [336]. Because of the potential for reduced [clopidogrel](#) efficacy, concomitant use of CYP2C19 inhibitors, including [fluoxetine](#), with [clopidogrel](#) should be avoided [335].
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Concomitant use of [clopidogrel](#) and a CYP2C19 inhibitor, such as [fluoxetine](#), should be avoided due to the potential for reduced [clopidogrel](#) efficacy[335] and an increased risk of bleeding that has been demonstrated with the concomitant use of some SSRIs and antiplatelet drugs [336].
- 7) Probable Mechanism: inhibition of CYP2C19-mediated [clopidogrel](#) metabolism to active metabolite by [fluoxetine](#); interference of serotonin reuptake to [platelets](#) by [fluoxetine](#) on hemostasis
- 8) Literature Reports

a) Exposure to the active metabolite and [platelet](#) inhibition of [clopidogrel](#) were significantly decreased following administration of [omeprazole](#) (another CYP2C19 inhibitor like [fluoxetine](#)) compared with the same dose of [clopidogrel](#) given alone for 5 days in a clinical study. The Cmax and AUC of the active metabolite of [clopidogrel](#) was decreased by 46% and 45%, respectively, on day 1 and 42% and 40%, respectively, on day 5 when subjects were coadministered [clopidogrel](#) at a 300-mg loading dose followed by 75 mg/day and [omeprazole](#) 80 mg/day. Inhibition of [platelet](#) aggregation also decreased by 39% on day 1 and 21% on day 5 when [clopidogrel](#) and [omeprazole](#) were given concomitantly. Results were similar when [clopidogrel](#) and [omeprazole](#) were given at the same doses administered 12 hours apart in another study. This indicates that an interaction between [clopidogrel](#) and [omeprazole](#) is not prevented even when administering the drugs at different times [335].

3.5.1.AX] 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[735][736][737][738][739][740]. 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](#) [730]. [Serotonin syndrome](#) is a condition of serotonergic hyperstimulation and manifests as restlessness, myoclonus, changes in mental status, hyperreflexia, diaphoresis, shivering, and tremor [730]. 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 [731].

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%) [732]. 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 [733]. 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 [734]. 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.AY] [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[485][486][487][488]. Certain adverse effects associated with [clozapine](#) are dose-dependent, including sedation [489] and seizures [490], 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.

7j) Probable Mechanism: inhibition by fluoxetine of N-dealkylation and N-oxidation of clozapine via the cytochrome P450 2D6 enzymatic pathway

8j) 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 [481].

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 [482].

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 [483].

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 [484].

3.5.1.AZ] Cyclobenzaprine

1j) Interaction Effect: an increased risk of QT prolongation

2j) 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[470].

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 [469].

3.5.1.BA] [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](#)[666][667][668][669].

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 [662][663][664]. 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 [662]. 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](#) [665]. [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 [cypheptadine](#) was discontinued. She declined to be rechallenged.

3.5.1.BB] [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[586][587][124]. 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](#) [124].

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[124].

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 [584]. In addition, both [fluoxetine](#) and [warfarin](#) are tightly bound to albumin. In combination, the possibility for protein-binding displacement of either drug is present [585].

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 [586].

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 [587].

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](#) [588][589].

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 [590].

3.5.1.BC] [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[586][587][124]. 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](#) [124].

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[124].

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 [584]. In addition, both [fluoxetine](#) and [warfarin](#) are tightly bound to albumin. In combination, the possibility for protein-binding displacement of either drug is present [585].

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 [586].

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 [587].

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](#) [588][589].

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 [590].

3.5.1.BD] 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[586][587][124]. 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](#) [124].

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[124].

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 [584]. In addition, both [fluoxetine](#) and [warfarin](#) are tightly bound to albumin. In combination, the possibility for protein-binding displacement of either drug is present [585].

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 [586].

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 [587].

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](#) [588][589].

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 [590].

3.5.1.BE] 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](#) [504]. DHEA was also noted to cause mania in a patient with no previous personal or family history of [bipolar disorder](#) [505]. Elevated DHEA levels have been found in patients with mental disorders; DHEA suppression has led to improvement in psychotic symptoms [506]. DHEA possesses proserotonergic activity which may predispose patients to [manic episodes](#) [507]. DHEA is a precursor to androgenic steroids, which in high doses may precipitate mania [505]. 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](#) [503].

3.5.1.BF] 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 [614]. 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.BG] 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[586][587][124]. 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](#) [124].

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[124].

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 [584]. In addition, both [fluoxetine](#) and [warfarin](#) are tightly bound to albumin. In combination, the possibility for protein-binding displacement of either drug is present [585].

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 [586].

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 [587].

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](#) [588][589].

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 [590].

3.5.1.BH] [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[680][681]. 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 [682]. In addition, concurrent use of [fluoxetine](#) and TCAs such as [desipramine](#), [nortriptyline](#), and [imipramine](#) has resulted in significant increases in TCA concentrations [683][683][684][685][686][687].

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 [674].

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 [675].

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 [676].

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 [677].

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 [678].

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 [679].

3.5.1.BI] 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[586][587][124]. 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](#) [124].

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[124].

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 [584]. In addition,

both [fluoxetine](#) and [warfarin](#) are tightly bound to albumin. In combination, the possibility for protein-binding displacement of either drug is present [585].

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 [586].

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 [587].

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](#) [588][589].

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 [590].

3.5.1.BJ] 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[704].

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[704].

7) Probable Mechanism: additive serotonergic effect

3.5.1.BK] 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](#)[550]. [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 [551]. Dexfenfluramine should not be used in combination with [fluoxetine](#) [552].

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.BL] Dexketoprofen

1) Interaction Effect: an increased risk of bleeding

2) Summary: Caution is recommended with the concomitant use of NSAIDs and SSRIs due to an increased risk of [gastrointestinal bleeding](#)[688][689]. Bleeding events have included [epistaxis](#), ecchymosis, [hematoma](#), [petechiae](#), and life-threatening hemorrhages [692][693][694][695].

3) Severity: major

4) Onset: unspecified

5) Substantiation: probable

6) Clinical Management: Use caution when prescribing NSAIDs to patients who take SSRIs. Concomitant use of NSAIDs and SSRIs may cause an increased risk of bleeding[688][689]. 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 (GI) bleeding and this effect is potentiated by concurrent use of NSAIDs or low-dose [aspirin](#). Hospitalizations for [upper GI 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 (CI), 2.7 to 4.7). Combined use of an SSRI and NSAIDs or low-dose [aspirin](#) increased the risk to 12.2 (95% CI, 7.1 to 19.5) and 5.2 (95% CI, 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 [690].

b)) Coadministration of ketorolac with psychoactive drugs (such as [fluoxetine](#)) has been associated with hallucinations in some patients [691].

3.5.1.BM] [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[542]. [Fluoxetine](#) inhibits [dextromethorphan](#) metabolism [543]. 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 [544], 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 [545][546].

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 [539]. 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](#) [540]. 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 [541].

3.5.1.BN] [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[289]. Conversely, a controlled study observed significant decreases in psychomotor performance when [diazepam](#) was added to [fluoxetine](#) [290]. The metabolism of [diazepam](#) is mediated by several P450 enzymes which may be inhibited by [fluoxetine](#) [291][292][293]. 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 [282].

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 [283].

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 [284] [285][286].

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 [287].

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 [288].

3.5.1.BO| 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[680][681]. 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 [682]. In addition, concurrent use of [fluoxetine](#) and TCAs such as [desipramine](#), [nortriptyline](#), and [imipramine](#) has resulted in significant increases in TCA concentrations [683][683][684][685][686][687].

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 [674].

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 [675].

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 [676].

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 [677].

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 [678].

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 [679].

3.5.1.BP] [Diclofenac](#)

1) Interaction Effect: an increased risk of bleeding

2) Summary: Caution is recommended with the concomitant use of NSAIDs and SSRIs due to an increased risk of [gastrointestinal bleeding](#)[688][689]. Bleeding events have included [epistaxis](#), ecchymosis, [hematoma](#), [petechiae](#), and life-threatening hemorrhages [692][693][694][695].

3) Severity: major

4) Onset: unspecified

5) Substantiation: probable

6) Clinical Management: Use caution when prescribing NSAIDs to patients who take SSRIs. Concomitant use of NSAIDs and SSRIs may cause an increased risk of bleeding[688][689]. 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 (GI) bleeding and this effect is potentiated by concurrent use of NSAIDs or low-dose [aspirin](#). Hospitalizations for [upper GI 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 (CI), 2.7 to 4.7). Combined use of an SSRI and NSAIDs or low-dose [aspirin](#) increased the risk to 12.2 (95% CI, 7.1 to 19.5) and 5.2 (95% CI, 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 [690].

b) Coadministration of ketorolac with psychoactive drugs (such as [fluoxetine](#)) has been associated with hallucinations in some patients [691].

3.5.1.BQ| 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[586][587][124]. 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](#) [124].

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[124].

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 [584]. In addition, both [fluoxetine](#) and [warfarin](#) are tightly bound to albumin. In combination, the possibility for protein-binding displacement of either drug is present [585].

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 [586].

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 [587].

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](#) [588][589].

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 [590].

3.5.1.BR] [Diflunisal](#)

1)) Interaction Effect: an increased risk of bleeding

2)) Summary: Caution is recommended with the concomitant use of NSAIDs and SSRIs due to an increased risk of [gastrointestinal bleeding](#)[688][689]. Bleeding events have included [epistaxis](#), ecchymosis, [hematoma](#), [petechiae](#), and life-threatening hemorrhages [692][693][694][695].

3)) Severity: major

4)) Onset: unspecified

5)) Substantiation: probable

6)) Clinical Management: Use caution when prescribing NSAIDs to patients who take SSRIs. Concomitant use of NSAIDs and SSRIs may cause an increased risk of bleeding[688][689]. 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 (GI) bleeding and this effect is potentiated by concurrent use of NSAIDs or low-dose [aspirin](#). Hospitalizations for [upper GI 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 (CI), 2.7 to 4.7). Combined use of an SSRI and NSAIDs or low-dose [aspirin](#) increased the risk to 12.2 (95% CI, 7.1 to 19.5) and 5.2 (95% CI, 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 [690].

b)) Coadministration of ketorolac with psychoactive drugs (such as [fluoxetine](#)) has been associated with hallucinations in some patients [691].

3.5.1.BS] [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](#)[709].

- 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.BT] [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](#)[511].
- 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 [510].

3.5.1.BU] [Dihydroergotamine](#)

- 1) Interaction Effect: increased plasma concentrations of ergot derivatives and increased risk of [ergotism](#) (nausea, vomiting, vasospastic ischemia)
- 2) Summary: Concomitant use of [fluoxetine](#), a weak CYP3A4 inhibitor, and an ergot derivative may result in increased plasma concentrations of the ergot derivative due to inhibition of CYP3A4-mediated ergot metabolism. Because of the potential for serious toxicity including [vasospasm](#) can occur, use caution with the concurrent use of [fluoxetine](#) and ergot derivatives[252][251].
- 3) Severity: moderate
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: [Fluoxetine](#) may increase the plasma concentrations of ergot derivatives. Use caution when [fluoxetine](#) is coadministered with an ergot derivative, such as [dihydroergotamine](#), [ergotamine](#), or [methylergonovine](#), due to the potential for serious toxicity including [vasospasm](#) that can occur[251][252].

7J) Probable Mechanism: inhibition of CYP3A4-mediated ergot metabolism by [fluoxetine](#)

3.5.1.BV] [Dipyridamole](#)

1J) Interaction Effect: an increased risk of bleeding

2J) Summary: The release of serotonin by [platelets](#) is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of selective serotonin reuptake inhibitors 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. Monitor patient for signs of increased bleeding when [fluoxetine](#) is administered with [dipyridamole](#) concomitantly[344].

3J) Severity: major

4J) Onset: unspecified

5J) Substantiation: probable

6J) Clinical Management: When [dipyridamole](#) and [fluoxetine](#) are given concurrently, monitor patient for signs of increased bleeding[344].

7J) Probable Mechanism: unknown

3.5.1.BW] [Dipyrrone](#)

1J) Interaction Effect: an increased risk of bleeding

2J) Summary: Caution is recommended with the concomitant use of NSAIDs and SSRIs due to an increased risk of [gastrointestinal bleeding](#)[688][689]. Bleeding events have included [epistaxis](#), ecchymosis, [hematoma](#), [petechiae](#), and life-threatening hemorrhages [692][693][694][695].

3J) Severity: major

4J) Onset: unspecified

5J) Substantiation: probable

6J) Clinical Management: Use caution when prescribing NSAIDs to patients who take SSRIs. Concomitant use of NSAIDs and SSRIs may cause an increased risk of bleeding[688][689]. When an SSRI and an NSAID are given concurrently, monitor patient for signs of increased bleeding.

7J) Probable Mechanism: unknown

8J) Literature Reports

aJ) SSRIs increase the risk of upper gastrointestinal (GI) bleeding and this effect is potentiated by concurrent use of NSAIDs or low-dose [aspirin](#). Hospitalizations for [upper GI 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 (CI), 2.7 to 4.7). Combined use of an SSRI and NSAIDs or low-dose [aspirin](#) increased the risk to 12.2 (95% CI, 7.1 to 19.5) and 5.2 (95% CI, 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 [690].

bJ) Coadministration of ketorolac with psychoactive drugs (such as [fluoxetine](#)) has been associated with hallucinations in some patients [691].

3.5.1.BX] [Disopyramide](#)

1J) 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[417]. [Fluoxetine](#) has demonstrated QT prolongation at therapeutic doses [418].
- 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.BY] [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[382][383][384]. [Fluoxetine](#) has been shown to prolong the QTc interval at the recommended therapeutic dose [385].
- 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.BZ] [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[380]. [Fluoxetine](#) has been shown to prolong the QTc interval at the recommended therapeutic dose [381].
- 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.CA] [Domperidone](#)

- 1) Interaction Effect: increased domperidone exposure and an increased risk of QT prolongation
- 2) Summary: Coadministration of [fluoxetine](#), a potential CYP3A4 inhibitor[145], with domperidone may result in increased plasma concentrations of domperidone and may have an effect on QT interval prolongation. Concomitant use of domperidone and [fluoxetine](#) may increase the risk of serious cardiac events, including [ventricular arrhythmias](#) and sudden cardiac death, and therefore should be undertaken with caution. Case-control studies demonstrated an association of serious [ventricular arrhythmias](#) and sudden cardiac death, particularly with domperidone doses greater than 30 mg/day and in patients older than 60 years. Domperidone should be initiated at the lowest possible dose and titrated with caution. Discontinue domperidone if the patient experiences dizziness, palpitations, syncope, or seizure [714].
- 3) Severity: major

- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Use caution with the concomitant administration of domperidone and [fluoxetine](#) as this may result in increased plasma concentrations of domperidone and may increase the risk of serious cardiac effects, including [ventricular arrhythmias](#) and sudden cardiac death, particularly at domperidone doses greater than 30 mg/day and in patients older than 60 years. Domperidone should be initiated at the lowest possible dose and titrated with caution. Discontinue domperidone if the patient experiences dizziness, palpitations, syncope, or seizure[714].
- 7) Probable Mechanism: inhibition of CYP3A4-mediated domperidone metabolism

3.5.1.CB] [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[680][681]. 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 [682]. In addition, concurrent use of [fluoxetine](#) and TCAs such as [desipramine](#), [nortriptyline](#), and [imipramine](#) has resulted in significant increases in TCA concentrations [683][683][684][685][686][687].
- 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 [674].

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 [675].

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 [676].

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 [677].

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 [678].

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 [679].

3.5.1.CC] [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[553][554].

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.CD] [Droxicam](#)

1) Interaction Effect: an increased risk of bleeding

2) Summary: Caution is recommended with the concomitant use of NSAIDs and SSRIs due to an increased risk of [gastrointestinal bleeding](#)[688][689]. Bleeding events have included [epistaxis](#), [ecchymosis](#), [hematoma](#), [petechiae](#), and life-threatening hemorrhages [692][693][694][695].

3) Severity: major

4) Onset: unspecified

5) Substantiation: probable

6) Clinical Management: Use caution when prescribing NSAIDs to patients who take SSRIs. Concomitant use of NSAIDs and SSRIs may cause an increased risk of bleeding[688][689]. 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 (GI) bleeding and this effect is potentiated by concurrent use of NSAIDs or low-dose [aspirin](#). Hospitalizations for [upper GI 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 (CI), 2.7 to 4.7). Combined use of an SSRI and NSAIDs or low-dose [aspirin](#) increased the risk to 12.2 (95% CI, 7.1 to 19.5) and 5.2 (95% CI, 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 [690].

b)) Coadministration of ketorolac with psychoactive drugs (such as [fluoxetine](#)) has been associated with hallucinations in some patients [691].

3.5.1.CE] [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](#)[758].

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[758].

7)) Probable Mechanism: [fluoxetine](#) inhibition of CYP2D6-mediated [duloxetine](#) metabolism; additive serotonergic effects

3.5.1.CF] [Eletriptan](#)

1)) Interaction Effect: increased risk of [serotonin syndrome](#)

2)) Summary: Concomitant use of [eletriptan](#) with an SSRI may result in [serotonin syndrome](#) due to additive serotonergic effects. Cases of life-threatening [serotonin syndrome](#) have been reported following coadministration of triptans and SSRIs. Symptoms may include agitation, hallucinations, coma, incoordination, [tachycardia](#), labile blood pressure, [hyperthermia](#), hyperreflexia, nausea, vomiting, and diarrhea. If treatment with [eletriptan](#) and an SSRI is required, the patient should be monitored closely for signs and symptoms of [serotonin syndrome](#), particularly during treatment initiation and dose increases[768].

3)) Severity: major

4)) Onset: unspecified

5)) Substantiation: theoretical

6)) Clinical Management: Concomitant use of [eletriptan](#) and an SSRI may result in [serotonin syndrome](#). Cases of life-threatening [serotonin syndrome](#) have been reported following coadministration of triptans and SSRIs. If concomitant use is warranted, closely observe the patient for signs and symptoms of [serotonin syndrome](#), especially during treatment initiation and dose increases[768].

7) Probable Mechanism: additive serotonergic effects

3.5.1.CG| 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](#)[270][271].

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.CH| 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[586][587][124]. 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](#) [124].

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[124].

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 [584]. In addition, both [fluoxetine](#) and [warfarin](#) are tightly bound to albumin. In combination, the possibility for protein-binding displacement of either drug is present [585].

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 [586].

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 [587].

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](#) [588][589].

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 [590].

3.5.1.CI] [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 selective serotonin reuptake inhibitors 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. Monitor patient for signs of increased bleeding when [fluoxetine](#) is administered with [eptifibatide](#) concomitantly[344].

3) Severity: major

4) Onset: unspecified

5) Substantiation: probable

6) Clinical Management: When [eptifibatide](#) and [fluoxetine](#) are given concurrently, monitor patient for signs of increased bleeding[344].

7) Probable Mechanism: unknown

3.5.1.CJ] [Ergoloid Mesylates](#)

1) Interaction Effect: increased plasma concentrations of ergot derivatives and increased risk of [ergotism](#) (nausea, vomiting, vasospastic ischemia)

2)) Summary: Concomitant use of [fluoxetine](#), a weak CYP3A4 inhibitor, and an ergot derivative may result in increased plasma concentrations of the ergot derivative due to inhibition of CYP3A4-mediated ergot metabolism. Because of the potential for serious toxicity including [vasospasm](#) can occur, use caution with the concurrent use of [fluoxetine](#) and ergot derivatives[252][251].

3)) Severity: moderate

4)) Onset: unspecified

5)) Substantiation: theoretical

6)) Clinical Management: [Fluoxetine](#) may increase the plasma concentrations of ergot derivatives. Use caution when [fluoxetine](#) is coadministered with an ergot derivative, such as [dihydroergotamine](#), [ergotamine](#), or [methylergonovine](#), due to the potential for serious toxicity including [vasospasm](#) that can occur[251][252].

7)) Probable Mechanism: inhibition of CYP3A4-mediated ergot metabolism by [fluoxetine](#)

3.5.1.CK] [Ergonovine](#)

1)) Interaction Effect: increased plasma concentrations of ergot derivatives and increased risk of [ergotism](#) (nausea, vomiting, vasospastic ischemia)

2)) Summary: Concomitant use of [fluoxetine](#), a weak CYP3A4 inhibitor, and an ergot derivative may result in increased plasma concentrations of the ergot derivative due to inhibition of CYP3A4-mediated ergot metabolism. Because of the potential for serious toxicity including [vasospasm](#) can occur, use caution with the concurrent use of [fluoxetine](#) and ergot derivatives[252][251].

3)) Severity: moderate

4)) Onset: unspecified

5)) Substantiation: theoretical

6)) Clinical Management: [Fluoxetine](#) may increase the plasma concentrations of ergot derivatives. Use caution when [fluoxetine](#) is coadministered with an ergot derivative, such as [dihydroergotamine](#), [ergotamine](#), or [methylergonovine](#), due to the potential for serious toxicity including [vasospasm](#) that can occur[251][252].

7)) Probable Mechanism: inhibition of CYP3A4-mediated ergot metabolism by [fluoxetine](#)

3.5.1.CL] [Ergotamine](#)

1)) Interaction Effect: increased plasma concentrations of ergot derivatives and increased risk of [ergotism](#) (nausea, vomiting, vasospastic ischemia)

2)) Summary: Concomitant use of [fluoxetine](#), a weak CYP3A4 inhibitor, and an ergot derivative may result in increased plasma concentrations of the ergot derivative due to inhibition of CYP3A4-mediated ergot metabolism. Because of the potential for serious toxicity including [vasospasm](#) can occur, use caution with the concurrent use of [fluoxetine](#) and ergot derivatives[252][251].

3)) Severity: moderate

4)) Onset: unspecified

5)) Substantiation: theoretical

6)) Clinical Management: [Fluoxetine](#) may increase the plasma concentrations of ergot derivatives. Use caution when [fluoxetine](#) is coadministered with an ergot derivative, such as [dihydroergotamine](#), [ergotamine](#), or [methylergonovine](#), due to the potential for serious toxicity including [vasospasm](#) that can occur[251][252].

7)) Probable Mechanism: inhibition of CYP3A4-mediated ergot metabolism by [fluoxetine](#)

3.5.1.CM] [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[763]. [Erythromycin](#) has demonstrated QTc prolongation in combination with other drugs that prolong the QT interval [764]. [Fluoxetine](#) has been associated with QT prolongation [765]. 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 [762].

3.5.1.CN] Escitalopram

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

2) Summary: Concurrent use of an SSRI together with another SSRI may result in [serotonin syndrome](#), which may be life-threatening, and is not recommended. 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[448][449][450][451]. If symptoms of [serotonin syndrome](#) occur, drug discontinuation is recommended [452][344]. Symptoms of [serotonin syndrome](#) include neuromuscular abnormalities (including hyperreflexia, 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 [248].

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Coadministration of an SSRI with another SSRI may result in a life-threatening condition called [serotonin syndrome](#) and is not recommended[448][449][450][451]. If these agents are used together, monitor closely for symptoms of [serotonin syndrome](#), especially during treatment initiation and dose increases, and discontinue therapy if symptoms occur [452][344]. Symptoms of [serotonin syndrome](#) include neuromuscular abnormalities (including hyperreflexia, 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 [248].

7J) Probable Mechanism: additive serotonergic effect

3.5.1.COJ Etodolac

1J) Interaction Effect: an increased risk of bleeding

2J) Summary: Caution is recommended with the concomitant use of NSAIDs and SSRIs due to an increased risk of [gastrointestinal bleeding](#)[688][689]. Bleeding events have included [epistaxis](#), ecchymosis, [hematoma](#), [petechiae](#), and life-threatening hemorrhages [692][693][694][695].

3J) Severity: major

4J) Onset: unspecified

5J) Substantiation: probable

6J) Clinical Management: Use caution when prescribing NSAIDs to patients who take SSRIs. Concomitant use of NSAIDs and SSRIs may cause an increased risk of bleeding[688][689]. When an SSRI and an NSAID are given concurrently, monitor patient for signs of increased bleeding.

7J) Probable Mechanism: unknown

8J) Literature Reports

aJ) SSRIs increase the risk of upper gastrointestinal (GI) bleeding and this effect is potentiated by concurrent use of NSAIDs or low-dose [aspirin](#). Hospitalizations for [upper GI 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 (CI), 2.7 to 4.7). Combined use of an SSRI and NSAIDs or low-dose [aspirin](#) increased the risk to 12.2 (95% CI, 7.1 to 19.5) and 5.2 (95% CI, 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 [690].

bJ) Coadministration of ketorolac with psychoactive drugs (such as [fluoxetine](#)) has been associated with hallucinations in some patients [691].

3.5.1.CPJ Etofenamate

1J) Interaction Effect: an increased risk of bleeding

2J) Summary: Caution is recommended with the concomitant use of NSAIDs and SSRIs due to an increased risk of [gastrointestinal bleeding](#)[688][689]. Bleeding events have included [epistaxis](#), ecchymosis, [hematoma](#), [petechiae](#), and life-threatening hemorrhages [692][693][694][695].

3J) Severity: major

4J) Onset: unspecified

5J) Substantiation: probable

6J) Clinical Management: Use caution when prescribing NSAIDs to patients who take SSRIs. Concomitant use of NSAIDs and SSRIs may cause an increased risk of bleeding[688][689]. When an SSRI and an NSAID are given concurrently, monitor patient for signs of increased bleeding.

7J) Probable Mechanism: unknown

8J) Literature Reports

aJ) SSRIs increase the risk of upper gastrointestinal (GI) bleeding and this effect is potentiated by concurrent use of NSAIDs or low-dose [aspirin](#). Hospitalizations for [upper GI 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 (CI), 2.7 to 4.7). Combined use of an SSRI and NSAIDs or low-dose [aspirin](#) increased the risk

to 12.2 (95% CI, 7.1 to 19.5) and 5.2 (95% CI, 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 [690].

b)) Coadministration of ketorolac with psychoactive drugs (such as [fluoxetine](#)) has been associated with hallucinations in some patients [691].

3.5.1.CQ] Felbinac

1)) Interaction Effect: an increased risk of bleeding

2)) Summary: Caution is recommended with the concomitant use of NSAIDs and SSRIs due to an increased risk of [gastrointestinal bleeding](#)[688][689]. Bleeding events have included [epistaxis](#), ecchymosis, [hematoma](#), [petechiae](#), and life-threatening hemorrhages [692][693][694][695].

3)) Severity: major

4)) Onset: unspecified

5)) Substantiation: probable

6)) Clinical Management: Use caution when prescribing NSAIDs to patients who take SSRIs. Concomitant use of NSAIDs and SSRIs may cause an increased risk of bleeding[688][689]. 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 (GI) bleeding and this effect is potentiated by concurrent use of NSAIDs or low-dose [aspirin](#). Hospitalizations for [upper GI 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 (CI), 2.7 to 4.7). Combined use of an SSRI and NSAIDs or low-dose [aspirin](#) increased the risk to 12.2 (95% CI, 7.1 to 19.5) and 5.2 (95% CI, 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 [690].

b)) Coadministration of ketorolac with psychoactive drugs (such as [fluoxetine](#)) has been associated with hallucinations in some patients [691].

3.5.1.CR] Fenbufen

1)) Interaction Effect: an increased risk of bleeding

2)) Summary: Caution is recommended with the concomitant use of NSAIDs and SSRIs due to an increased risk of [gastrointestinal bleeding](#)[688][689]. Bleeding events have included [epistaxis](#), ecchymosis, [hematoma](#), [petechiae](#), and life-threatening hemorrhages [692][693][694][695].

3)) Severity: major

4)) Onset: unspecified

5)) Substantiation: probable

6)) Clinical Management: Use caution when prescribing NSAIDs to patients who take SSRIs. Concomitant use of NSAIDs and SSRIs may cause an increased risk of bleeding[688][689]. 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 (GI) bleeding and this effect is potentiated by concurrent use of NSAIDs or low-dose [aspirin](#). Hospitalizations for [upper GI 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 (CI), 2.7 to 4.7). Combined use of an SSRI and NSAIDs or low-dose [aspirin](#) increased the risk to 12.2 (95% CI, 7.1 to 19.5) and 5.2 (95% CI, 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 [690].

b) Coadministration of ketorolac with psychoactive drugs (such as [fluoxetine](#)) has been associated with hallucinations in some patients [691].

3.5.1.CS| [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](#)[579]. [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 [580]. 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.CT| [Fenoprofen](#)

1) Interaction Effect: an increased risk of bleeding

2) Summary: Caution is recommended with the concomitant use of NSAIDs and SSRIs due to an increased risk of [gastrointestinal bleeding](#)[688][689]. Bleeding events have included [epistaxis](#), ecchymosis, [hematoma](#), [petechiae](#), and life-threatening hemorrhages [692][693][694][695].

3) Severity: major

4) Onset: unspecified

5) Substantiation: probable

6) Clinical Management: Use caution when prescribing NSAIDs to patients who take SSRIs. Concomitant use of NSAIDs and SSRIs may cause an increased risk of bleeding[688][689]. 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 (GI) bleeding and this effect is potentiated by concurrent use of NSAIDs or low-dose [aspirin](#). Hospitalizations for [upper GI 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 (CI), 2.7 to 4.7). Combined use of an SSRI and NSAIDs or low-dose **aspirin** increased the risk to 12.2 (95% CI, 7.1 to 19.5) and 5.2 (95% CI, 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 [690].

b) Coadministration of ketorolac with psychoactive drugs (such as **fluoxetine**) has been associated with hallucinations in some patients [691].

3.5.1.CU] **Fentanyl**

1) Interaction Effect: increased risk of **serotonin syndrome** or neuroleptic malignant syndrome-like reactions

2) Summary: **Fentanyl** has been associated with **serotonin syndrome**, when used in combination with other serotonergic drugs, including SSRIs[430][431][433] and ergot alkaloids [432]. Coadministration of **fluoxetine** with other serotonergic drugs [107], such as **fentanyl**, may result in **serotonin syndrome** or **neuroleptic malignant syndrome** (NMS)-like reactions. Symptoms include mental status changes (agitation, hallucinations, or coma), autonomic instability (**tachycardia**, labile blood pressure, or **hyperthermia**), neuromuscular effects (hyperreflexia or incoordination), or gastrointestinal symptoms (nausea, vomiting, or diarrhea). Use caution when using both medications together and discontinue therapy if signs or symptoms of **serotonin syndrome** or NMS-like reactions occur [107].

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Use caution when using **fluoxetine** with other serotonergic drugs[107], such as **fentanyl** [430][431][432][433], due to the potential for **serotonin syndrome** or **neuroleptic malignant syndrome** (NMS)-like reactions. Symptoms include mental status changes (agitation, hallucinations, or coma), autonomic instability (**tachycardia**, labile blood pressure, or **hyperthermia**), neuromuscular effects (hyperreflexia or incoordination), or gastrointestinal symptoms (nausea, vomiting, or diarrhea). Treatment should be discontinued in any patient exhibiting signs or symptoms of **serotonin syndrome** or NMS-like reactions [107].

7) Probable Mechanism: additive serotonergic effect

8) Literature Reports

a) A 65-year-old woman treated with **citalopram** for depression experienced **serotonin syndrome** following initiation of **fentanyl** patch. She was recently diagnosed with myelodysplastic/myeloproliferative disease and her regular medication regimen included **rabeprazole**, **tolterodine**, **hydrocodone**, and over-the-counter NSAIDs. She was hospitalized upon presentation of abdominal pain and worsening back pain, and a spontaneous retroperitoneal hemorrhage was discovered. While hospitalized, her worsening back pain was treated with **fentanyl** transdermal patch (25 mcg/hr). Within 24 hours of **fentanyl** initiation, she progressively developed increasing confusion, agitation, combativeness, tremors in the upper extremities, myoclonic jerks, hyperreflexia, and unsteady gait; consistent with **serotonin syndrome**. **Tachycardia** was also observed (110 to 120 beats per minute). A **CT scan** and laboratory values did not reveal any abnormalities. **Fentanyl** was discontinued, and all of her symptoms resolved within 24 to 36 hours. Her symptoms did not recur with initiation of **oxycodone** for the treatment of the back pain. The association of this **serotonin syndrome** with the coadministration of **fentanyl**

and [citalopram](#) in this case was deemed probable based on the Naranjo adverse event probability scale [433].

b) Serotonin syndrome associated with intrathecal [fentanyl](#) was observed in a 25-year-old man also using an ergot alkaloid and multiple illicit drugs. The patient received [spinal anesthesia](#) at the L3-L4 interspace with [bupivacaine](#) 0.5% and [fentanyl](#) 20 mcg. Ten minutes after the [spinal injection](#), sensorial block was achieved; however, the patient also became agitated and experienced excessive shivering and rigidity in the upper extremities and tremor. He later developed visual and auditory hallucinations after receiving IV [midazolam](#) (5 mg) for sedation and progressive muscle rigidity while receiving a [propofol](#) infusion for hallucinations. Following the induction of general [anesthesia](#) with [propofol](#) (1.5 mg/kg), [fentanyl](#) (2 mcg/kg) and vecuronium (0.1 mg/kg), his body temperature gradually increased and flushing was detected on the upper body, end-tidal carbon dioxide increased to 46 mmHg, heart rate increased to 140 beats per minute, and extensive external cooling was required for the duration of the procedure. With continued external cooling for 2 hours postoperatively, the patients body temperature normalized, but the heart rate and blood pressure remained elevated. Intravenous [morphine](#), [diphenhydramine](#), and [dexamethasone](#) were administered, the erythema disappeared, and blood pressure and heart rate eventually normalized. The duration between the adverse event and exposure to the other substances were 24 hours for the [dihydroergotamine](#), 2 weeks for marijuana, and 3 weeks for 3,4-methylenedioxymethamphetamine [432].

c) Serotonin syndrome associated with [fentanyl](#) use during an [esophagogastroduodenoscopy](#) was reported in a 39-year-old woman also taking [sertraline](#) 100 mg daily as an outpatient. The patient initially presented with [hematemesis](#) and a history of [alcoholic cirrhosis](#). Prior to the [esophagogastroduodenoscopy](#), an [octreotide](#) and [pantoprazole](#) drip was started, 2 doses of [fentanyl](#) 50 micrograms, and 2 doses of [midazolam](#) 1 mg were administered. The patient became somnolent and extremely rigid in all four extremities following the procedure, and vecuronium and [etomidate](#) were given for immediate intubation. The rigidity progressed with diffuse diaphoresis, horizontal [roving eye movements](#), and a fever of 105 degrees F. Due to the potential for seizure activity, [lorazepam](#) 2 mg IV was given with no improvement and a [propofol](#) drip was started for continued sedation during intubation. A CPK value of 2800 units/L and an ammonia level of 340 micromols/L indicated [rhabdomyolysis](#). An acute intracranial process was ruled out on a [CT scan](#) of the brain and the neurology team made the diagnosis of [serotonin syndrome](#) secondary to an interaction between [fentanyl](#) and [sertraline](#). [Propofol](#) was continued for sedation and the patient received supportive treatment with a cooling blanket and [cyproheptadine](#). After 3 days, the patient's temperature and CPK level normalized and she later extubated with no further complications [431].

d) Serotonin syndrome following the administration of IV [fentanyl](#) during surgical procedures was reported in 2 patients also taking SSRIs ([sertraline](#) and [escitalopram](#)). The first patient received IV [fentanyl](#) (50 micrograms), [midazolam](#) (2 mg), and 2 doses [propofol](#) (60 mg and 40 mg) in an [outpatient surgery](#) center prior to a [carpal tunnel release](#) procedure. Postoperatively the patient began shivering and became increasingly agitated for which she was transferred to the emergency department. On presentation the patient was combative, diaphoretic, confused, was unable to follow commands, tachycardic, hypertensive, had hyperreflexia, and ankle clonus. Baseline [creatinine](#) kinase rose to 613 units/L on day 2 of hospitalization. The toxicology service treated her with escalating doses of benzodiazepines with no improvement. The patient was subsequently intubated and sedated with a continuous [propofol](#) infusion. After 2 days the patient was extubated and by day 3 all symptoms had resolved and the patient was discharged home. The second patient was a 59-year-old woman admitted for an [omentectomy](#) for which she received IV [fentanyl](#) 250

micrograms, [etomidate](#), vecuronium, [morphine](#) and cephazolin. Following [extubation](#) the patient became hypoxic and acidotic and was reintubated and transferred to the ICU. On postoperative day 1 she was extubated and later became tachycardic and was unable to follow commands. On examination the patient was agitated and diaphoretic, had patellar hyperreflexia and a bilateral 3 to 4 beat ankle clonus. Laboratory evaluation was remarkable for a peak [creatinine kinase](#) of 1161 units/L on postoperative day 2. The patient was treated with [lorazepam](#) and [cyproheptadine](#) with resolution of symptoms after 3 days [430].

3.5.1.CV] Fentiazac

- 1) Interaction Effect: an increased risk of bleeding
- 2) Summary: Caution is recommended with the concomitant use of NSAIDs and SSRIs due to an increased risk of [gastrointestinal bleeding](#)[688][689]. Bleeding events have included [epistaxis](#), ecchymosis, [hematoma](#), [petechiae](#), and life-threatening hemorrhages [692][693][694][695].
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: probable
- 6) Clinical Management: Use caution when prescribing NSAIDs to patients who take SSRIs. Concomitant use of NSAIDs and SSRIs may cause an increased risk of bleeding[688][689]. 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 (GI) bleeding and this effect is potentiated by concurrent use of NSAIDs or low-dose [aspirin](#). Hospitalizations for [upper GI 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 (CI), 2.7 to 4.7). Combined use of an SSRI and NSAIDs or low-dose [aspirin](#) increased the risk to 12.2 (95% CI, 7.1 to 19.5) and 5.2 (95% CI, 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 [690].

b) Coadministration of ketorolac with psychoactive drugs (such as [fluoxetine](#)) has been associated with hallucinations in some patients [691].

3.5.1.CW] [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[446]. [Fluoxetine](#) has been shown to prolong the QTc interval at the recommended therapeutic dose [447].
- 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.CX] Floctafenine

- 1) Interaction Effect: an increased risk of bleeding
- 2) Summary: Caution is recommended with the concomitant use of NSAIDs and SSRIs due to an increased risk of [gastrointestinal bleeding](#)[688][689]. Bleeding events have included [epistaxis](#), ecchymosis, [hematoma](#), [petechiae](#), and life-threatening hemorrhages [692][693][694][695].
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: probable
- 6) Clinical Management: Use caution when prescribing NSAIDs to patients who take SSRIs. Concomitant use of NSAIDs and SSRIs may cause an increased risk of bleeding[688][689]. 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 (GI) bleeding and this effect is potentiated by concurrent use of NSAIDs or low-dose [aspirin](#). Hospitalizations for [upper GI 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 (CI), 2.7 to 4.7). Combined use of an SSRI and NSAIDs or low-dose [aspirin](#) increased the risk to 12.2 (95% CI, 7.1 to 19.5) and 5.2 (95% CI, 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 [690].

b) Coadministration of ketorolac with psychoactive drugs (such as [fluoxetine](#)) has been associated with hallucinations in some patients [691].

3.5.1.CY] 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](#)[348][349]. [Fluoxetine](#) has been shown to prolong the QTc interval at the recommended therapeutic dose [350]. 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.CZ] Flufenamic Acid

- 1) Interaction Effect: an increased risk of bleeding
- 2) Summary: Caution is recommended with the concomitant use of NSAIDs and SSRIs due to an increased risk of [gastrointestinal bleeding](#)[688][689]. Bleeding events have included [epistaxis](#), ecchymosis, [hematoma](#), [petechiae](#), and life-threatening hemorrhages [692][693][694][695].
- 3) Severity: major
- 4) Onset: unspecified

5) Substantiation: probable

6) Clinical Management: Use caution when prescribing NSAIDs to patients who take SSRIs. Concomitant use of NSAIDs and SSRIs may cause an increased risk of bleeding[688][689]. 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 (GI) bleeding and this effect is potentiated by concurrent use of NSAIDs or low-dose aspirin. Hospitalizations for upper GI 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 (CI), 2.7 to 4.7). Combined use of an SSRI and NSAIDs or low-dose aspirin increased the risk to 12.2 (95% CI, 7.1 to 19.5) and 5.2 (95% CI, 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 [690].

b) Coadministration of ketorolac with psychoactive drugs (such as fluoxetine) has been associated with hallucinations in some patients [691].

3.5.1.DA] 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[729].

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 [728].

3.5.1.DB] Flurbiprofen

1) Interaction Effect: an increased risk of bleeding

2) Summary: Caution is recommended with the concomitant use of NSAIDs and SSRIs due to an increased risk of gastrointestinal bleeding[688][689]. Bleeding events have included epistaxis, ecchymosis, hematoma, petechiae, and life-threatening hemorrhages [692][693][694][695].

3) Severity: major

4) Onset: unspecified

5) Substantiation: probable

6) Clinical Management: Use caution when prescribing NSAIDs to patients who take SSRIs. Concomitant use of NSAIDs and SSRIs may cause an increased risk of bleeding[688][689]. 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 (GI) bleeding and this effect is potentiated by concurrent use of NSAIDs or low-dose aspirin. Hospitalizations for upper GI 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 (CI), 2.7 to 4.7). Combined use of an SSRI and NSAIDs or low-dose aspirin increased the risk to 12.2 (95% CI, 7.1 to 19.5) and 5.2 (95% CI, 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 [690].

b) Coadministration of ketorolac with psychoactive drugs (such as fluoxetine) has been associated with hallucinations in some patients [691].

3.5.1.DC] Fluvoxamine

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

2) Summary: Concurrent use of an SSRI together with another SSRI may result in serotonin syndrome, which may be life-threatening, and is not recommended. 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[448][449][450][451]. If symptoms of serotonin syndrome occur, drug discontinuation is recommended [452][344]. Symptoms of serotonin syndrome include neuromuscular abnormalities (including hyperreflexia, 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 [248].

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Coadministration of an SSRI with another SSRI may result in a life-threatening condition called serotonin syndrome and is not recommended[448][449][450][451]. If these agents are used together, monitor closely for symptoms of serotonin syndrome, especially during treatment initiation and dose increases, and discontinue therapy if symptoms occur [452][344]. Symptoms of serotonin syndrome include neuromuscular abnormalities (including hyperreflexia, 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 [248].

7) Probable Mechanism: additive serotonergic effect

3.5.1.DD] 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[586][587][124]. 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 [124].

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[124].

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 [584]. In addition, both fluoxetine and warfarin are tightly bound to albumin. In combination, the possibility for protein-binding displacement of either drug is present [585].

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 [586].

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 [587].

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 [588][589].

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 [590].

3.5.1.DE] 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[249][250].
- 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.DF] 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**[530]. Several case reports indicate that concurrent use of **fluoxetine** and **phenytoin** can result in significantly increased **phenytoin** serum levels leading to toxicity [531][532][533]. 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 [534].
- 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) [527].

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 [528]. 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 [528]. 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](#) [529].

3.5.1.DG| [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)[766]. Because [frovatriptan](#) is a 5HT 1B/1D agonist, a similar interaction between SSRIs and [frovatriptan](#) may occur [767]. 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](#) [259].

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).

7J) Probable Mechanism: additive pharmacologic effects resulting in excessive serotonergic stimulation

3.5.1.DHJ Furazolidone

1J) Interaction Effect: weakness, hyperreflexia, and incoordination

2J) 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[274].

3J) Severity: contraindicated

4J) Onset: delayed

5J) Substantiation: theoretical

6J) 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).

7J) Probable Mechanism: additive pharmacologic effects resulting in excessive serotonergic stimulation

3.5.1.DIJ Galantamine

1J) Interaction Effect: increased galantamine plasma concentrations

2J) 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[277].

3J) Severity: moderate

4J) Onset: unspecified

5J) Substantiation: probable

6J) 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[277].

7J) Probable Mechanism: inhibition of cytochrome CYP2D6-mediated galantamine metabolism

3.5.1.DJJ Gemifloxacin

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

2J) Summary: Gemifloxacin should be avoided in patients receiving fluoxetine. Gemifloxacin has the potential to prolong the QT interval in some patients[404]. Additive effects on QT prolongation may occur with the concomitant use of fluoxetine and gemifloxacin [130].

3J) Severity: major

4J) Onset: unspecified

5J) Substantiation: probable

6J) Clinical Management: The concurrent administration of two drugs that prolong the QT interval, such as gemifloxacin and fluoxetine, is not recommended.

7J) Probable Mechanism: additive effects on QT prolongation

3.5.1.DK] 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[463]. 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 [464][465], and has demonstrated serotonergic activity in animals [466] 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 [467]. Ginkgo biloba extract inhibited MAO-A/MAO-B in the rat brain in vitro [464][465] and MAO-B in human [platelets](#) in vitro [465]. No significant MAO inhibition was found in mice following oral consumption [468].

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 [462].

3.5.1.DL] Glimepiride

1) Interaction Effect: excessive [hypoglycemia](#)

2) Summary: The hypoglycemic potential of [glimepiride](#) may be increased with concomitant [fluoxetine](#) therapy. The mechanism of this interaction is unknown. During concurrent therapy, monitor blood glucose levels closely and observe for signs and symptoms of [hypoglycemia](#) (eg, fatigue, restlessness, malaise, irritability, weakness, increased perspiration). Lower doses of [glimepiride](#) may be required to avoid excessive [hypoglycemia](#). When [fluoxetine](#) therapy is withdrawn, careful monitoring of the patient is recommended to observe for loss of glucose control[549].

3) Severity: moderate

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: During concurrent therapy, monitor blood glucose levels closely and observe for signs and symptoms of [hypoglycemia](#) (eg, fatigue, restlessness, malaise, irritability, weakness, increased perspiration). Lower doses of [glimepiride](#) may be required to avoid excessive [hypoglycemia](#). When

[fluoxetine](#) therapy is withdrawn, careful monitoring of the patient is recommended to observe for loss of glucose control[549].

7J) Probable Mechanism: unknown

3.5.1.DM] [Glyburide](#)

1J) Interaction Effect: excessive [hypoglycemia](#)

2J) Summary: The hypoglycemic potential of [glyburide](#) may be increased with concomitant [fluoxetine](#) therapy. The mechanism of this interaction is unknown. Blood glucose levels should be closely monitored when [fluoxetine](#) is added in a patient receiving [glyburide](#). Lower doses of [glyburide](#) may be required to avoid excessive [hypoglycemia](#). When [fluoxetine](#) therapy is withdrawn, careful monitoring of the patient is recommended to observe for loss of glucose control[272].

3J) Severity: moderate

4J) Onset: unspecified

5J) Substantiation: theoretical

6J) Clinical Management: The hypoglycemic potential of [glyburide](#) may be increased with concomitant [fluoxetine](#) therapy. Blood glucose levels should be closely monitored when [fluoxetine](#) is added in a patient receiving [glyburide](#). Lower doses of [glyburide](#) may be required to avoid excessive [hypoglycemia](#). When [fluoxetine](#) therapy is withdrawn, careful monitoring of the patient is recommended to observe for loss of glucose control[272].

7J) Probable Mechanism: unknown

3.5.1.DN] [Halofantrine](#)

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

2J) 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[612][613].

3J) Severity: major

4J) Onset: unspecified

5J) Substantiation: theoretical

6J) Clinical Management: The concurrent administration of [halofantrine](#) and [fluoxetine](#) is not recommended.

7J) Probable Mechanism: additive cardiac effects

3.5.1.DO] [Haloperidol](#)

1J) Interaction Effect: [haloperidol](#) toxicity (pseudoparkinsonism, [akathisia](#), tongue stiffness) and an increased risk of [cardiotoxicity](#) (QT prolongation, [torsades de pointes](#), [cardiac arrest](#))

2J) Summary: [Haloperidol](#) is associated with QTc prolongation and [torsade de pointes](#)[517][518]. [Fluoxetine](#) has been shown to prolong the QTc interval at the recommended therapeutic dose [519]. 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 [520][521][522][523].

3J) Severity: major

4J) Onset: delayed

5J) Substantiation: probable

6J) Clinical Management: The concurrent administration of [fluoxetine](#) and [haloperidol](#) is not recommended.

- 7j) Probable Mechanism: inhibition of [haloperidol](#) metabolism by [fluoxetine](#); theoretical additive effects on QT prolongation
- 8j) 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](#) [513].

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 [514].

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 [515].

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](#) [516].

3.5.1.DP] [Halothane](#)

- 1j) Interaction Effect: an increased risk of [cardiotoxicity](#) (QT prolongation, [torsades de pointes](#), [cardiac arrest](#))
- 2j) 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](#)[591][592].
- 3j) Severity: major
- 4j) Onset: unspecified
- 5j) Substantiation: theoretical
- 6j) Clinical Management: The concurrent administration of [halothane](#) with other agents that can prolong the QT interval, such as [fluoxetine](#), is not recommended.
- 7j) Probable Mechanism: additive effect on QT interval

3.5.1.DQ| 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[586][587][124]. 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](#) [124].

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[124].

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 [584]. In addition, both [fluoxetine](#) and [warfarin](#) are tightly bound to albumin. In combination, the possibility for protein-binding displacement of either drug is present [585].

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 [586].

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 [587].

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](#) [588][589].

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 [590].

3.5.1.DR| 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[417]. [Fluoxetine](#) has demonstrated QT prolongation at therapeutic doses [418].
- 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.DS| 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)[296]. 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](#) [295].

3.5.1.DT] [Ibuprofen](#)

- 1) Interaction Effect: an increased risk of bleeding
- 2) Summary: Caution is recommended with the concomitant use of NSAIDs and SSRIs due to an increased risk of [gastrointestinal bleeding](#)[688][689]. Bleeding events have included [epistaxis](#), ecchymosis, [hematoma](#), [petechiae](#), and life-threatening hemorrhages [692][693][694][695].
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: probable
- 6) Clinical Management: Use caution when prescribing NSAIDs to patients who take SSRIs. Concomitant use of NSAIDs and SSRIs may cause an increased risk of bleeding[688][689]. 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 (GI) bleeding and this effect is potentiated by concurrent use of NSAIDs or low-dose [aspirin](#). Hospitalizations for [upper GI 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 (CI), 2.7 to 4.7). Combined use of an SSRI and NSAIDs or low-dose [aspirin](#) increased the risk to 12.2 (95% CI, 7.1 to 19.5) and 5.2 (95% CI, 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 [690].

b) Coadministration of ketorolac with psychoactive drugs (such as [fluoxetine](#)) has been associated with hallucinations in some patients [691].

3.5.1.DU] [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[382][383][384]. [Fluoxetine](#) has been shown to prolong the QTc interval at the recommended therapeutic dose [385].
- 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.DV] 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[273].
- 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[273].
- 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 [273].

3.5.1.DW] 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[680][681]. 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 [682]. In addition, concurrent use of [fluoxetine](#) and TCAs such as [desipramine](#), [nortriptyline](#), and [imipramine](#) has resulted in significant increases in TCA concentrations [683][683][684][685][686][687].
- 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 [674].

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 [675].

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 [676].

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 [677].

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 [678].

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 [679].

3.5.1.DX] [Indomethacin](#)

1) Interaction Effect: an increased risk of bleeding

2) Summary: Caution is recommended with the concomitant use of NSAIDs and SSRIs due to an increased risk of [gastrointestinal bleeding](#)[688][689]. Bleeding events have included [epistaxis](#), ecchymosis, [hematoma](#), [petechiae](#), and life-threatening hemorrhages [692][693][694][695].

3) Severity: major

4) Onset: unspecified

5) Substantiation: probable

6) Clinical Management: Use caution when prescribing NSAIDs to patients who take SSRIs. Concomitant use of NSAIDs and SSRIs may cause an increased risk of bleeding[688][689]. 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 (GI) bleeding and this effect is potentiated by concurrent use of NSAIDs or low-dose [aspirin](#). Hospitalizations for [upper GI 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 (CI), 2.7 to 4.7). Combined use of an SSRI and NSAIDs or low-dose [aspirin](#) increased the risk to 12.2 (95% CI, 7.1 to 19.5) and 5.2 (95% CI, 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 [690].

b) Coadministration of ketorolac with psychoactive drugs (such as [fluoxetine](#)) has been associated with hallucinations in some patients [691].

3.5.1.DY] Indoprofen

1) Interaction Effect: an increased risk of bleeding

2) Summary: Caution is recommended with the concomitant use of NSAIDs and SSRIs due to an increased risk of [gastrointestinal bleeding](#)[688][689]. Bleeding events have included [epistaxis](#), ecchymosis, [hematoma](#), [petechiae](#), and life-threatening hemorrhages [692][693][694][695].

3) Severity: major

4) Onset: unspecified

5) Substantiation: probable

6) Clinical Management: Use caution when prescribing NSAIDs to patients who take SSRIs. Concomitant use of NSAIDs and SSRIs may cause an increased risk of bleeding[688][689]. 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 (GI) bleeding and this effect is potentiated by concurrent use of NSAIDs or low-dose [aspirin](#). Hospitalizations for [upper GI 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 (CI), 2.7 to 4.7). Combined use of an SSRI and NSAIDs or low-dose [aspirin](#) increased the risk to 12.2 (95% CI, 7.1 to 19.5) and 5.2 (95% CI, 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 [690].

b) Coadministration of ketorolac with psychoactive drugs (such as [fluoxetine](#)) has been associated with hallucinations in some patients [691].

3.5.1.DZ] [Insulin](#) Aspart, Recombinant

1) Interaction Effect: [hypoglycemia](#)

2) Summary: [Fluoxetine](#) may increase the blood glucose-lowering effect of [insulin](#) and the susceptibility to [hypoglycemia](#)[436][437][438][439][440].

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.EA] Insulin Detemir

- 1) Interaction Effect: hypoglycemia
- 2) Summary: Fluoxetine may increase the blood glucose-lowering effect of insulin and the susceptibility to hypoglycemia[436][437][438][439][440].
- 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.EB] Insulin Glargine, Recombinant

- 1) Interaction Effect: hypoglycemia
- 2) Summary: Fluoxetine may increase the blood glucose-lowering effect of insulin and the susceptibility to hypoglycemia[436][437][438][439][440].
- 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.EC] Insulin Glulisine

- 1) Interaction Effect: hypoglycemia
- 2) Summary: Fluoxetine may increase the blood glucose-lowering effect of insulin and the susceptibility to hypoglycemia[436][437][438][439][440].
- 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.ED] Insulin Human Inhaled

- 1) Interaction Effect: hypoglycemia
- 2) Summary: Fluoxetine may increase the blood glucose-lowering effect of insulin and the susceptibility to hypoglycemia[436][437][438][439][440].
- 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.

7J) Probable Mechanism: additive [hypoglycemia](#)

3.5.1.EE] Iproniazid

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

2J) 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[374][375][376][377][378][379]. Concomitant use is contraindicated.

3J) Severity: contraindicated

4J) Onset: rapid

5J) Substantiation: probable

6J) 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.

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

8J) Literature Reports

aJ) Concomitant use of serotonin specific reuptake inhibitors and monoamine oxidase inhibitors can produce a toxic reaction known as [serotonin syndrome](#) [369]. [Serotonin syndrome](#) is a condition of serotonergic hyperstimulation and manifests as restlessness, myoclonus, changes in mental status, hyperreflexia, diaphoresis, shivering, and tremor [369]. If the syndrome is not recognized and correctly treated, death can result.

bJ) 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 [370].

cJ) 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%) [371]. All but one of the patients were taking other medications (ie, benzodiazepines, neuroleptics, anticonvulsants, antidepressants) that may have contributed to the adverse reactions.

dJ) Ten hours after her last dose of [fluoxetine](#), a 45-year-old woman began [tranylcypromine](#) therapy [372]. 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.

eJ) 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 [373].

3.5.1.EF] [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[643][644][645][646][647][648]. Concomitant use is contraindicated [649].

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](#) [638]. [Serotonin syndrome](#) is a condition of serotonergic hyperstimulation and manifests as restlessness, myoclonus, changes in mental status, hyperreflexia, diaphoresis, shivering, and tremor [638]. 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 [639].

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%) [640]. 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 [641]. 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 [642]. 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.EG] 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](#)[415][416].
- 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.EH] Isoxicam

- 1) Interaction Effect: an increased risk of bleeding
- 2) Summary: Caution is recommended with the concomitant use of NSAIDs and SSRIs due to an increased risk of [gastrointestinal bleeding](#)[688][689]. Bleeding events have included [epistaxis](#), ecchymosis, [hematoma](#), [petechiae](#), and life-threatening hemorrhages [692][693][694][695].
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: probable
- 6) Clinical Management: Use caution when prescribing NSAIDs to patients who take SSRIs. Concomitant use of NSAIDs and SSRIs may cause an increased risk of bleeding[688][689]. 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 (GI) bleeding and this effect is potentiated by concurrent use of NSAIDs or low-dose [aspirin](#). Hospitalizations for [upper GI 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 (CI), 2.7 to 4.7). Combined use of an SSRI and NSAIDs or low-dose [aspirin](#) increased the risk to 12.2 (95% CI, 7.1 to 19.5) and 5.2 (95% CI, 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 [690].

b) Coadministration of ketorolac with psychoactive drugs (such as [fluoxetine](#)) has been associated with hallucinations in some patients [691].

3.5.1.EI] 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[471].
- 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.EJ] [Ketoprofen](#)

- 1) Interaction Effect: an increased risk of bleeding
- 2) Summary: Caution is recommended with the concomitant use of NSAIDs and SSRIs due to an increased risk of [gastrointestinal bleeding](#)[688][689]. Bleeding events have included [epistaxis](#), ecchymosis, [hematoma](#), [petechiae](#), and life-threatening hemorrhages [692][693][694][695].
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: probable
- 6) Clinical Management: Use caution when prescribing NSAIDs to patients who take SSRIs. Concomitant use of NSAIDs and SSRIs may cause an increased risk of bleeding[688][689]. 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 (GI) bleeding and this effect is potentiated by concurrent use of NSAIDs or low-dose [aspirin](#). Hospitalizations for [upper GI 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 (CI), 2.7 to 4.7). Combined use of an SSRI and NSAIDs or low-dose [aspirin](#) increased the risk to 12.2 (95% CI, 7.1 to 19.5) and 5.2 (95% CI, 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 [690].

b) Coadministration of ketorolac with psychoactive drugs (such as [fluoxetine](#)) has been associated with hallucinations in some patients [691].

3.5.1.EK] [Ketorolac](#)

- 1) Interaction Effect: an increased risk of bleeding
- 2) Summary: Caution is recommended with the concomitant use of NSAIDs and SSRIs due to an increased risk of [gastrointestinal bleeding](#)[688][689]. Bleeding events have included [epistaxis](#), ecchymosis, [hematoma](#), [petechiae](#), and life-threatening hemorrhages [692][693][694][695].
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: probable
- 6) Clinical Management: Use caution when prescribing NSAIDs to patients who take SSRIs. Concomitant use of NSAIDs and SSRIs may cause an increased risk of bleeding[688][689]. 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 (GI) bleeding and this effect is potentiated by concurrent use of NSAIDs or low-dose [aspirin](#). Hospitalizations for [upper GI 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 (CI), 2.7 to 4.7). Combined use of an SSRI and NSAIDs or low-dose [aspirin](#) increased the risk to 12.2 (95% CI, 7.1 to 19.5) and 5.2 (95% CI, 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 [690].

b) Coadministration of ketorolac with psychoactive drugs (such as [fluoxetine](#)) has been associated with hallucinations in some patients [691].

3.5.1.EL] 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[341].

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.EM] 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[702][703]. 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.EN] 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](#)[408][409][407][161]. 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 [407]. 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 [161].

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](#)[407]. 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 [161]. 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 [248].

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 [408].

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](#) [409].

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 [410].

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](#) [411].

3.5.1.EO] [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[628]. 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](#) [629][630]. Two studies have failed to identify a pharmacokinetic interaction between [lithium](#) and [citalopram](#) [631][632]. 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 [633]. Concurrent use of fluvoxamine and lithium has led to case reports of increased lithium levels and neurotoxicity, serotonin syndrome, somnolence, and mania [628][634][635] [636]. No pharmacokinetic interference was apparent during a multiple-dose study of coadministered lithium and paroxetine [637]. 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) [634][628].

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 [620]. 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 [621].

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 [622].

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](#) [623].

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 [624].

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 [625].

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 [626].

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 [627].

3.5.1.EP] 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[446]. [Fluoxetine](#) has been shown to prolong the QTc interval at the recommended therapeutic dose [447].

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

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

3.5.1.EQJ Lorcaserin

- 1J) Interaction Effect: increased risk of [serotonin syndrome](#) ([hypertension](#), [tachycardia](#), [hyperthermia](#), myoclonus, mental status changes)
- 2J) Summary: Lorcaserin is a serotonergic drug and concomitant use with another agent that affects the serotonergic neurotransmitter system, such as an SSRI, serotonin-norepinephrine reuptake inhibitor, or tricyclic antidepressant, may result in an increased risk of [serotonin syndrome](#) and should be approached with extreme caution. [Serotonin syndrome](#) may be life threatening and symptoms may include mental status changes (eg, agitation, hallucinations, coma), autonomic instability (eg, [tachycardia](#), labile blood pressure, [hyperthermia](#)), neuromuscular aberrations (eg, hyperreflexia, incoordination), and/or gastrointestinal symptoms (eg, nausea, vomiting, diarrhea). If coadministration is required, monitor closely for signs and symptoms of [serotonin syndrome](#), especially during initiation of the coadministered drug and during dosage increases of either drug. If [serotonin syndrome](#) develops, discontinue both agents and initiate supportive symptomatic therapy[334].
- 3J) Severity: major
- 4J) Onset: unspecified
- 5J) Substantiation: theoretical
- 6J) Clinical Management: Use extreme caution with concomitant administration of lorcaserin and another serotonergic drug, such as an SSRI, serotonin-norepinephrine reuptake inhibitor, or tricyclic antidepressant, as this may result in additive serotonergic effects and may increase the risk of [serotonin syndrome](#). If coadministration is required, careful monitoring is recommended, especially during treatment initiation and dose increases. Drug discontinuation and supportive symptomatic treatment is recommended if [serotonin syndrome](#) develops[334].
- 7J) Probable Mechanism: additive serotonergic effects

3.5.1.ERJ Lornoxicam

- 1J) Interaction Effect: an increased risk of bleeding
- 2J) Summary: Caution is recommended with the concomitant use of NSAIDs and SSRIs due to an increased risk of [gastrointestinal bleeding](#)[688][689]. Bleeding events have included [epistaxis](#), ecchymosis, [hematoma](#), [petechiae](#), and life-threatening hemorrhages [692][693][694][695].
- 3J) Severity: major
- 4J) Onset: unspecified
- 5J) Substantiation: probable
- 6J) Clinical Management: Use caution when prescribing NSAIDs to patients who take SSRIs. Concomitant use of NSAIDs and SSRIs may cause an increased risk of bleeding[688][689]. When an SSRI and an NSAID are given concurrently, monitor patient for signs of increased bleeding.
- 7J) Probable Mechanism: unknown
- 8J) Literature Reports

aJ) SSRIs increase the risk of upper gastrointestinal (GI) bleeding and this effect is potentiated by concurrent use of NSAIDs or low-dose [aspirin](#). Hospitalizations for [upper GI 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 (CI), 2.7 to 4.7). Combined use of an SSRI and NSAIDs or low-dose [aspirin](#) increased the risk to 12.2 (95% CI, 7.1 to 19.5) and 5.2 (95% CI, 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 [690].

b)) Coadministration of ketorolac with psychoactive drugs (such as [fluoxetine](#)) has been associated with hallucinations in some patients [691].

3.5.1.ES] [Magnesium Salicylate](#)

1)) Interaction Effect: an increased risk of bleeding

2)) Summary: Caution is recommended with the concomitant use of NSAIDs and SSRIs due to an increased risk of [gastrointestinal bleeding](#)[688][689]. Bleeding events have included [epistaxis](#), ecchymosis, [hematoma](#), [petechiae](#), and life-threatening hemorrhages [692][693][694][695].

3)) Severity: major

4)) Onset: unspecified

5)) Substantiation: probable

6)) Clinical Management: Use caution when prescribing NSAIDs to patients who take SSRIs. Concomitant use of NSAIDs and SSRIs may cause an increased risk of bleeding[688][689]. 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 (GI) bleeding and this effect is potentiated by concurrent use of NSAIDs or low-dose [aspirin](#). Hospitalizations for [upper GI 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 (CI), 2.7 to 4.7). Combined use of an SSRI and NSAIDs or low-dose [aspirin](#) increased the risk to 12.2 (95% CI, 7.1 to 19.5) and 5.2 (95% CI, 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 [690].

b)) Coadministration of ketorolac with psychoactive drugs (such as [fluoxetine](#)) has been associated with hallucinations in some patients [691].

3.5.1.ET] [Meclofenamate](#)

1)) Interaction Effect: an increased risk of bleeding

2)) Summary: Caution is recommended with the concomitant use of NSAIDs and SSRIs due to an increased risk of [gastrointestinal bleeding](#)[688][689]. Bleeding events have included [epistaxis](#), ecchymosis, [hematoma](#), [petechiae](#), and life-threatening hemorrhages [692][693][694][695].

3)) Severity: major

4)) Onset: unspecified

5)) Substantiation: probable

6)) Clinical Management: Use caution when prescribing NSAIDs to patients who take SSRIs. Concomitant use of NSAIDs and SSRIs may cause an increased risk of bleeding[688][689]. 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 (GI) bleeding and this effect is potentiated by concurrent use of NSAIDs or low-dose [aspirin](#). Hospitalizations for [upper GI 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 (CI), 2.7 to 4.7). Combined use of an SSRI and NSAIDs or low-dose [aspirin](#) increased the risk to 12.2 (95% CI, 7.1 to 19.5) and 5.2 (95% CI, 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 [690].

b) Coadministration of ketorolac with psychoactive drugs (such as [fluoxetine](#)) has been associated with hallucinations in some patients [691].

3.5.1.EU] [Mefenamic Acid](#)

1) Interaction Effect: an increased risk of bleeding

2) Summary: Caution is recommended with the concomitant use of NSAIDs and SSRIs due to an increased risk of [gastrointestinal bleeding](#)[688][689]. Bleeding events have included [epistaxis](#), ecchymosis, [hematoma](#), [petechiae](#), and life-threatening hemorrhages [692][693][694][695].

3) Severity: major

4) Onset: unspecified

5) Substantiation: probable

6) Clinical Management: Use caution when prescribing NSAIDs to patients who take SSRIs. Concomitant use of NSAIDs and SSRIs may cause an increased risk of bleeding[688][689]. 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 (GI) bleeding and this effect is potentiated by concurrent use of NSAIDs or low-dose [aspirin](#). Hospitalizations for [upper GI 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 (CI), 2.7 to 4.7). Combined use of an SSRI and NSAIDs or low-dose [aspirin](#) increased the risk to 12.2 (95% CI, 7.1 to 19.5) and 5.2 (95% CI, 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 [690].

b) Coadministration of ketorolac with psychoactive drugs (such as [fluoxetine](#)) has been associated with hallucinations in some patients [691].

3.5.1.EV] [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[402]. 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 [403].

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

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

7J) Probable Mechanism: additive effects on QT prolongation

3.5.1.EW] Meloxicam

1J) Interaction Effect: an increased risk of bleeding

2J) Summary: Caution is recommended with the concomitant use of NSAIDs and SSRIs due to an increased risk of [gastrointestinal bleeding](#)[688][689]. Bleeding events have included [epistaxis](#), ecchymosis, [hematoma](#), [petechiae](#), and life-threatening hemorrhages [692][693][694][695].

3J) Severity: major

4J) Onset: unspecified

5J) Substantiation: probable

6J) Clinical Management: Use caution when prescribing NSAIDs to patients who take SSRIs. Concomitant use of NSAIDs and SSRIs may cause an increased risk of bleeding[688][689]. When an SSRI and an NSAID are given concurrently, monitor patient for signs of increased bleeding.

7J) Probable Mechanism: unknown

8J) Literature Reports

aJ) SSRIs increase the risk of upper gastrointestinal (GI) bleeding and this effect is potentiated by concurrent use of NSAIDs or low-dose [aspirin](#). Hospitalizations for [upper GI 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 (CI), 2.7 to 4.7). Combined use of an SSRI and NSAIDs or low-dose [aspirin](#) increased the risk to 12.2 (95% CI, 7.1 to 19.5) and 5.2 (95% CI, 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 [690].

bJ) Coadministration of ketorolac with psychoactive drugs (such as [fluoxetine](#)) has been associated with hallucinations in some patients [691].

3.5.1.EX] Meperidine

1J) Interaction Effect: an increased risk of [serotonin syndrome](#)

2J) Summary: A 43-year-old male on [fluoxetine](#) every other day experienced [serotonin syndrome](#) immediately after intravenous [meperidine](#) was administered[247]. 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 [248].

3J) Severity: major

4J) Onset: rapid

5J) Substantiation: probable

6J) Clinical Management: A case of [serotonin syndrome](#) was reported with coadministration of [fluoxetine](#) and [meperidine](#) and therefore, concomitant use is discouraged[247]. 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 [248].

7J) Probable Mechanism: additive pharmacologic effects

8J) 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 Fahrenheit. 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 [247].

3.5.1.EY] 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[444]. Although citing no data, the manufacturer of mesoridazine states that concomitant use with other drugs which prolong the QT interval is contraindicated [445].
- 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.EZ] Methylene Blue

- 1) Interaction Effect: an increased risk of serotonin syndrome (labile blood pressure, hyperthermia, neuromuscular abnormalities, mental status changes, gastrointestinal symptoms) or neuroleptic malignant syndrome-like reactions
- 2) Summary: Concurrent use of fluoxetine and methylene blue (an MAOI) is contraindicated. Concurrent administration may result in serotonin syndrome or neuroleptic malignant syndrome-like reactions with symptoms including neuromuscular abnormalities (eg, hyperreflexia, incoordination), autonomic instability (eg, tachycardia, labile blood pressure, hyperthermia), and mental status changes (eg, agitation, hallucinations, coma). There have been reports of serious reactions, including fatalities, in patients receiving concomitant fluoxetine and MAOIs. In settings where urgent treatment with methylene blue is not required, discontinue fluoxetine at least 5 weeks prior to initiating treatment with methylene blue, or longer if fluoxetine use is chronic or in higher doses.[386]. If no alternative pharmacological or non-pharmacological treatment is available and urgent treatment with methylene blue is required, and the potential benefits outweigh the risk of serotonin syndrome in a patient on fluoxetine therapy, fluoxetine must be discontinued immediately. Monitor for serotonin syndrome or neuroleptic malignant syndrome reactions for 5 weeks or until 24 hours after the last dose of methylene blue has been administered, whichever comes first. Fluoxetine may be resumed 24 hours after the last dose of methylene blue has been given [387].

- 3) Severity: contraindicated
- 4) Onset: unspecified
- 5) Substantiation: probable
- 6) Clinical Management: Concurrent use of [fluoxetine](#) and methylene blue (an MAOI) is contraindicated. In settings where urgent treatment with methylene blue is not required, discontinue [fluoxetine](#) at least 5 weeks prior to initiating treatment with methylene blue, or longer if [fluoxetine](#) use is chronic or in higher doses[386]. If no alternative pharmacological or non-pharmacological treatment is available and urgent treatment with methylene blue is required in a patient on [fluoxetine](#) therapy, and the potential benefits outweigh the risk of [serotonin syndrome](#), [fluoxetine](#) must be discontinued immediately. Monitor for [serotonin syndrome](#) or [neuroleptic malignant syndrome](#) reactions for 5 weeks or until 24 hours after the last dose of methylene blue has been administered, whichever comes first. [Fluoxetine](#) may be resumed 24 hours after the last dose of methylene blue has been given [387].
- 7) Probable Mechanism: inhibition of MAO-mediated serotonin metabolism by methylene blue
- 8) Literature Reports

a) There have been reports of serious reactions, including fatalities, in patients receiving concomitant [fluoxetine](#) and MAOIs. Reactions have included myoclonus, [hyperthermia](#), rapid fluctuations of vital signs, and extreme agitation progressing to [delirium](#) and coma [386].

3.5.1.FA] [Methylergonovine](#)

- 1) Interaction Effect: increased plasma concentrations of ergot derivatives and increased risk of [ergotism](#) (nausea, vomiting, vasospastic ischemia)
- 2) Summary: Concomitant use of [fluoxetine](#), a weak CYP3A4 inhibitor, and an ergot derivative may result in increased plasma concentrations of the ergot derivative due to inhibition of CYP3A4-mediated ergot metabolism. Because of the potential for serious toxicity including [vasospasm](#) can occur, use caution with the concurrent use of [fluoxetine](#) and ergot derivatives[252][251].
- 3) Severity: moderate
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: [Fluoxetine](#) may increase the plasma concentrations of ergot derivatives. Use caution when [fluoxetine](#) is coadministered with an ergot derivative, such as [dihydroergotamine](#), [ergotamine](#), or [methylergonovine](#), due to the potential for serious toxicity including [vasospasm](#) that can occur[251][252].
- 7) Probable Mechanism: inhibition of CYP3A4-mediated ergot metabolism by [fluoxetine](#)

3.5.1.FB] [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[512].
- 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[512].

7)) Probable Mechanism: inhibition of selective serotonin reuptake inhibitor metabolism by [methylphenidate](#)

3.5.1.FC] [Methysergide](#)

1)) Interaction Effect: increased plasma concentrations of ergot derivatives and increased risk of [ergotism](#) (nausea, vomiting, vasospastic ischemia)

2)) Summary: Concomitant use of [fluoxetine](#), a weak CYP3A4 inhibitor, and an ergot derivative may result in increased plasma concentrations of the ergot derivative due to inhibition of CYP3A4-mediated ergot metabolism. Because of the potential for serious toxicity including [vasospasm](#) can occur, use caution with the concurrent use of [fluoxetine](#) and ergot derivatives[252][251].

3)) Severity: moderate

4)) Onset: unspecified

5)) Substantiation: theoretical

6)) Clinical Management: [Fluoxetine](#) may increase the plasma concentrations of ergot derivatives. Use caution when [fluoxetine](#) is coadministered with an ergot derivative, such as [dihydroergotamine](#), [ergotamine](#), or [methylergonovine](#), due to the potential for serious toxicity including [vasospasm](#) that can occur[251][252].

7)) Probable Mechanism: inhibition of CYP3A4-mediated ergot metabolism by [fluoxetine](#)

3.5.1.FD] [Metoclopramide](#)

1)) Interaction Effect: an increased risk of extrapyramidal reactions or [neuroleptic malignant syndrome](#)

2)) Summary: Concomitant use of [fluoxetine](#) with [metoclopramide](#) may increase the risk of extrapyramidal symptoms, such as [tardive dyskinesia](#) or [neuroleptic malignant syndrome](#), and is contraindicated[705]. If concurrent therapy is required, monitor patients for signs and symptoms of extrapyramidal reactions or [neuroleptic malignant syndrome](#) (fever, sweating, confusion, muscle stiffness). Discontinue [metoclopramide](#) if patient develops signs and symptoms of extrapyramidal reactions. Injection of [diphenhydramine](#) 50 mg intramuscularly or [benztropine](#) 1 to 2 mg intramuscularly may reverse the extrapyramidal reactions [706].

3)) Severity: contraindicated

4)) Onset: unspecified

5)) Substantiation: theoretical

6)) Clinical Management: Concomitant use of [fluoxetine](#) with [metoclopramide](#) is contraindicated[705]. If concurrent therapy is required, monitor patients for signs and symptoms of extrapyramidal reactions or [neuroleptic malignant syndrome](#) (fever, sweating, confusion, muscle stiffness). Discontinue [metoclopramide](#) if patient develops signs and symptoms of extrapyramidal reactions or [neuroleptic malignant syndrome](#). Injection of [diphenhydramine](#) 50 mg intramuscularly or [benztropine](#) 1 to 2 mg intramuscularly may reverse the extrapyramidal reactions [706].

7)) Probable Mechanism: unknown

3.5.1.FE] [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[760]. [Fluoxetine](#) is a potent inhibitor of hepatic cytochrome P450 2D6, the isoenzyme that catalyzes [metoprolol](#) metabolism [761]. 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 [759].

3.5.1.FF] Milnacipran

- 1) Interaction Effect: increased risk of [serotonin syndrome](#) ([hypertension](#), [hyperthermia](#), myoclonus, mental status changes)
- 2) Summary: Concurrent use of milnacipran and an SSRI or a serotonin [norepinephrine](#) reuptake inhibitor (SNRI) 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[509].
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Coadministration of milnacipran and an SSRI or a serotonin [norepinephrine](#) reuptake inhibitor (SNRI) 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[509].
- 7) Probable Mechanism: additive serotonergic effect

3.5.1.FG] 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[599]. 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 [248].
- 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[599]. 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 [248].

7J) Probable Mechanism: potentially additive pharmacologic effects

8J) Literature Reports

aJ) 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 [599].

3.5.1.FHJ Moclobemide

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

2J) 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[606][607][608][609][610][611]. Although not reported specifically with moclobemide in therapeutic doses, a similar interaction may occur. Concomitant use is contraindicated.

3J) Severity: contraindicated

4J) Onset: rapid

5J) Substantiation: probable

6J) 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.

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

8J) Literature Reports

aJ) Concomitant use of serotonin specific reuptake inhibitors and monoamine oxidase inhibitors can produce a toxic reaction known as [serotonin syndrome](#) [600]. [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.

bJ) Ten hours after her last dose of [fluoxetine](#), a 45-year-old woman began [tranylcypromine](#) therapy [601]. 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 [602]. 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 [603].

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 [604].

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 [605].

3.5.1.FI] [Nabumetone](#)

1) Interaction Effect: an increased risk of bleeding

2) Summary: Caution is recommended with the concomitant use of NSAIDs and SSRIs due to an increased risk of [gastrointestinal bleeding](#)[688][689]. Bleeding events have included [epistaxis](#), ecchymosis, [hematoma](#), [petechiae](#), and life-threatening hemorrhages [692][693][694][695].

3) Severity: major

4) Onset: unspecified

5) Substantiation: probable

6) Clinical Management: Use caution when prescribing NSAIDs to patients who take SSRIs. Concomitant use of NSAIDs and SSRIs may cause an increased risk of bleeding[688][689]. 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 (GI) bleeding and this effect is potentiated by concurrent use of NSAIDs or low-dose aspirin. Hospitalizations for upper GI 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 (CI), 2.7 to 4.7). Combined use of an SSRI and NSAIDs or low-dose aspirin increased the risk to 12.2 (95% CI, 7.1 to 19.5) and 5.2 (95% CI, 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 [690].

b) Coadministration of ketorolac with psychoactive drugs (such as fluoxetine) has been associated with hallucinations in some patients [691].

3.5.1.FJ] 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[586][587][124]. 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 [124].

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[124].

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 [584]. In addition, both fluoxetine and warfarin are tightly bound to albumin. In combination, the possibility for protein-binding displacement of either drug is present [585].

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 [586].

cj) 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 [587].

dj) 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** [588][589].

ej) 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 [590].

3.5.1.FK] **Naproxen**

1j) Interaction Effect: an increased risk of bleeding

2j) Summary: Caution is recommended with the concomitant use of NSAIDs and SSRIs due to an increased risk of **gastrointestinal bleeding**[688][689]. Bleeding events have included **epistaxis**, ecchymosis, **hematoma**, **petechiae**, and life-threatening hemorrhages [692][693][694][695].

3j) Severity: major

4j) Onset: unspecified

5j) Substantiation: probable

6j) Clinical Management: Use caution when prescribing NSAIDs to patients who take SSRIs. Concomitant use of NSAIDs and SSRIs may cause an increased risk of bleeding[688][689]. When an SSRI and an NSAID are given concurrently, monitor patient for signs of increased bleeding.

7j) Probable Mechanism: unknown

8j) Literature Reports

aj) SSRIs increase the risk of upper gastrointestinal (GI) bleeding and this effect is potentiated by concurrent use of NSAIDs or low-dose **aspirin**. Hospitalizations for **upper GI 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 (CI), 2.7 to 4.7). Combined use of an SSRI and NSAIDs or low-dose [aspirin](#) increased the risk to 12.2 (95% CI, 7.1 to 19.5) and 5.2 (95% CI, 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 [690].

b) Coadministration of ketorolac with psychoactive drugs (such as [fluoxetine](#)) has been associated with hallucinations in some patients [691].

3.5.1.FL] [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[401]. 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](#) [259].

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.FM] [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 C_{max}, 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[535].

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[535].

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

3.5.1.FN] [Nepafenac](#)

1) Interaction Effect: an increased risk of bleeding

2) Summary: Caution is recommended with the concomitant use of NSAIDs and SSRIs due to an increased risk of [gastrointestinal bleeding](#)[688][689]. Bleeding events have included [epistaxis](#), ecchymosis, [hematoma](#), [petechiae](#), and life-threatening hemorrhages [692][693][694][695].

3) Severity: major

4) Onset: unspecified

5) Substantiation: probable

6) Clinical Management: Use caution when prescribing NSAIDs to patients who take SSRIs. Concomitant use of NSAIDs and SSRIs may cause an increased risk of bleeding[688][689]. 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 (GI) bleeding and this effect is potentiated by concurrent use of NSAIDs or low-dose [aspirin](#). Hospitalizations for [upper GI 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 (CI), 2.7 to 4.7). Combined use of an SSRI and NSAIDs or low-dose [aspirin](#) increased the risk to 12.2 (95% CI, 7.1 to 19.5) and 5.2 (95% CI, 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 [690].

b) Coadministration of ketorolac with psychoactive drugs (such as [fluoxetine](#)) has been associated with hallucinations in some patients [691].

3.5.1.FO] 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[328][329][330][331][332][333]. 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](#) [323]. [Serotonin syndrome](#) is a condition of serotonergic hyperstimulation and manifests as restlessness, myoclonus, changes in mental status, hyperreflexia, diaphoresis, shivering, and tremor [323]. 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 [324].

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%) [325]. 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 [326]. 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](#) [327]. 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.FP] [Nifedipine](#)

- 1) Interaction Effect: increased [nifedipine](#) exposure
- 2) Summary: [Fluoxetine](#) is an inhibitor of the CYP3A4 isoenzyme and may inhibit the metabolism of [nifedipine](#). [Nifedipine](#) plasma concentrations may be increased by the presence of [fluoxetine](#). Clinical monitoring for [nifedipine](#) toxicity and possible dose reduction is recommended[461].
- 3) Severity: moderate
- 4) Onset: delayed
- 5) Substantiation: theoretical
- 6) Clinical Management: Concomitant administration of [nifedipine](#) and [fluoxetine](#) may increase exposure to [nifedipine](#). Monitor for clinical signs of [nifedipine](#) toxicity, including hypotension, peripheral edema, and bradycardia. Consider a dose reduction of [nifedipine](#)[461].
- 7) Probable Mechanism: inhibition of CYP3A-mediated [nifedipine](#) metabolism

3.5.1.FQ] [Niflumic Acid](#)

- 1) Interaction Effect: an increased risk of bleeding
- 2) Summary: Caution is recommended with the concomitant use of NSAIDs and SSRIs due to an increased risk of [gastrointestinal bleeding](#)[688][689]. Bleeding events have included [epistaxis](#), [ecchymosis](#), [hematoma](#), [petechiae](#), and life-threatening hemorrhages [692][693][694][695].
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: probable

6j) Clinical Management: Use caution when prescribing NSAIDs to patients who take SSRIs. Concomitant use of NSAIDs and SSRIs may cause an increased risk of bleeding[688][689]. When an SSRI and an NSAID are given concurrently, monitor patient for signs of increased bleeding.

7j) Probable Mechanism: unknown

8j) Literature Reports

a) SSRIs increase the risk of upper gastrointestinal (GI) bleeding and this effect is potentiated by concurrent use of NSAIDs or low-dose [aspirin](#). Hospitalizations for [upper GI 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 (CI), 2.7 to 4.7). Combined use of an SSRI and NSAIDs or low-dose [aspirin](#) increased the risk to 12.2 (95% CI, 7.1 to 19.5) and 5.2 (95% CI, 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 [690].

b) Coadministration of ketorolac with psychoactive drugs (such as [fluoxetine](#)) has been associated with hallucinations in some patients [691].

3.5.1.FR| Nimesulide

1j) Interaction Effect: an increased risk of bleeding

2j) Summary: Caution is recommended with the concomitant use of NSAIDs and SSRIs due to an increased risk of [gastrointestinal bleeding](#)[688][689]. Bleeding events have included [epistaxis](#), ecchymosis, [hematoma](#), [petechiae](#), and life-threatening hemorrhages [692][693][694][695].

3j) Severity: major

4j) Onset: unspecified

5j) Substantiation: probable

6j) Clinical Management: Use caution when prescribing NSAIDs to patients who take SSRIs. Concomitant use of NSAIDs and SSRIs may cause an increased risk of bleeding[688][689]. When an SSRI and an NSAID are given concurrently, monitor patient for signs of increased bleeding.

7j) Probable Mechanism: unknown

8j) Literature Reports

a) SSRIs increase the risk of upper gastrointestinal (GI) bleeding and this effect is potentiated by concurrent use of NSAIDs or low-dose [aspirin](#). Hospitalizations for [upper GI 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 (CI), 2.7 to 4.7). Combined use of an SSRI and NSAIDs or low-dose [aspirin](#) increased the risk to 12.2 (95% CI, 7.1 to 19.5) and 5.2 (95% CI, 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 [690].

b) Coadministration of ketorolac with psychoactive drugs (such as [fluoxetine](#)) has been associated with hallucinations in some patients [691].

3.5.1.FS| [Nortriptyline](#)

1j) 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[680][681]. 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 [682]. In addition, concurrent use of fluoxetine and TCAs such as desipramine, nortriptyline, and imipramine has resulted in significant increases in TCA concentrations [683][683][684][685][686][687].

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 [674].

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 [675].

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 [676].

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 [677].

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 [678].

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 [679].

3.5.1.FT| [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[310][311]. 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.FU| [Oxaprozin](#)

1) Interaction Effect: an increased risk of bleeding

2) Summary: Caution is recommended with the concomitant use of NSAIDs and SSRIs due to an increased risk of [gastrointestinal bleeding](#)[688][689]. Bleeding events have included [epistaxis](#), ecchymosis, [hematoma](#), [petechiae](#), and life-threatening hemorrhages [692][693][694][695].

3) Severity: major

4) Onset: unspecified

5) Substantiation: probable

6) Clinical Management: Use caution when prescribing NSAIDs to patients who take SSRIs. Concomitant use of NSAIDs and SSRIs may cause an increased risk of bleeding[688][689]. 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 (GI) bleeding and this effect is potentiated by concurrent use of NSAIDs or low-dose [aspirin](#). Hospitalizations for [upper GI 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 (CI), 2.7 to 4.7). Combined use of an SSRI and NSAIDs or low-dose [aspirin](#) increased the risk to 12.2 (95% CI, 7.1 to 19.5) and 5.2 (95% CI, 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 [690].

b) Coadministration of ketorolac with psychoactive drugs (such as [fluoxetine](#)) has been associated with hallucinations in some patients [691].

3.5.1.FV| [Oxyphenbutazone](#)

1) Interaction Effect: an increased risk of bleeding

2) Summary: Caution is recommended with the concomitant use of NSAIDs and SSRIs due to an increased risk of [gastrointestinal bleeding](#)[688][689]. Bleeding events have included [epistaxis](#), ecchymosis, [hematoma](#), [petechiae](#), and life-threatening hemorrhages [692][693][694][695].

3) Severity: major

4) Onset: unspecified

5) Substantiation: probable

6) Clinical Management: Use caution when prescribing NSAIDs to patients who take SSRIs. Concomitant use of NSAIDs and SSRIs may cause an increased risk of bleeding[688][689]. 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 (GI) bleeding and this effect is potentiated by concurrent use of NSAIDs or low-dose [aspirin](#). Hospitalizations for [upper GI 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 (CI), 2.7 to 4.7). Combined use of an SSRI and NSAIDs or low-dose [aspirin](#) increased the risk to 12.2 (95% CI, 7.1 to 19.5) and 5.2 (95% CI, 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 [690].

b) Coadministration of ketorolac with psychoactive drugs (such as [fluoxetine](#)) has been associated with hallucinations in some patients [691].

3.5.1.FW] 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[358][359][360][361][362][363]. 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](#) [353]. [Serotonin syndrome](#) is a condition of serotonergic hyperstimulation and manifests as restlessness, myoclonus, changes in mental status, hyperreflexia, diaphoresis, shivering, and tremor [353]. 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 [354].

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%) [355]. 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 [356]. 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](#) [357]. 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.FX] 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[586][587][124]. 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](#) [124].

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[124].

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 [584]. In addition, both [fluoxetine](#) and [warfarin](#) are tightly bound to albumin. In combination, the possibility for protein-binding displacement of either drug is present [585].

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 [586].

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 [587].

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** [588][589].

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 [590].

3.5.1.FY] **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[422].
- 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.FZ] [Paroxetine](#)

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

2) Summary: Concurrent use of an SSRI together with another SSRI may result in [serotonin syndrome](#), which may be life-threatening, and is not recommended. 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[448][449][450][451]. If symptoms of [serotonin syndrome](#) occur, drug discontinuation is recommended [452][344]. Symptoms of [serotonin syndrome](#) include neuromuscular abnormalities (including hyperreflexia, 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 [248].

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Coadministration of an SSRI with another SSRI may result in a life-threatening condition called [serotonin syndrome](#) and is not recommended[448][449][450][451]. If these agents are used together, monitor closely for symptoms of [serotonin syndrome](#), especially during treatment initiation and dose increases, and discontinue therapy if symptoms occur [452][344]. Symptoms of [serotonin syndrome](#) include neuromuscular abnormalities (including hyperreflexia, 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 [248].

7) Probable Mechanism: additive serotonergic effect

3.5.1.GA] [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[423][424]. 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.GB] [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[368].
- 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 [366].

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 [367].

3.5.1.GC] [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[586][587][124]. 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](#) [124].
- 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[124].
- 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 [584]. In addition, both [fluoxetine](#) and [warfarin](#) are tightly bound to albumin. In combination, the possibility for protein-binding displacement of either drug is present [585].

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 [586].

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 [587].

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 [588][589].

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 [590].

3.5.1.GD) 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[496][497][498][499][500][501]. 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 serotonergic agents [502].
- 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](#) [491]. [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 [492].

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%) [493]. 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 [494]. 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 [495]. 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.GE] 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[586][587][124]. 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](#) [124].

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[124].

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 [584]. In addition, both [fluoxetine](#) and [warfarin](#) are tightly bound to albumin. In combination, the possibility for protein-binding displacement of either drug is present [585].

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 [586].

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 [587].

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](#) [588][589].

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 [590].

3.5.1.GF] 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[586][587][124]. 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](#) [124].
- 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[124].
- 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 [584]. In addition, both [fluoxetine](#) and [warfarin](#) are tightly bound to albumin. In combination, the possibility for protein-binding displacement of either drug is present [585].

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 [586].

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 [587].

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](#) [588][589].

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 [590].

3.5.1.GG| [Phenylbutazone](#)

1) Interaction Effect: an increased risk of bleeding

2) Summary: Caution is recommended with the concomitant use of NSAIDs and SSRIs due to an increased risk of [gastrointestinal bleeding](#)[688][689]. Bleeding events have included [epistaxis](#), ecchymosis, [hematoma](#), [petechiae](#), and life-threatening hemorrhages [692][693][694][695].

3) Severity: major

4) Onset: unspecified

5) Substantiation: probable

6) Clinical Management: Use caution when prescribing NSAIDs to patients who take SSRIs. Concomitant use of NSAIDs and SSRIs may cause an increased risk of bleeding[688][689]. 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 (GI) bleeding and this effect is potentiated by concurrent use of NSAIDs or low-dose [aspirin](#). Hospitalizations for [upper GI 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 (CI), 2.7 to 4.7). Combined use of an SSRI and NSAIDs or low-dose [aspirin](#) increased the risk to 12.2 (95% CI, 7.1 to 19.5) and 5.2 (95% CI, 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 [690].

b) Coadministration of ketorolac with psychoactive drugs (such as [fluoxetine](#)) has been associated with hallucinations in some patients [691].

3.5.1.GH| Phenytoin

1j) Interaction Effect: an increased risk of **phenytoin** toxicity (ataxia, hyperreflexia, **nystagmus**, tremor)
2j) Summary: Several case reports indicate that concurrent use of **fluoxetine** and **phenytoin** can result in significantly increased **phenytoin** serum levels leading to toxicity[574][575][576]. 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 [577]. 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 [578].

3j) Severity: moderate

4j) Onset: delayed

5j) Substantiation: probable

6j) 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.

7j) Probable Mechanism: decreased **phenytoin** metabolism

8j) Literature Reports

aj) 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) [571].

bj) 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 [572]. 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.

cj) 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 [572]. 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.

dj) 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 [573].

3.5.1.GI] 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[405]. 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 [406].
- 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 [405].

3.5.1.GJ] Pirazolac

- 1) Interaction Effect: an increased risk of bleeding
- 2) Summary: Caution is recommended with the concomitant use of NSAIDs and SSRIs due to an increased risk of gastrointestinal bleeding[688][689]. Bleeding events have included epistaxis, ecchymosis, hematoma, petechiae, and life-threatening hemorrhages [692][693][694][695].
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: probable
- 6) Clinical Management: Use caution when prescribing NSAIDs to patients who take SSRIs. Concomitant use of NSAIDs and SSRIs may cause an increased risk of bleeding[688][689]. 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 (GI) bleeding and this effect is potentiated by concurrent use of NSAIDs or low-dose aspirin. Hospitalizations for upper GI 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 (CI), 2.7 to 4.7). Combined use of an SSRI and NSAIDs or low-dose aspirin increased the risk to 12.2 (95% CI, 7.1 to 19.5) and 5.2 (95% CI, 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 [690].

b) Coadministration of ketorolac with psychoactive drugs (such as [fluoxetine](#)) has been associated with hallucinations in some patients [691].

3.5.1.GK] 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[417]. [Fluoxetine](#) has demonstrated QT prolongation at therapeutic doses [418].
- 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.GL] Piroxicam

- 1) Interaction Effect: an increased risk of bleeding
- 2) Summary: Caution is recommended with the concomitant use of NSAIDs and SSRIs due to an increased risk of [gastrointestinal bleeding](#)[688][689]. Bleeding events have included [epistaxis](#), ecchymosis, [hematoma](#), [petechiae](#), and life-threatening hemorrhages [692][693][694][695].
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: probable
- 6) Clinical Management: Use caution when prescribing NSAIDs to patients who take SSRIs. Concomitant use of NSAIDs and SSRIs may cause an increased risk of bleeding[688][689]. 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 (GI) bleeding and this effect is potentiated by concurrent use of NSAIDs or low-dose [aspirin](#). Hospitalizations for [upper GI 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 (CI), 2.7 to 4.7). Combined use of an SSRI and NSAIDs or low-dose [aspirin](#) increased the risk to 12.2 (95% CI, 7.1 to 19.5) and 5.2 (95% CI, 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 [690].

b) Coadministration of ketorolac with psychoactive drugs (such as [fluoxetine](#)) has been associated with hallucinations in some patients [691].

3.5.1.GM] Pirprofen

- 1) Interaction Effect: an increased risk of bleeding
- 2) Summary: Caution is recommended with the concomitant use of NSAIDs and SSRIs due to an increased risk of [gastrointestinal bleeding](#)[688][689]. Bleeding events have included [epistaxis](#), ecchymosis, [hematoma](#), [petechiae](#), and life-threatening hemorrhages [692][693][694][695].

- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: probable
- 6) Clinical Management: Use caution when prescribing NSAIDs to patients who take SSRIs. Concomitant use of NSAIDs and SSRIs may cause an increased risk of bleeding[688][689]. 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 (GI) bleeding and this effect is potentiated by concurrent use of NSAIDs or low-dose [aspirin](#). Hospitalizations for [upper GI 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 (CI), 2.7 to 4.7). Combined use of an SSRI and NSAIDs or low-dose [aspirin](#) increased the risk to 12.2 (95% CI, 7.1 to 19.5) and 5.2 (95% CI, 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 [690].

b) Coadministration of ketorolac with psychoactive drugs (such as [fluoxetine](#)) has been associated with hallucinations in some patients [691].

3.5.1.GN] [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[417]. [Fluoxetine](#) has demonstrated QT prolongation at therapeutic doses [418].
- 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.GO] [Prasugrel](#)

- 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 selective serotonin reuptake inhibitors 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. Monitor patient for signs of increased bleeding when [fluoxetine](#) is administered with prasugrel concomitantly[344].
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: probable
- 6) Clinical Management: When [fluoxetine](#) and prasugrel are given concurrently, monitor patient for signs of increased bleeding[344].
- 7) Probable Mechanism: unknown

3.5.1.GP| Probuco

- 1) Interaction Effect: an increased risk of **cardiotoxicity** (QT prolongation, **torsades de pointes**, **cardiac arrest**)
- 2) Summary: **Fluoxetine** and **probuco** have been shown to prolong the QTc interval at the recommended therapeutic dose[345][346][347]. 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 **probuco** is not recommended.
- 7) Probable Mechanism: additive effects on QT prolongation

3.5.1.GQ| 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[417]. **Fluoxetine** has demonstrated QT prolongation at therapeutic doses [418].
- 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.GR| 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[304][305][306][307][308][309]. 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** [299]. **Serotonin syndrome** is a condition of serotonergic hyperstimulation and manifests as restlessness, myoclonus, changes in mental status, hyperreflexia, diaphoresis, shivering, and tremor [299]. 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 [300].

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%) [301]. 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 [302]. 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](#) [303]. 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.GS] [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[397][398][399] . 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 [400].

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.GT] [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[279]. [Fluoxetine](#) has been shown to prolong the QTc interval at the recommended therapeutic dose [280]. 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 [281].

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 [278].

3.5.1.GU] 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[338]. 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 [339].

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 [337].

3.5.1.GV] Propyphenazone

1) Interaction Effect: an increased risk of bleeding

- 2) Summary: Caution is recommended with the concomitant use of NSAIDs and SSRIs due to an increased risk of [gastrointestinal bleeding](#)[688][689]. Bleeding events have included [epistaxis](#), ecchymosis, [hematoma](#), [petechiae](#), and life-threatening hemorrhages [692][693][694][695].
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: probable
- 6) Clinical Management: Use caution when prescribing NSAIDs to patients who take SSRIs. Concomitant use of NSAIDs and SSRIs may cause an increased risk of bleeding[688][689]. 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 (GI) bleeding and this effect is potentiated by concurrent use of NSAIDs or low-dose [aspirin](#). Hospitalizations for [upper GI 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 (CI), 2.7 to 4.7). Combined use of an SSRI and NSAIDs or low-dose [aspirin](#) increased the risk to 12.2 (95% CI, 7.1 to 19.5) and 5.2 (95% CI, 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 [690].

b) Coadministration of ketorolac with psychoactive drugs (such as [fluoxetine](#)) has been associated with hallucinations in some patients [691].

3.5.1.GW] Proquazone

- 1) Interaction Effect: an increased risk of bleeding
- 2) Summary: Caution is recommended with the concomitant use of NSAIDs and SSRIs due to an increased risk of [gastrointestinal bleeding](#)[688][689]. Bleeding events have included [epistaxis](#), ecchymosis, [hematoma](#), [petechiae](#), and life-threatening hemorrhages [692][693][694][695].
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: probable
- 6) Clinical Management: Use caution when prescribing NSAIDs to patients who take SSRIs. Concomitant use of NSAIDs and SSRIs may cause an increased risk of bleeding[688][689]. 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 (GI) bleeding and this effect is potentiated by concurrent use of NSAIDs or low-dose [aspirin](#). Hospitalizations for [upper GI 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 (CI), 2.7 to 4.7). Combined use of an SSRI and NSAIDs or low-dose [aspirin](#) increased the risk to 12.2 (95% CI, 7.1 to 19.5) and 5.2 (95% CI, 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 [690].

b)) Coadministration of ketorolac with psychoactive drugs (such as [fluoxetine](#)) has been associated with hallucinations in some patients [691].

3.5.1.GX] [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[388]. 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 [389], [quetiapine](#) [390], sertindole [391], sultopride [392], and zotepine [393].

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.GY] [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[651]. [Fluoxetine](#) has demonstrated QT prolongation at therapeutic doses [652]. In addition, [quinidine](#) inhibits CYP2D6 which may reduce [fluoxetine](#) metabolism [653] and [fluoxetine](#) inhibits CYP3A4, which may reduce [quinidine](#) metabolism [654].

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% [650]. 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.GZ] [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](#)[556].

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](#) [555]. [Serotonin syndrome](#) is a condition of serotonergic hyperstimulation and manifests as restlessness, myoclonus, changes in mental status, hyperreflexia, diaphoresis, shivering, and tremor [555]. If the syndrome is not recognized and correctly treated, death can result.

3.5.1.HA] 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[586][587][124]. 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](#) [124].

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[124].

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 [584]. In addition, both [fluoxetine](#) and [warfarin](#) are tightly bound to albumin. In combination, the possibility for protein-binding displacement of either drug is present [585].

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 [586].

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 [587].

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](#) [588][589].

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 [590].

3.5.1.HB) [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 sedation, 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](#). The [risperidone](#) dose should be reevaluated if [fluoxetine](#) is initiated or discontinued[616][617]. Monitoring the patient for side effects indicative of increased [risperidone](#) plasma levels may be necessary [617]. . If coadministration of [fluoxetine](#) and intramuscular [risperidone](#) is necessary, a lower [risperidone](#) dose 2 to 4 weeks prior to [fluoxetine](#) initiation may be considered. Patients receiving the standard [risperidone](#) injection dose of 25 mg may continue that dose when [fluoxetine](#) is initiated, unless clinical judgement necessitates the initiation of a lower [risperidone](#) dose of 12.5 mg. When [risperidone](#) injection is initiated in patients

already on [fluoxetine](#), a reduced starting dose of 12.5 mg may be utilized; however, the efficacy of 12.5 mg dose has not been proven in clinical trials [615].

3J) Severity: moderate

4J) Onset: unspecified

5J) Substantiation: probable

6J) Clinical Management: Concomitant use of [fluoxetine](#) and [risperidone](#) has resulted in increased [risperidone](#) plasma concentrations and an increased risk of [risperidone](#) side effects. Reevaluate the dose of [risperidone](#) when concomitant [fluoxetine](#) is initiated or discontinued[615][616]. Carefully monitor patients for increased plasma [risperidone](#) levels and side effects (drowsiness, sedation, extrapyramidal symptoms, and [cardiotoxicity](#)) when [fluoxetine](#) is coadministered with [risperidone](#) [617]. If coadministration of [fluoxetine](#) and intramuscular [risperidone](#) is necessary, a lower [risperidone](#) dose 2 to 4 weeks prior to [fluoxetine](#) initiation may be considered. Patients receiving the standard [risperidone](#) injection dose of 25 mg may continue that dose when [fluoxetine](#) is initiated, unless clinical judgement necessitates the initiation of a lower [risperidone](#) dose of 12.5 mg. When [risperidone](#) injection is initiated in patients already on [fluoxetine](#), a reduced starting dose of 12.5 mg may be utilized; however, the efficacy of 12.5 mg dose has not been proven in clinical trials [615].

7J) Probable Mechanism: inhibition of CYP2D6-mediated metabolism of [risperidone](#)

8J) Literature Reports

aJ) [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 [616].

bJ) [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 [617].

3.5.1.HCJ [Ritonavir](#)

1J) Interaction Effect: increased [fluoxetine](#) exposure, with potential for alterations in cardiac and/or neurologic function

2J) Summary: The concurrent administration of [fluoxetine](#), a selective serotonin reuptake inhibitor with metabolism involving the CYP2D6 system[336], with [ritonavir](#), a CYP2D6 inhibitor, has resulted in increased systemic exposure to [fluoxetine](#). Additionally, cardiac and neurologic events have been reported following concomitant administration of [fluoxetine](#) and [ritonavir](#). If coadministration is indicated, a

decrease in the [fluoxetine](#) dose may be needed; monitor for changes in cardiac and/or neurologic function [618][619].

3) Severity: moderate

4) Onset: delayed

5) Substantiation: established

6) Clinical Management: Use caution with concomitant administration of [fluoxetine](#) and [ritonavir](#) as this may result in increased [fluoxetine](#) exposure. Also, monitoring for changes in cardiac and/or neurologic function, and a [fluoxetine](#) dose decrease may be warranted [618][619].

7) Probable Mechanism: inhibition of CYP2D6-mediated [fluoxetine](#) metabolism

8) Literature Reports

a) Coadministration of [fluoxetine](#) 30 mg twice daily for 8 days and [ritonavir](#) 600 mg as a single dose in 16 patients resulted in a 19% increase in [ritonavir](#) AIC, although no changes in the [ritonavir](#) C_{max} were noted. During postmarketing experience, cardiac and neurologic events have been reported following coadministration of [fluoxetine](#) and [ritonavir](#) [618][619].

3.5.1.HD) [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) [413]. Because [rizatriptan](#) is a 5HT 1B/1D receptor agonist, a similar interaction between SSRIs and [rizatriptan](#) may occur [414]. 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](#) [259].

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](#) [412].

3.5.1.HE) [Salicylic Acid](#)

1) Interaction Effect: an increased risk of bleeding

2) Summary: Caution is recommended with the concomitant use of NSAIDs and SSRIs due to an increased risk of [gastrointestinal bleeding](#) [688][689]. Bleeding events have included [epistaxis](#), ecchymosis, [hematoma](#), [petechiae](#), and life-threatening hemorrhages [692][693][694][695].

3) Severity: major

- 4) Onset: unspecified
- 5) Substantiation: probable
- 6) Clinical Management: Use caution when prescribing NSAIDs to patients who take SSRIs. Concomitant use of NSAIDs and SSRIs may cause an increased risk of bleeding[688][689]. 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 (GI) bleeding and this effect is potentiated by concurrent use of NSAIDs or low-dose [aspirin](#). Hospitalizations for [upper GI 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 (CI), 2.7 to 4.7). Combined use of an SSRI and NSAIDs or low-dose [aspirin](#) increased the risk to 12.2 (95% CI, 7.1 to 19.5) and 5.2 (95% CI, 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 [690].

b) Coadministration of ketorolac with psychoactive drugs (such as [fluoxetine](#)) has been associated with hallucinations in some patients [691].

3.5.1.HF] [Salsalate](#)

- 1) Interaction Effect: an increased risk of bleeding
- 2) Summary: Caution is recommended with the concomitant use of NSAIDs and SSRIs due to an increased risk of [gastrointestinal bleeding](#)[688][689]. Bleeding events have included [epistaxis](#), ecchymosis, [hematoma](#), [petechiae](#), and life-threatening hemorrhages [692][693][694][695].
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: probable
- 6) Clinical Management: Use caution when prescribing NSAIDs to patients who take SSRIs. Concomitant use of NSAIDs and SSRIs may cause an increased risk of bleeding[688][689]. 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 (GI) bleeding and this effect is potentiated by concurrent use of NSAIDs or low-dose [aspirin](#). Hospitalizations for [upper GI 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 (CI), 2.7 to 4.7). Combined use of an SSRI and NSAIDs or low-dose [aspirin](#) increased the risk to 12.2 (95% CI, 7.1 to 19.5) and 5.2 (95% CI, 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 [690].

b) Coadministration of ketorolac with psychoactive drugs (such as [fluoxetine](#)) has been associated with hallucinations in some patients [691].

3.5.1.HG] [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[750][751][752][753][754][755]. 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](#) [756].
- 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](#) [555]. [Serotonin syndrome](#) is a condition of serotonergic hyperstimulation and manifests as restlessness, myoclonus, changes in mental status, hyperreflexia, diaphoresis, shivering, and tremor [555]. 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 [746].

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%) [747]. 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 [748]. 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 [749]. 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.HH] 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[382][383][384]. [Fluoxetine](#) has been shown to prolong the QTc interval at the recommended therapeutic dose [385].
- 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.HI] 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[388]. 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 [389], [quetiapine](#) [390], sertindole [391], sultopride [392], and zotepine [393].
- 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.HJ] Sertraline

- 1) Interaction Effect: increased risk of [serotonin syndrome](#) ([hypertension](#), [hyperthermia](#), myoclonus, mental status changes)
- 2) Summary: Concurrent use of an SSRI together with another SSRI may result in [serotonin syndrome](#), which may be life-threatening, and is not recommended. 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[448][449][450][451]. If symptoms of [serotonin syndrome](#) occur, drug discontinuation is recommended [452][344]. Symptoms of [serotonin syndrome](#) include neuromuscular abnormalities (including hyperreflexia, 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 [248].
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical

6)) Clinical Management: Coadministration of an SSRI with another SSRI may result in a life-threatening condition called [serotonin syndrome](#) and is not recommended[448][449][450][451]. If these agents are used together, monitor closely for symptoms of [serotonin syndrome](#), especially during treatment initiation and dose increases, and discontinue therapy if symptoms occur [452][344]. Symptoms of [serotonin syndrome](#) include neuromuscular abnormalities (including hyperreflexia, 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 [248].

7)) Probable Mechanism: additive serotonergic effect

3.5.1.HK] [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[594].

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 [593].

3.5.1.HL] [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[382][383][384]. [Fluoxetine](#) has been shown to prolong the QTc interval at the recommended therapeutic dose [385].

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.HM] [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[342][343]. 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.HN] 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[564][565][566][567]. A patient exhibited a syndrome resembling sedative/hypnotic intoxication after adding St. John's Wort to paroxetine therapy [568]. St. John's Wort is thought to inhibit serotonin reuptake and may have mild monoamine oxidase inhibitory activity [569][570], 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 [559].

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 [560].

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 [561].

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 orchiectomy](#) 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's Wort, 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 [562].

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 [563].

3.5.1.HO] [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[557][558]. 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.HP] Sulindac

1) Interaction Effect: an increased risk of bleeding

2) Summary: Caution is recommended with the concomitant use of NSAIDs and SSRIs due to an increased risk of gastrointestinal bleeding[688][689]. Bleeding events have included epistaxis, ecchymosis, hematoma, petechiae, and life-threatening hemorrhages [692][693][694][695].

3) Severity: major

4) Onset: unspecified

5) Substantiation: probable

6) Clinical Management: Use caution when prescribing NSAIDs to patients who take SSRIs. Concomitant use of NSAIDs and SSRIs may cause an increased risk of bleeding[688][689]. 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 (GI) bleeding and this effect is potentiated by concurrent use of NSAIDs or low-dose aspirin. Hospitalizations for upper GI 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 (CI), 2.7 to 4.7). Combined use of an SSRI and NSAIDs or low-dose aspirin increased the risk to 12.2 (95% CI, 7.1 to 19.5) and 5.2 (95% CI, 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 [690].

b) Coadministration of ketorolac with psychoactive drugs (such as fluoxetine) has been associated with hallucinations in some patients [691].

3.5.1.HQ] 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[388]. 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 [389], quetiapine [390], sertindole [391], sultopride [392], and zotepine [393].

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.HR] [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)[258]. 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](#) [259].
- 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](#) [257].

3.5.1.HS] [Suprofen](#)

- 1) Interaction Effect: an increased risk of bleeding
- 2) Summary: Caution is recommended with the concomitant use of NSAIDs and SSRIs due to an increased risk of [gastrointestinal bleeding](#)[688][689]. Bleeding events have included [epistaxis](#), ecchymosis, [hematoma](#), [petechiae](#), and life-threatening hemorrhages [692][693][694][695].
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: probable
- 6) Clinical Management: Use caution when prescribing NSAIDs to patients who take SSRIs. Concomitant use of NSAIDs and SSRIs may cause an increased risk of bleeding[688][689]. 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 (GI) bleeding and this effect is potentiated by concurrent use of NSAIDs or low-dose [aspirin](#). Hospitalizations for [upper GI 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 (CI), 2.7 to 4.7). Combined use of an SSRI and NSAIDs or low-dose [aspirin](#) increased the risk to 12.2 (95% CI, 7.1 to 19.5) and 5.2 (95% CI, 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 [690].

b) Coadministration of ketorolac with psychoactive drugs (such as [fluoxetine](#)) has been associated with hallucinations in some patients [691].

3.5.1.HT] [Tamoxifen](#)

1) Interaction Effect: decreased plasma concentrations of the active metabolites of [tamoxifen](#)

2) Summary: Results from a large, population-based, retrospective study demonstrated that concomitant use of [paroxetine](#) and [tamoxifen](#) is associated with an increased risk of death from [breast cancer](#), which appears to be directly related to the duration of concomitant therapy, while the risk is not increased with other SSRIs[441] while another 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 [443]. However, one retrospective analysis did not demonstrate an increase in [breast cancer](#) recurrence with concurrent use of [tamoxifen](#) and some CYP2D6 inhibitors, including [fluoxetine](#) [442] . 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: major

4) Onset: delayed

5) Substantiation: theoretical

6) Clinical Management: Studies report mixed results as to whether or not coadministration of [fluoxetine](#) and [tamoxifen](#) result in decreased concentrations of endoxifen (active metabolite of [tamoxifen](#)), thereby decreasing [tamoxifen](#) efficacy[441][442][443]. If administered concurrently, monitor closely for decreased [tamoxifen](#) efficacy.

7) Probable Mechanism: inhibition of CYP2D6-mediated [tamoxifen](#) metabolism

8) Literature Reports

a) Results from a population-based, retrospective, cohort study demonstrated that concomitant use of [paroxetine](#) and [tamoxifen](#) is associated with an increased risk of death from [breast cancer](#), which appears to be directly related to the duration of concomitant therapy, while the risk is not increased with other SSRIs, including [fluoxetine](#). Participants in the study included females at least 66 years old who were newly treated with [tamoxifen](#) for [breast cancer](#) and who also received a single SSRI antidepressant. The primary outcome measurement was death from [breast cancer](#) after [tamoxifen](#) treatment, expressed as a function of the length of [tamoxifen](#) exposure. Of the 2430 women who were identified for the primary analysis, 2025 initiated [tamoxifen](#) within 1 year of being diagnosed with [breast cancer](#) and the median duration of [tamoxifen](#) therapy was 4 years. The SSRI prescribing was as follows: [paroxetine](#) (n=630), [sertraline](#) (n=541), [citalopram](#) (n=467), [venlafaxine](#) (n=365), [fluoxetine](#) (n=253), and [fluvoxamine](#) (n=174). After a mean follow-up of 2.38 years, 374 women died of [breast cancer](#). After adjusting for age, duration of [tamoxifen](#) treatment, and other confounders, absolute increases of 25%, 50%, and 75% in the proportion of time on [tamoxifen](#) concomitantly with [paroxetine](#) were associated with hazard ratios (HR) of 1.24 (95% confidence interval (CI), 1.08 to 1.42), 1.54 (95% CI, 1.17 to 2.03), and 1.91 (95% CI, 1.26 to 2.89), respectively. No other SSRI was associated with an increased risk of [breast cancer](#) mortality when administered during [tamoxifen](#) therapy [441].

b) A retrospective analysis of patients with early-stage, estrogen receptor-positive **breast cancer** did not demonstrate an increase in **breast cancer** recurrence with concurrent use of **tamoxifen** and some CYP2D6 inhibitors, including **fluoxetine**. Using the Danish Breast Cancer Cooperative Group Registry, a total of 366 cases of **breast cancer** recurrence and 366 matched **breast cancer** controls were identified. Based on pharmacy claims, 120 cases and 103 controls who received at least 1 of 15 different CYP2D6 inhibitors while taking **tamoxifen** were identified. The pooled odds ratio for **breast cancer** recurrence was 1.0 (95% CI, 0.8% to 1.3%) across all CYP2D6 inhibitors [442].

c) 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 [443].

3.5.1.HU] 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[425]. 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[425]. 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.HV] 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[699].

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[699].

7) Probable Mechanism: additive serotonergic effect

3.5.1.HW] 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[382][383][384]. [Fluoxetine](#) has been shown to prolong the QTc interval at the recommended therapeutic dose [385].

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.HX] 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](#)[700][701].

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.HY] Tenidap

1) Interaction Effect: an increased risk of bleeding

2) Summary: Caution is recommended with the concomitant use of NSAIDs and SSRIs due to an increased risk of [gastrointestinal bleeding](#)[688][689]. Bleeding events have included [epistaxis](#), ecchymosis, [hematoma](#), [petechiae](#), and life-threatening hemorrhages [692][693][694][695].

3) Severity: major

4) Onset: unspecified

5) Substantiation: probable

6) Clinical Management: Use caution when prescribing NSAIDs to patients who take SSRIs. Concomitant use of NSAIDs and SSRIs may cause an increased risk of bleeding[688][689]. 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 (GI) bleeding and this effect is potentiated by concurrent use of NSAIDs or low-dose [aspirin](#). Hospitalizations for [upper GI 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 (CI), 2.7 to 4.7). Combined use of an SSRI and NSAIDs or low-dose [aspirin](#) increased the risk to 12.2 (95% CI, 7.1 to 19.5) and 5.2 (95% CI, 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 [690].

b) Coadministration of ketorolac with psychoactive drugs (such as [fluoxetine](#)) has been associated with hallucinations in some patients [691].

3.5.1.HZ] Tenoxicam

1) Interaction Effect: an increased risk of bleeding

2) Summary: Caution is recommended with the concomitant use of NSAIDs and SSRIs due to an increased risk of [gastrointestinal bleeding](#)[688][689]. Bleeding events have included [epistaxis](#), ecchymosis, [hematoma](#), [petechiae](#), and life-threatening hemorrhages [692][693][694][695].

3) Severity: major

4) Onset: unspecified

5) Substantiation: probable

6) Clinical Management: Use caution when prescribing NSAIDs to patients who take SSRIs. Concomitant use of NSAIDs and SSRIs may cause an increased risk of bleeding[688][689]. 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 (GI) bleeding and this effect is potentiated by concurrent use of NSAIDs or low-dose [aspirin](#). Hospitalizations for [upper GI 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 (CI), 2.7 to 4.7). Combined use of an SSRI and NSAIDs or low-dose [aspirin](#) increased the risk to 12.2 (95% CI, 7.1 to 19.5) and 5.2 (95% CI, 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 [690].

b) Coadministration of ketorolac with psychoactive drugs (such as [fluoxetine](#)) has been associated with hallucinations in some patients [691].

3.5.1.IA] Terfenadine

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

2j) 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](#)[658][659][660]. [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 [661].

3j) Severity: contraindicated

4j) Onset: delayed

5j) Substantiation: probable

6j) Clinical Management: The concomitant administration of [fluoxetine](#) and [terfenadine](#) is contraindicated.

7j) Probable Mechanism: decreased [terfenadine](#) metabolism

8j) 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 [655].

b) A 39-year old woman experienced [cardiac toxicity](#) due to a possible interaction of [terfenadine](#) and [fluoxetine](#) [656]. 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 [657].

3.5.1.IBj Tetrabenazine

1j) Interaction Effect: increased exposure to tetrabenazine

2j) Summary: Coadministration of [fluoxetine](#), a strong CYP2D6 inhibitor, with tetrabenazine whose active metabolites (alpha-HTBZ and beta-HTBZ) are substrates for CYP2D6 may result in markedly increased exposure to these metabolites. Although coadministration of [fluoxetine](#) and tetrabenazine

was not specifically studied, following 10 days of daily administration of a strong CYP2D6 inhibitor ([paroxetine](#) 20 mg daily), a single dose of tetrabenazine 50 mg resulted in increased alpha-HTBZ and beta-HTBZ exposure in 25 healthy volunteers. When compared with tetrabenazine alone, coadministration with [paroxetine](#) caused an approximately 30% increase in C_{max} 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 C_{max} 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](#). If [fluoxetine](#) is coadministered with tetrabenazine, the total daily dose of tetrabenazine should not exceed 50 mg and single doses should not exceed 25 mg[538].

3) Severity: moderate

4) Onset: unspecified

5) Substantiation: probable

6) Clinical Management: Concomitant use of [fluoxetine](#) and tetrabenazine may result in higher serum concentrations of the active metabolites of tetrabenazine (alpha-HTBZ and beta-HTBZ). Patients who are already receiving a stable dose of tetrabenazine should have their daily dose of tetrabenazine decreased if coadministration with [fluoxetine](#) is necessary. During coadministration, total daily doses of tetrabenazine exceeding 50 mg or single doses exceeding 25 mg are not recommended[538].

7) Probable Mechanism: inhibition of CYP2D6-mediated tetrabenazine metabolism by [fluoxetine](#)

3.5.1.IC| [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[547]. [Fluoxetine](#) has been shown to prolong the QTc interval at the recommended therapeutic dose [548]. Although citing no data, the manufacturer of [thioridazine](#) states that concomitant use with other drugs which prolong the QT interval is contraindicated [547].

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.ID| [Tiaprofenic Acid](#)

1) Interaction Effect: an increased risk of bleeding

2) Summary: Caution is recommended with the concomitant use of NSAIDs and SSRIs due to an increased risk of [gastrointestinal bleeding](#)[688][689]. Bleeding events have included [epistaxis](#), ecchymosis, [hematoma](#), [petechiae](#), and life-threatening hemorrhages [692][693][694][695].

3) Severity: major

4) Onset: unspecified

5) Substantiation: probable

6) Clinical Management: Use caution when prescribing NSAIDs to patients who take SSRIs. Concomitant use of NSAIDs and SSRIs may cause an increased risk of bleeding[688][689]. 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 (GI) bleeding and this effect is potentiated by concurrent use of NSAIDs or low-dose [aspirin](#). Hospitalizations for [upper GI 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 (CI), 2.7 to 4.7). Combined use of an SSRI and NSAIDs or low-dose [aspirin](#) increased the risk to 12.2 (95% CI, 7.1 to 19.5) and 5.2 (95% CI, 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 [690].

b) Coadministration of ketorolac with psychoactive drugs (such as [fluoxetine](#)) has been associated with hallucinations in some patients [691].

3.5.1.IE] [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 selective serotonin reuptake inhibitors 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. Monitor patient for signs of increased bleeding when [fluoxetine](#) is administered with [ticlopidine](#) concomitantly[344].

3) Severity: major

4) Onset: unspecified

5) Substantiation: probable

6) Clinical Management: When [fluoxetine](#) and [ticlopidine](#) are given concurrently, monitor patient for signs of increased bleeding[344].

7) Probable Mechanism: unknown

3.5.1.IF] [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[586][587][124]. 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](#) [124].

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[124].

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 [584]. In addition, both [fluoxetine](#) and [warfarin](#) are tightly bound to albumin. In combination, the possibility for protein-binding displacement of either drug is present [585].

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 [586].

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 [587].

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](#) [588][589].

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 [590].

3.5.1.IG] [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[508].

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](#)[508].

7) Probable Mechanism: unknown

3.5.1.IH] [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 selective serotonin reuptake inhibitors 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. Monitor patient for signs of increased bleeding when [fluoxetine](#) is administered with [tirofiban](#) concomitantly[344].

3) Severity: major

4) Onset: unspecified

5) Substantiation: probable

6) Clinical Management: When [fluoxetine](#) and [tirofiban](#) are given concurrently, monitor patient for signs of increased bleeding[344].

7) Probable Mechanism: unknown

3.5.1.II] [Tolmetin](#)

1) Interaction Effect: an increased risk of bleeding

2) Summary: Caution is recommended with the concomitant use of NSAIDs and SSRIs due to an increased risk of [gastrointestinal bleeding](#)[688][689]. Bleeding events have included [epistaxis](#), ecchymosis, [hematoma](#), [petechiae](#), and life-threatening hemorrhages [692][693][694][695].

3) Severity: major

4) Onset: unspecified

5) Substantiation: probable

6) Clinical Management: Use caution when prescribing NSAIDs to patients who take SSRIs. Concomitant use of NSAIDs and SSRIs may cause an increased risk of bleeding[688][689]. 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 (GI) bleeding and this effect is potentiated by concurrent use of NSAIDs or low-dose [aspirin](#). Hospitalizations for [upper GI 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 (CI), 2.7 to 4.7). Combined use of an SSRI and NSAIDs or low-dose [aspirin](#) increased the risk to 12.2 (95% CI, 7.1 to 19.5) and 5.2 (95% CI, 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 [690].

b)) Coadministration of ketorolac with psychoactive drugs (such as [fluoxetine](#)) has been associated with hallucinations in some patients [691].

3.5.1.IJ] 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[317][318][319][320][321][322]. 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](#) [312]. [Serotonin syndrome](#) is a condition of serotonergic hyperstimulation and manifests as restlessness, myoclonus, changes in mental status, hyperreflexia, diaphoresis, shivering, and tremor [312]. 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 [313].

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%) [314]. 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 [315]. 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](#) [316]. 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.IK] 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[597]. [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](#) [598].

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 [596].

3.5.1.IL] 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[721][722][723][724][725][726][727]. Concomitant use is contraindicated.

3j) Severity: contraindicated

4j) Onset: rapid

5j) Substantiation: probable

6j) 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.

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

8j) Literature Reports

a) Concomitant use of serotonin specific reuptake inhibitors and monoamine oxidase inhibitors can produce a toxic reaction known as [serotonin syndrome](#) [715]. [Serotonin syndrome](#) is a condition of serotonergic hyperstimulation and manifests as restlessness, myoclonus, changes in mental status, hyperreflexia, diaphoresis, shivering, and tremor [715]. 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 [716].

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%) [717]. 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 [718]. 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 [719]. 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 [720]. 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.IM] [Trazodone](#)

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

2) Summary: Both [fluoxetine](#) and [trazodone](#) affect the serotonergic neurotransmitter systems. Concomitant use should be approached with caution due to the additive effects and the potential for increased risk of [serotonin syndrome](#)[336][472]. Coadministration of [trazodone](#) and [fluoxetine](#) has been reported to result in speech dysfunction in a 43-year old man following [traumatic brain injury](#) [477]. There have also been several reports of [serotonin syndrome](#) due to interactions between selective serotonin reuptake inhibitors and antidepressants [478][479][480] Further clinical studies are necessary to determine the incidence and implications of [serotonin syndrome](#) associated with this drug combination. Monitoring for signs and symptoms of [serotonin syndrome](#) is warranted if [fluoxetine](#) and [trazodone](#) are used concurrently, particularly during treatment initiation and dose increases [472].

3) Severity: major

4) Onset: unspecified

5) Substantiation: probable

6) Clinical Management: Use caution with concomitant administration of [fluoxetine](#), a selective serotonin reuptake inhibitor, and [trazodone](#), as this may result in additive serotonergic effects and may increase the risk of [serotonin syndrome](#)[336][472]. If coadministration is required, appropriate monitoring is warranted, particularly during treatment initiation and dose increases [472].

7) Probable Mechanism: additive serotonergic effects

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 [473].

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 [474].

c) 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 [475].

d)) 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 [476].

3.5.1.IN] [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[397][398][399]. 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 [400].

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.IO] [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[557][558]. 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.IP] [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[680][681]. 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 [682]. In addition, concurrent use of [fluoxetine](#) and TCAs such as [desipramine](#), [nortriptyline](#), and [imipramine](#) has resulted in significant increases in TCA concentrations [683][683][684][685][686][687].

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 [674].

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 [675].

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 [676].

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 [677].

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 [678].

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 [679].

3.5.1.IQ] 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[712][713]. 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 [710].

b) Concurrent [paroxetine](#) (another SSRI) and tryptophan have been linked to headache, nausea, sweating, and dizziness [711]. 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.IR] 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[364][365]. 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.IS] 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[581][582]. 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](#) [583].

- 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.IT] Vilazodone

- 1) Interaction Effect: increased risk of [serotonin syndrome](#) or [neuroleptic malignant syndrome](#)
- 2) Summary: Concurrent use of vilazodone with an SSRI may result in [serotonin syndrome](#) or a [neuroleptic malignant syndrome](#) (NMS)-like reaction, which may be life-threatening. Symptoms may include agitation, hallucinations, coma, incoordination, [tachycardia](#), labile blood pressure, [hyperthermia](#), hyperreflexia, nausea, vomiting, and diarrhea. If treatment with vilazodone and an SSRI is required, use caution and monitor patient for signs and symptoms of [serotonin syndrome](#) or NMS. Immediately discontinue both agents if a reaction occurs[294].
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Coadministration of vilazodone with an SSRI may result in [serotonin syndrome](#) or a [neuroleptic malignant syndrome](#) (NMS)-like reaction through additive serotonergic effects. Use caution if the coadministration of vilazodone with an SSRI is required. Closely monitor for signs and/or symptoms of [serotonin syndrome](#) or NMS, especially during treatment initiation and dose increases, and immediately discontinue both agents if symptoms occur[294].
- 7) Probable Mechanism: additive serotonergic effect

3.5.1.IU] 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[586][587][124]. 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](#) [124].
- 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[124].
- 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 [584]. In addition, both [fluoxetine](#) and [warfarin](#) are tightly bound to albumin. In combination, the possibility for protein-binding displacement of either drug is present [585].

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 [586].

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 [587].

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** [588][589].

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 [590].

3.5.1.IV] 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**[697][698].

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](#) [696].

3.5.1.IW] [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[395][396]. 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](#) [259].
- 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 [394].

3.5.1.IX] [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[428]. 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](#) [429].

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 (C_{max}), or time to reach peak concentration (T_{max}) 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, C_{max} 167.94 ng/mL on day 28, 175.91 ng/mL on day 32, T_{max} 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, C_{max} 133.48 ng/mL on day 27, 142.23 ng/mL on day 32, T_{max} 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](#) [426].

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 [427].

3.5.1.IY] Zomepirac

1) Interaction Effect: an increased risk of bleeding

2) Summary: Caution is recommended with the concomitant use of NSAIDs and SSRIs due to an increased risk of [gastrointestinal bleeding](#)[688][689]. Bleeding events have included [epistaxis](#), ecchymosis, [hematoma](#), [petechiae](#), and life-threatening hemorrhages [692][693][694][695].

3) Severity: major

4) Onset: unspecified

5) Substantiation: probable

6j) Clinical Management: Use caution when prescribing NSAIDs to patients who take SSRIs. Concomitant use of NSAIDs and SSRIs may cause an increased risk of bleeding[688][689]. When an SSRI and an NSAID are given concurrently, monitor patient for signs of increased bleeding.

7j) Probable Mechanism: unknown

8j) Literature Reports

a) SSRIs increase the risk of upper gastrointestinal (GI) bleeding and this effect is potentiated by concurrent use of NSAIDs or low-dose [aspirin](#). Hospitalizations for [upper GI 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 (CI), 2.7 to 4.7). Combined use of an SSRI and NSAIDs or low-dose [aspirin](#) increased the risk to 12.2 (95% CI, 7.1 to 19.5) and 5.2 (95% CI, 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 [690].

b) Coadministration of ketorolac with psychoactive drugs (such as [fluoxetine](#)) has been associated with hallucinations in some patients [691].

3.5.1.1Z] Zotepine

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

2j) Summary: [Fluoxetine](#) has been shown to prolong the QTc interval at the recommended therapeutic dose[388]. 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 [389], [quetiapine](#) [390], sertindole [391], sultopride [392], and zotepine [393].

3j) Severity: major

4j) Onset: unspecified

5j) Substantiation: theoretical

6j) Clinical Management: The concurrent administration of [fluoxetine](#) and antipsychotics is not recommended.

7j) 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

1j) Therapeutic

a) [ATTENTION DEFICIT HYPERACTIVITY DISORDER \(ADHD\)](#)

1j) 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)

2j) Improvement in cognitive performance (i.e., reading, memory and mathematical skills)**3j) All children should receive a drug-free trial every year.****bj) BULIMIA**

1j) 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).

cj) DEPRESSION

1j) 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).

dj) NARCOLEPSY

1j) Reduction in daytime sedation with sleep attacks

2j) Reduction in fatigue, impaired performance

3j) Improved night time sleep

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

ej) PANIC ATTACKS

1j) 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).

fj) POSTTRAUMATIC STRESS DISORDER

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

2J) 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).

gJ) OBSESSIVE-COMPULSIVE DISORDER

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

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

hJ) PREMENSTRUAL SYNDROME

1J) 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).

iJ) SOCIAL PHOBIA

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

jJ) TRICHOTILLOMANIA

1J) Reduction or resolution of alopecia and hair pulling

2J) Toxic

aJ) 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 [833][221]. .

bJ) 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 [833][221].

cJ) [Psychosis](#), [hypomania](#) or mania, hallucinations, euphoria, [akathisia](#) or ataxia

dJ) 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 Hydrochloride

Treats depression, obsessive compulsive disorder (OCD), eating disorders, and panic disorders. Sarafem® treats premenstrual dysphoric disorder (PMDD), which is a mood disorder 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. Do 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 use thioridazine (Mellaril®) or an MAOI for at least 5 weeks after you stop taking this medicine. You should not use this medicine if you are using pimozone (Orap®).

How to Use This Medicine:

Capsule, Delayed Release Capsule, Liquid, Tablet

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. Keep using this medicine for the full treatment time. If you feel that the medicine is not working well, do not take more than your prescribed dose. Call your doctor for instructions.

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.

Use only the brand of this medicine that your doctor prescribed. Different brands may not work the same way.

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.

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 outdated medicine or medicine no longer needed.

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 St. John's wort, [alprazolam](#) ([Xanax®](#)), [diazepam](#) ([Valium®](#)), [digoxin](#) ([Lanoxin®](#)), [linezolid](#) ([Zyvox®](#)), [lithium](#) ([Eskalith®](#), [Lithane®](#), [Lithobid®](#)), [tramadol](#) ([Ultram®](#)), tryptophan, [vinblastine](#) ([Velban®](#)), medicine to treat migraine headaches (such as [rizatriptan](#), [sumatriptan](#), [zolmitriptan](#), [Imitrex®](#), [Maxalt®](#), or [Zomig®](#)), pain or [arthritis](#) medicines, sometimes called “NSAIDs” (such as [aspirin](#), [ibuprofen](#), [naproxen](#), [Advil®](#), [Aleve®](#), [Bextra®](#), [Celebrex®](#), [Ecotrin®](#), or [Motrin®](#)), or a blood thinner (such as [warfarin](#), [Coumadin®](#)).

Tell your doctor if you are using other medicines to treat depression (such as [amitriptyline](#), [desipramine](#), [doxepin](#), [imipramine](#), [nortriptyline](#), [Pamelor®](#), or [Sinequan®](#)), medicine to treat mental illness (such as [clozapine](#), [haloperidol](#), [Clozaril®](#), or [Haldol®](#)), medicine for seizures (such as [carbamazepine](#), [phenytoin](#), [Dilantin®](#), or [Tegretol®](#)), or medicine for heart rhythm problems (such as [flecainide](#), [propafenone](#), [Rhythmol®](#), or [Tambocor®](#)).

Tell your doctor if you are also using any other medicine that contains [fluoxetine](#) such as [Symbyax®](#).

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 or planning to become pregnant. Tell your doctor if you have [kidney disease](#), liver disease, [heart disease](#), bleeding problems, [diabetes](#), [epilepsy](#) or seizures, [glaucoma](#), low sodium in the blood, a recent [heart attack](#), or a history of mania or drug abuse. Tell your doctor if you are receiving [electroconvulsive therapy](#) (ECT).

Do not breastfeed while you are using this medicine.

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.

This medicine may cause a serious condition called [serotonin syndrome](#) and [neuroleptic malignant syndrome](#) (NMS)-like reactions when it is taken with certain medicines. Check with your doctor first before taking any other medicines.

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.

[Hyponatremia](#) (low sodium in the blood) may occur with this medicine. Stop using the medicine and check with your doctor right away if you have confusion, difficulty concentrating, headaches, memory problems, weakness, and unsteadiness.

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.

This medicine may raise or lower your blood sugar, or it may cover up symptoms of very low blood sugar ([hypoglycemia](#)).

Your doctor will need to check your progress at regular visits while you are using this medicine. Be sure to keep all appointments. Blood tests may be needed to check for unwanted effects.

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**, or red skin rash.
 Change in how much or how often you urinate.
 Changes in behavior, or thoughts of hurting yourself or others.
 Chest pain, or fast, pounding, or uneven heartbeat.
 Confusion, body weakness, and muscle twitching.
 Dry mouth, increased thirst, muscle cramps, nausea, or vomiting.
 Feelings of intense anxiety, agitation, or irritability.
 Fever, chills, **cough**, sore throat, and body aches.
 Painful, prolonged erection of your penis.
 Seizures or tremors.
 Trouble sleeping or unusual dreams.
 Unusual bleeding, bruising, or weakness.
 Vomiting blood or something that looks like coffee grounds.
 Weight loss.

If you notice these less serious side effects, talk with your doctor:

Changes in appetite with weight gain or loss.
 Diarrhea, constipation, gas, or upset stomach.
 Dizziness, drowsiness, sleepiness, or yawning more than usual.
 Ear pain or ringing in your ears.
 Headache.
 Mild skin rash.
 Nervousness, shakiness, or sweating.
 Stuffy or runny nose.
 Tiredness.
 Trouble having sex.

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 [834].

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 [835].

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 [816]. The chemical structure of **fluoxetine** differs from that of tricyclic antidepressants [10]; 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 [12].

2) **Fluoxetine** has been demonstrated to be a specific inhibitor of serotonin uptake in vitro and in vivo in man and animals [803][817][818][807][816][819] while producing little effect on the noradrenergic system [820][803][818][816][821]. 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 [816][819]. **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 [816]. 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% [801].

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) [816][822].

B) REVIEW ARTICLES

1) A comparison of selective serotonin reuptake inhibitors with a guide to selection is provided [823].

- 2) Two reviews provide a discussion of the efficacy of selective serotonin reuptake inhibitors and other antidepressants for treatment of severe depression [824][825].
- 3) The efficacy of antidepressants in reducing panic attack frequency, symptoms of depression, social avoidance, and overall impairments from [panic disorder](#) is addressed [826].
- 4) A review article described the treatment of [panic disorder](#), including the place of selective serotonin reuptake inhibitors for this disorder [827].
- 5) Treatment of elderly patients with selective serotonin reuptake inhibitors is discussed with emphasis on improved tolerability compared to other antidepressants [828].
- 6) A review article discussed the rational treatment of depression and included a discussion of each class of antidepressants [829].
- 7) Pharmacologic comparisons of the various selective serotonin reuptake inhibitors and their potential therapeutic distinctions were provided in a review [830].
- 8) Drug-interactions of antidepressants are reviewed in German language [831].

4.5] Therapeutic Uses

4.5.A] [Fluoxetine](#)

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](#)

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 [57].

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 with 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 with 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 with placebo. Patients were randomly assigned to placebo or [fluoxetine](#) 20 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 [57].

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 [58]

Ineffective during a small (n=31), placebo-controlled trial when added to a structured psychological and behavioral program [59]

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 BMI, 15.4 +/-1.8 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 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 [58].

2j) 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 mg daily which was increased over 1 week to 60 mg daily. At 7 weeks (study endpoint), 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 [59].

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 mg/day was effective in the treatment of overanxious disorder, [social phobia](#), or separation anxiety disorder in an analysis of twenty-one patients 11 to 17 years of age [63].

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 [60].

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 [61].

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 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 [61].

4.5.B.6] 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](#) [62].

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 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% compared with 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 [62].

4.5.B.7] 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](#) [2]

[Fluoxetine](#) is effective in the treatment of [bulimia](#); beneficial effects may be seen as early as one week after initiation of therapy [3][4][5].

In a small, open-label study, [fluoxetine](#) therapy reduced symptoms of [bulimia nervosa](#) in pediatric patients [6].

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 mg/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 [3].

2) Addition of medication to psychological therapy resulted in greater improvement in binge eating, vomiting, and depression than psychological therapy alone [4]. 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 mg/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 mg/day was effective in the treatment of [bulimia nervosa](#) in an uncontrolled study involving 10 patients [5].

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 [7].

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 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=non-significant). 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) [6].

4.5.B.8] [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 [66]

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 mg 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%) [66].

4.5.B.9] [Cancer pain](#)

See Drug Consult reference: MANAGEMENT OF CANCER-RELATED PAIN IN ADULT PATIENTS

4.5.B.10] 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 [70][71][72].

Improved motor performance after [stroke](#) reported in a limited number of patients [73]

Antidepressant treatment given during the first six months following [stroke](#) increased long-term survival in depressed and non-depressed patients [74].

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 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/mL. 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 (HAMD). 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 vs 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 ($p=0.09$ vs 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 [70].

2) 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 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 with patients who received antidepressant therapy (87.8% vs 35.3%, respectively, $p=0.0005$) [74].

3) A single dose of [fluoxetine](#) 20 mg, 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 [73].

4j) **Fluoxetine** reduced post-stroke emotionalism in 8 of 9 patients compared with none of the control patients. Twenty patients with emotionalism of greater than 4 weeks duration were randomly assigned to **fluoxetine** 20 mg 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 [71].

4.5.B.11] **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 [64].

4.5.B.12] **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 patients with **diabetes** [65].

c) Adult:

1j) **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 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 vs 13.6, $p=0.03$; HAMD, 9.4 vs 14.1, $p=0.01$). The percentage of patients with significant clinical improvement measured by the BDI was greater with [fluoxetine](#) than placebo (66.7% vs 37%, $p=0.03$). Although [fluoxetine](#)-treated patients demonstrated a greater reduction in mean GHb levels compared with the placebo group, the difference was not statistically significant (-0.4% vs -0.07%, $p=0.13$). 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 [65].

4.5.B.13] 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 with [fluoxetine](#) treatment in 78% of women with HIV [67][68].

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 mg/day or [sertraline](#) 50 mg/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 [67].

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 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 with 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 [68].

4.5.B.14] [Dysthymia](#)**a) Overview**

FDA Approval: Adult, no; [Pediatric, no](#)

Efficacy: Adult, Evidence favors efficacy

Recommendation: Adult, Class IIb

Strength of Evidence: Adult, Category B

See Drug Consult reference: [RECOMMENDATION AND EVIDENCE RATINGS](#)

b) Summary:

Small, uncontrolled clinical studies have shown that [fluoxetine](#) improves [dysthymia](#) in adult and elderly patients. Larger, controlled clinical trials are needed for this indication [75][76][77].

c) Adult:

1) In a study of patients with [primary dysthymia](#), [fluoxetine](#) resulted in significant improvement in clinical and social functioning compared with placebo; non-responders also showed improvement with an increase in [fluoxetine](#) dose. Patients showing a response at 3 months continued [fluoxetine](#) 20 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](#) [75].

2) [Fluoxetine](#) 20 to 60 mg/day has demonstrated efficacy in [primary dysthymia](#) [76]. 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% vs 25%, respectively). Full efficacy of [fluoxetine](#) treatment for [dysthymia](#) may not be seen for a period of 16 weeks [77].

3) [Fluoxetine](#) (mean dose, 35.5 mg/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 [78].

4.5.B.15] [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](#) [79]

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 NSAIDs) and [acetaminophen](#) on their usual schedules. [Fluoxetine](#) was started at 20 mg/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 [79].

4.5.B.16] 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](#) [80].

[Fluoxetine](#) lacks efficacy for treating migraine [80].

S-fluoxetine is more effective than placebo in the prevention of migraine headache [81].

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 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 [81].

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/day and advanced to 40 mg/day 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 [80].

4.5.B.17] 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](#) [82]

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, crossover trial, 68 women experiencing at least 14 hot flashes per week were given [fluoxetine](#) 20 mg/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](#) [82].

4.5.B.18] [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) [83].

c) Adult:

1) Thirty patients were randomly assigned to receive placebo or [fluoxetine](#) 20 mg/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 with 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 [83].

4.5.B.19) 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](#) [2]

Effective in placebo-controlled studies using doses from 20 to 80 mg daily [8][9](Wernicke et al, 1987; Rickels et al, 1986)

Similar onset of antidepressant effect to [amitriptyline](#) and [imipramine](#) [10][11][12]

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 mg) was effective in the treatment of mild to severe

depression. All patients were treatment-naïve and had an average decrease of 4.6 points on the Hamilton Depression Rating Scale after 12 weeks of therapy [13].

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 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. [Fluoxetine](#) therapy was initiated with 20 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 [14].

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 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](#) compared with 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 [15].

b) The efficacy of [fluoxetine](#) in treating depression may be enhanced by coadministered [pindolol](#), according to a 6-week randomized, double-blind study. Overall, 41 of 55 patients (75%) administered [fluoxetine](#) 20 mg/day with [pindolol](#) 7.5 mg/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 [16]. The advantage of the combination therapy may relate to [pindolol's](#) action in blocking the decrease in serotonergic neural activity caused by SSRIs, thus enhancing therapeutic effects of the SSRI.

3) Maintenance Therapy

a) Once-weekly dosing of [fluoxetine](#) with the enteric-coated 90-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 [17].

b) In a small, double blind, placebo-controlled trial, once weekly [fluoxetine](#), 60 mg, was as effective as [fluoxetine](#) 20 mg/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 [18].

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 mg/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 [19]. The use of [fluoxetine](#) 90-mg enteric-coated tablets once weekly was associated with increased compliance compared with 20 mg of regular-release [fluoxetine](#) once daily (85.9% vs 79.4%) in a 12-week, open-label, randomized trial (n=109) [20].

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 mg daily of [fluoxetine](#) in a 12- to 14-wk 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](#) [21].

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 [22]. After a 4-week evaluation phase, patients were randomly assigned to receive placebo or [fluoxetine](#) 20 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 with placebo; 56% compared with 33% of patients treated with [fluoxetine](#) and placebo improved on the CGI scale. Dropouts 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 and 17 years with a primary diagnosis of major depressive disorder. Patients were randomized to fluoxetine 10 to 40 mg/day, CBT alone, CBT with fluoxetine 10 to 40 mg/day, 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 with placebo) [23].

4.5.B.20] Migraine; Prophylaxis

See Drug Consult reference: MIGRAINE -- RECOMMENDATIONS FOR PROPHYLAXIS IN ADULTS

4.5.B.21] 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 myocardial infarction [84]

c) Adult:

1) In a case-control study comprised of 653 cases of first myocardial infarction (MI) and 2990 control subjects, results indicated that 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 with 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 [84].

4.5.B.22| 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 mg/day was effective for promoting weight loss in non-depressed patients, but patients tended to regain weight after fluoxetine was stopped [85](Levine et al, 1987). The drug has been as effective as benzphetamine [85]. Optimal doses appear to be 60 to 80 mg 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 [7]. 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 mg/day compared with placebo in promoting weight loss was evaluated in a 52-week multicenter trial [86]. Study sites that demonstrated the greatest benefit with fluoxetine also utilized nutrition and behavior counseling.

4.5.B.23| 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 [2].

c) Adult:

1) Of the SSRIs (ie, [fluoxetine](#), [sertraline](#), [paroxetine](#), [fluvoxamine](#)) with United States 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 [38][39]. 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](#) [39]. 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 [39]. 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 [40]. 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 [40].

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 mg daily [41]. 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 [42]. 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 with baseline [43]. 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 mg/day, titrated upward as tolerated to a maximum of 80 mg/day; the mean maximal dose was 75 mg/day. Doses above 20 mg/day were divided (not necessarily evenly) into morning and afternoon allotments.

5j) 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 mg/day to 60 to 100 mg/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 [44].

6j) Fluoxetine-treated patients experienced significant improvements (compared with 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** [45]. **Fluoxetine** was titrated from an initial daily dose of 20 mg/day to 80 mg/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.

dj) Pediatric:

1j) 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 [46].

2j) 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 mg/day was associated with decreased tic severity, and improvement in attention abilities and social functioning [47]. Scores on measures of obsessive-compulsive symptoms, however, showed some improvement, but were not statistically different from placebo.

3j) **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**) [48]. 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.24j **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](#) [2]

c) Adult:

1) [Fluoxetine](#) (20 to 60 mg 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 with 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 [2].

2) [Fluoxetine](#) was useful for treating [panic disorder](#) in a 10-week study [49]. In a double-blind study, 243 patients with confirmed [panic disorder](#) were randomly assigned to placebo, [fluoxetine](#) 10 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 with 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 with 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 mg/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 mg/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](#) [50].

4) [Fluoxetine](#) up to 80 mg daily was effective in the treatment of panic attacks in 7 of 16 patients in an open study [51]. 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 mg daily, suggesting idiosyncrasy. Controlled studies are required to allow full evaluation of the efficacy of [fluoxetine](#) in panic attacks.

4.5.B.25] 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 [87]

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 of 25 years, took [fluoxetine](#) for 6 weeks, starting at 20 mg/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 [87].

4.5.B.26] 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 [69].

c) Adult:

1) [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 [69].

4.5.B.27] 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 [91][92]

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 mg/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 [91].

2) Fluoxetine was more effective than placebo for treating **posttraumatic stress disorder** (PTSD). In a 12-week, double-blind study, 54 patients were randomly assigned to placebo or **fluoxetine** 10 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% vs 19%; p less than 0.0005). The Davidson Trauma Scale (DTS) total scores were also significantly lower in patients treated with **fluoxetine** compared with 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 [92].

4.5.B.28] 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 [88][89][90].

c) Adult:

1) Treatment with either 20 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 0.5 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, [88].

2) Latency time to ejaculation increased from slightly less than 1 minute to nearly 10 minutes during 8 weeks of open-label treatment among 11 men with [fluoxetine](#) 40 mg daily (maximum, 60 mg), with confirmation in a placebo-controlled trial of 17 men [89][90]. Significant subjective changes included increased sexual desire, partner satisfaction, and decreased anxiety concerning [premature ejaculation](#) [89].

4.5.B.29) 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:

[Fluoxetine](#) is indicated for the treatment of [premenstrual dysphoric disorder](#) (PMDD) [52] [Fluoxetine](#) 90 mg given twice during the luteal phase was more effective than placebo in reducing symptoms of [premenstrual dysphoric disorder](#) in a randomized, double-blind, multicenter, placebo-controlled trial (n=257) [53].

In a double-blind, randomized, multicenter, placebo-controlled trial (n=260), [fluoxetine](#) 20 mg given daily during the luteal phase was more effective than either [fluoxetine](#) 10 mg or placebo at reducing symptoms of [premenstrual dysphoric disorder](#) [54]

c) Adult:

1) Enteric-coated [fluoxetine](#) 90 mg given twice during the luteal phase was more effective than placebo in reducing symptoms of [premenstrual dysphoric disorder](#) (PMDD) in women aged 18 to 45 years during a randomized, double-blind, multicenter, placebo-controlled trial (n=257). Patients used the validated Daily Record of Severity of Problems (DRSP) scale to self-report symptoms in 11 defined categories of PMDD. Women who did not meet the criteria for PMDD in at least 2 consecutive menstrual cycles, those using hormonal contraceptives, or those with a major axis I psychiatric disorder were excluded. After a one-cycle, single-blind, placebo run-in period, patients were randomized to one of 3 treatment arms for 3 consecutive menstrual cycles: [fluoxetine](#) 90 mg on days 14 and 7 (twice luteal phase weekly dosing (LPWDx2); n=84); placebo on day 14 and [fluoxetine](#) 90 mg on day 7 (once luteal phase weekly dosing (LPWDx1); n=83); or placebo on days 14 and 7 (n=80). Baseline DRSP total scores during the luteal phase ranged from 76.7 and 78.3, and were comparable amongst treatment groups. In the intent-to-treat analysis, the mean change in DRSP total score (primary efficacy outcome) during the luteal phase was -30.4 +/- 19.7 in the LPWDx2 group compared with -25.3 +/- 16.5 in the LPWDx1 group (p=0.022) and -25.9 +/- 18.6 in the placebo group (p=0.043). However, there was no statistical significant difference in DRSP score reduction between the LPWDx1 and the placebo group (p=0.793). LPWDx2 was more effective than placebo in improving DRSP subcategory of mood (-14.5 vs -11.6; p=0.006) and social functioning (-5.3 vs -4.5; p=0.035), but not in physical symptoms (p=0.098) [53].

2) In a double-blind, randomized, multicenter, placebo-controlled trial (n=260), [fluoxetine](#) 20 mg given daily during the luteal phase was more effective than either [fluoxetine](#) 10 mg or placebo at reducing symptoms of [premenstrual dysphoric disorder](#) (PMDD) in women aged 18 to 45 years. Patients used the validated Daily Record of Severity of Problems (DRSP) scale to self-report symptoms in 11 defined categories of PMDD. Women who did not meet the criteria for PMDD during the screening period, those using hormonal contraceptives, or those with an axis I psychiatric disorder other than PMDD, were excluded. After a one-cycle, single-blind placebo run-in period, patients were randomized to daily treatment during their luteal phase (day 14 prior to expected onset of menses up to the first day of active bleeding) with either [fluoxetine](#) 20 mg (n=86), [fluoxetine](#) 10 mg (n=86) or placebo (n=88). Treatment was given for 3 consecutive menstrual cycles. The mean change in DRSP total luteal score (primary outcome) was significant for the [fluoxetine](#) 20-mg group compared with the placebo group (-31.3 +/- 17.6, baseline 80.9 vs -23.2 +/- 16.8, baseline 78.1; p=0.005). However, the mean change in DRSP total luteal score for [fluoxetine](#) 10 mg (-27.5 +/- 20.1) did not reach statistical significance relatively to [fluoxetine](#) 20 mg (p=0.234) or placebo (p=0.1). Physical symptoms, such as breast tenderness, bloating, headache, and joint or muscle pain, were significantly improved in all 3 treatment cycles in the [fluoxetine](#) 20-mg group. Decreased libido was reported only in the [fluoxetine](#) treatment groups, 9.3% with [fluoxetine](#) 20 mg and 5.8% with [fluoxetine](#) 10 mg [54].

3) [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 mg 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](#) [55]. 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 mg/daily, or **fluoxetine** 60 mg/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 [56]. **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.

4.5.B.30] **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** [93]
More effective in women than in men [93]

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 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 [93].

4.5.B.31] **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 [94]

[Fluoxetine](#) reduced the effectiveness of [olanzapine](#) treatment [95]

[Fluoxetine](#) did not reduce olanzapine-induced weight gain [95].

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 mg/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 [95].

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 with the baseline value (p less than 0.001). Furthermore, [fluoxetine](#) decreased depressive symptoms as measured by the Hamilton Rating Scale for Depression and Anxiety (HAM-D) (p less than 0.05). The effect of adjunctive [fluoxetine](#) on negative schizophrenic symptoms was evaluated in 34 inpatients with [chronic schizophrenia](#). [Fluoxetine](#) 20 mg/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 [94].

4.5.B.32] [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](#) [96].

c) Adult:

1j) [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 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 [96].

4.5.B.33] [Severe major depression with psychotic features](#)

See Drug Consult reference: [PSYCHOTIC DEPRESSION - DRUG THERAPY](#)

4.5.B.34] [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 [97]

Another trial found no significant difference between placebo and [fluoxetine](#) related to improvement of [social phobia](#) [98]

[Fluoxetine](#) may be effective in ameliorating social phobic symptoms during [clozapine](#) treatment in schizophrenic patients [99].

c) Adult:

1j) 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 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 compared with placebo; p=0.09 overall active treatment compared with 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 [97].

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 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 posttreatment 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). Dropouts 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%) [98].

3) Fluoxetine was effective for ameliorating social phobia that emerged during clozapine treatment. Twelve patients (5 women and 7 men, 19 to 28 years of age) 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 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) [99].

4.5.B.35] Tinnitus

See Drug Consult reference: DRUG THERAPY OF TINNITUS

4.5.B.36] [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 [100][101][102]; however, it was ineffective in a small clinical trial which evaluated [fluoxetine](#) for treating [trichotillomania](#) [103]. 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 [103].

2) Case reports of [trichotillomania](#) and other forms of self-injurious behaviors have noted some benefit with [fluoxetine](#) therapy [100][101][102]. These behaviors are often associated with depression or [obsessive-compulsive disorder](#) which may account for the efficacy of [fluoxetine](#).

4.5.B.37] [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, 15 to 70 years of age, with a history of untreated VVS [1]

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 yr; range, 15 to 70 yr) who had experienced at least 5 syncope 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 mg/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 with 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 with 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) [1].

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 yr; range, 15 to 70 yr) who had experienced at least 5 syncope 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 mg/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 with 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 with 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) [1].

4.6] Comparative Efficacy / Evaluation With Other Therapies

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 [888].

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 [850].

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 [851]. These preliminary results should be confirmed in further trials.

4.6.C] Amitriptyline

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 [892][893][894][895] [896]; (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](#) [897]. 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 [892]. Similar results were reported in another study (n=40) [896].

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 [899]. 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 [898]. 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 [891]. 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 [900].

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 [848]. 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 [849][848], 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 [905].

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) [904].

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 [840].

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 [841].

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](#) [902].

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 outpatient visits. Although drug costs were higher, total treatment costs were slightly lower for the [fluoxetine](#) group; however, this difference was not statistically significant [903].

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 [839]. 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 [867]. 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 [854].

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](#) [855].

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](#) [855]. 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 [856].

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 [847].

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 [857].

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 outpatient visits. Although drug costs were higher, total treatment costs were slightly lower for the [fluoxetine](#) group; however, this difference was not statistically significant [858].

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](#) [859][860][861]. [Fluoxetine](#) was as effective as [imipramine](#) doses of 150 to 300 milligrams/day [862]. However, in one report [863], [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](#) [860]. 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](#) [860]. 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 [863]. [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 [901]. 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 mianserin, and 43% for placebo). The incidence of side effects was high, 92%, 88%, and 44% for fluoxetine, mianserin, and placebo, respectively [852].

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 [869][870]. 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 [871]; 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 [872][870][873]. 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 [870].

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 [876]. 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](#) [864].

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](#) [865]. 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 [866].

4.6.Q] [Nefazodone](#)

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](#) [874].

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](#) [875]. 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=0.003) but not for those with [secondary Raynaud's phenomenon](#). Reductions with [nifedipine](#) were not statistically significant for those subgroups [877].

4.6.S] [Nortriptyline](#)

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 [890].

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](#) [889].

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 [887].

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 [885].

b) [Paroxetine](#) and [fluoxetine](#) demonstrated similar efficacy following 6 weeks of treatment in depressed patients [886]. 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 [868].

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 [882].

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 [883][884].

4.6.Y] Sertraline

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 [878].

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 (HAM-D), 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 [879]. Investigation in a larger population is warranted to definitively establish the comparative efficacy and safety of the two drugs [879].

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](#) [880].

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[881].

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 [853].

4.6.AA] Trazodone

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 [836]. 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 [837]. 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 trazodone, fluoxetine-treated patients manifested symptoms of mania more slowly than trazodone-treated patients [838]. 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

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 [844].

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 [845].

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 [846]. 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 [843].

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%) [842].

6.0] References

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