

DRUGDEX-EV 2540

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FLUVOXAMINE

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0.0] Overview

1) Class

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

Antidepressant
Central Nervous System Agent

2) Dosing Information

a) [Fluvoxamine](#) Maleate

1) Adult

a) Depression

1) 50 to 300 mg/day orally (off-label dosage) [9][10][11]

b) [Obsessive-compulsive disorder](#)

1) (Immediate-release) Initial, 50 mg/day orally at bedtime; may increase by 50-mg increments every 4 to 7 days to MAX 300 mg/day; usual effective range, 100 to 300 mg/day; divide into 2 doses when total dose exceeds 100 mg/day (FDA dosage) [20]

2) (Extended-release) Initial, 100 mg/day orally at bedtime; may increase by 50-mg increments every week to MAX 300 mg/day; usual effective range, 100 to 300 mg/day (FDA dosage) [1]

3) Initial, 50 mg/day orally; may increase by 50 mg/day once every week to usual target dose of 200 mg/day; MAX 300 to 450 mg/day, especially in rapid metabolizers or those with inadequate response after 8 weeks on MAX FDA dosage (guideline dosage) [21]

4)) Discontinuation, gradual dose reduction is preferred to abrupt cessation because of withdrawal symptoms [1][20]

c)) Social phobia

1)) (Extended-release) 100 mg/day orally at bedtime; may increase by 50-mg increments every week to MAX 300 mg/day (usual effective range, 100 to 300 mg/day) (off-label dosage) [34]

2)) Pediatric

a)) Extended-release [fluvoxamine](#) maleate has not been evaluated for use in pediatric patients; in pediatric patients naive to [fluvoxamine](#), the lowest available dose of extended-release [fluvoxamine](#) may not be appropriate [22].

1)) Obsessive-compulsive disorder

a)) (Immediate-release, 8 to 11 years) Initial, 25 mg/day orally at bedtime; may increase by 25-mg increments every 4 to 7 days to MAX 200 mg/day; usual effective range, 50 to 200 mg/day; divide into 2 doses when total dose exceeds 50 mg/day [20]

b)) (Immediate-release, 12 to 17 years) Initial, 25 mg/day orally at bedtime; may increase by 25-mg increments every 4 to 7 days to MAX 300 mg/day; usual effective range, 50 to 200 mg/day; divide into 2 doses when dosage exceeds 50 mg/day [20]

c)) (Extended-release) The lowest available dose may not be appropriate, especially in pediatric patients naive to fluvoxamine [1]

d)) Discontinuation, gradual dose reduction is preferred to abrupt cessation because of withdrawal symptoms [20]

3)) Contraindications

a)) [Fluvoxamine](#) Maleate

1)) Concomitant use with [aloseptron](#), [pimozide](#), [thioridazine](#), [tizanidine](#) [40][22], or [ramelteon](#) [1]

2)) Concomitant use of MAOIs, including [linezolid](#) or IV methylene blue, within 14 days of [fluvoxamine](#) discontinuation or use of [fluvoxamine](#) within 14 days of discontinuing an MAOI; increased risk of [serotonin syndrome](#) [20][1]

4)) Serious Adverse Effects

a)) [Fluvoxamine](#) Maleate

1)) [Agranulocytosis](#)

- 2)) [Anaphylaxis](#)
- 3)) Depression, worsening
- 4)) Hemorrhage, Abnormal
- 5)) [Hyponatremia](#)
- 6)) [Neuroleptic malignant syndrome](#)
- 7)) Seizure
- 8)) [Serotonin syndrome](#)
- 9)) [Stevens-Johnson syndrome](#)
- 10)) Suicidal thoughts
- 11)) Suicide
- 12)) [Toxic epidermal necrolysis](#)

5)) Clinical Applications

a)) [Fluvoxamine](#) Maleate

1)) FDA Approved Indications

a)) [Obsessive-compulsive disorder](#)

2)) Non-FDA Approved Indications

a)) Depression

b)) [Social phobia](#)

1.0) Dosing Information

[Drug Properties](#)

[Storage and Stability](#)

[Adult Dosage](#)

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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

[Fluvoxamine](#)

[Fluvoxamine](#) Maleate

C)) Physicochemical Properties

1)) Molecular Weight

a)) **Fluvoxamine** base: 318.3 [769]; **Fluvoxamine** maleate: 434.41 [770]

2)) Solubility

a)) Systemic: **Fluvoxamine** maleate is sparingly soluble in water [771] and freely soluble in ethanol [771].

1.2) Storage and Stability**A)) **Fluvoxamine** Maleate****1)) Preparation****a)) Oral route****1)) Immediate-release Formulation**

a)) Take at bedtime [40].

b)) Divide total daily doses greater than 100 mg of immediate-release tablets into 2 doses; if 2 doses of unequal size are to be taken daily, the larger dose should be taken at bedtime [40].

2)) Extended-release Formulation

a)) Take at bedtime [22].

b)) Do not crush or chew extended-release capsules [22].

B)) **Fluvoxamine Maleate****1)) Oral route****a)) Capsule, Extended Release/Tablet**

1)) Store at controlled room temperature of 25 degrees C (77 degrees F), with excursions permitted between 15 and 30 degrees C (59 and 86 degrees F). Protect from high humidity [40][22].

2)) Do not expose extended-release capsules to temperatures above 30 degrees C (86 degrees F) [22].

1.3) Adult Dosage**1.3.1) Normal Dosage**

1.3.1.A] Important Note

j) Discontinue MAOIs intended to treat psychiatric disorders at least 14 days prior to the administration of fluvoxamine. Allow at least 14 days to elapse between discontinuation of fluvoxamine and initiation of MAOIs intended to treat psychiatric disorders [1].

j) Do not initiate fluvoxamine in a patient receiving linezolid or IV methylene blue. If a patient is already receiving fluvoxamine and treatment with linezolid or IV methylene blue is unavoidable, and the potential benefit of therapy outweighs the risk for serotonin syndrome, discontinue fluvoxamine. Monitor for symptoms of serotonin syndrome for 2 weeks or for 24 hours after the last dose of linezolid or IV methylene blue, whichever comes first. Resume fluvoxamine therapy 24 hours after the last dose of linezolid or IV methylene blue [1].

j) Beers Criteria: Use caution or avoid use as potentially inappropriate in older adults [2].

1.3.1.B] Fluvoxamine Maleate**1.3.1.B.1] Oral route****1.3.1.B.1.a] Depression**

1j) Off-label dosage: 50 to 300 mg/day orally [9][10][11]. A single night time dose of fluvoxamine appears to be best tolerated (Siddigui et al, 1985).

1.3.1.B.1.b] Obsessive-compulsive disorder**1j) FDA Dosage**

a) Usual dosage: 100 to 300 mg/day [1][20]. Give extended-release capsule once daily at bedtime [1], and divide total daily dose greater than 100 mg into 2 doses when using immediate-release tablet. If the doses are not equal, give larger dose at bedtime [20].

b) Initial dosage and titration (immediate-release tablet): 50 mg orally once daily; may titrate by 50 mg/day once every 4 to 7 days, as tolerated [20]

c) Initial dosage and titration (extended-release capsule): 100 mg orally once daily; may titrate by 50 mg/day once every week, as tolerated [1]

d) Maintenance dosage: Use lowest effect dosage and periodically reassess long-term use [1][20].

e) Maximum dosage: 300 mg/day [1][20]

f) Discontinuation: Gradual dose reduction is preferred to abrupt cessation because of withdrawal symptoms [1][20].

2j) Guideline Dosage

a) Usual dosage: 200 mg/day [21].

b) Initial dosage and titration: 50 mg/day orally; may increase by 50 mg/day once every week during the first month of therapy. If little or no response is seen in first 4 weeks, continue to increase weekly or biweekly to the maximum dosage tolerated, with a period of at least 4 to 6 weeks at the highest comfortably tolerated dosage [21].

c) Maintenance dosage: Continue effective dosage for 1 to 2 years before considering discontinuation [21].

d) Maximum dosage: 300 to 450 mg/day, especially in rapid metabolizers or those with no or minimal side effects and inadequate response after 8 weeks on the maximum FDA dosage [21].

e) Discontinuation: Gradually reduce dose over several months or more [21].

See Drug Consult reference: Class Comparison: SSRIs and Serotonin [Norepinephrine](#) Reuptake Inhibitors (SNRIs) (Selected)

1.3.1.B.1.c] [Social phobia](#)

1) In a clinical study of adult patients with generalized [social anxiety disorder](#), the dose of [fluvoxamine](#) extended-release capsules used was an initial dose of 100 mg/day orally, titrated weekly in 50 mg increments, to a maximum dose of 300 mg/day (usual effective range, 100 to 300 mg/day) [34].

1.3.2] Dosage in [Renal Failure](#)

A) [Fluvoxamine](#) Maleate

1) [Renal impairment](#) does not appear to affect the pharmacokinetics of [fluvoxamine](#) (Raghoebar & Roseboom, 1988). However, a low starting dosage along with careful monitoring is recommended, especially during the first month of treatment.

1.3.3] Dosage in [Hepatic Insufficiency](#)

A) [Fluvoxamine](#) Maleate

1) Immediate-release Formulation

a) Because [fluvoxamine](#) undergoes extensive hepatic metabolism, a reduction in the initial dose and slower dose titration may be required in patients with [hepatic insufficiency](#) [40]; (Harten et al, 1993)[41][42]. A 30% decrease in [fluvoxamine](#) clearance was noted in patients with [hepatic insufficiency](#) [40].

b) The pharmacokinetics of [fluvoxamine](#) were studied in 13 patients with biopsy-proven [liver cirrhosis](#) [43]. They received a single oral 100 mg dose as an enteric-coated tablet and plasma samples were collected up to one week after administration. The mean elimination half-life was 25 hours and it increased with higher plasma [bilirubin](#) levels although no relationship between [bilirubin](#) and AUC was observed. The AUC was about 50% higher in patients than in healthy volunteers. The authors recommended that in patients with signs of active liver disease, it is wise to initiate [fluvoxamine](#) treatment at a lower daily dose and to carefully monitor the patient during subsequent dose increases.

2) Extended-release Formulation

a) Initiate at 100 mg/day orally; titrate slowly in patients with [hepatic impairment](#) as their [fluvoxamine](#) maleate clearance was decreased [22].

1.3.4] Dosage in Geriatric Patients

A) Fluvoxamine Maleate

1) Immediate-release Formulation

a) Mean fluvoxamine plasma concentrations are reported to be 40% higher in elderly versus young subjects following doses of 50 or 100 mg. Fluvoxamine clearance is also reduced by 50% in the elderly. Fluvoxamine dosage should be slowly titrated in elderly patients following the initial 100 mg/day dose [40].

2) Extended-release Formulation

a) Initiate at 100 mg/day orally; titrate slowly in geriatric patients as their fluvoxamine maleate clearance was decreased [22].

1.4] Pediatric Dosage

1.4.1] Normal Dosage

1.4.1.A] Important Note

J) Discontinue MAOIs intended to treat psychiatric disorders at least 14 days prior to the administration of fluvoxamine. Allow at least 14 days to elapse between discontinuation of fluvoxamine and initiation of MAOIs intended to treat psychiatric disorders [1].

J) Do not initiate fluvoxamine in a patient receiving linezolid or IV methylene blue. If a patient is already receiving fluvoxamine and treatment with linezolid or IV methylene blue is unavoidable, and the potential benefit of therapy outweighs the risk for serotonin syndrome, discontinue fluvoxamine. Monitor for symptoms of serotonin syndrome for 2 weeks or for 24 hours after the last dose of linezolid or IV methylene blue, whichever comes first. Resume fluvoxamine therapy 24 hours after the last dose of linezolid or IV methylene blue [1].

J) Beers Criteria: Use caution or avoid use as potentially inappropriate in older adults [2].

1.4.1.B] Fluvoxamine Maleate

1.4.1.B.1] Oral route

1.4.1.B.1.a] Obsessive-compulsive disorder

1) FDA Dosage, Immediate-release Tablet

a) 8 to 11 Years

1) Usual dosage: 50 to 200 mg/day. Divide into 2 doses when total dose exceeds 50 mg/day, and if doses are not equal, give larger dose at bedtime [20].

2) Initial dosage and titration: 25 mg orally at bedtime; may titrate by 25 mg/day once every 4 to 7 days, as tolerated [20]

3) Maximum dosage: 200 mg/day [20]

4) Discontinuation: Gradual dose reduction is preferred to abrupt cessation because of withdrawal symptoms [20]

b) 12 to 17 Years

1) Usual dosage: 50 to 200 mg/day. Divide into 2 doses when total dose exceeds 50 mg/day, and if doses are not equal, give larger dose at bedtime [20].

2) Initial dosage and titration: 25 mg orally at bedtime; may titrate by 25 mg/day once every 4 to 7 days, as tolerated [20]

3) Maximum dosage: 300 mg/day [20]

4) Discontinuation: Gradual dose reduction is preferred to abrupt cessation because of withdrawal symptoms [20].

2) Extended-release Capsule

a) Extended-release [fluvoxamine](#) maleate has not been evaluated for use in pediatric patients and is not indicated for use in this population. In pediatric patients naive to [fluvoxamine](#), the lowest available dose of extended-release [fluvoxamine](#) may not be appropriate [1].

See Drug Consult reference: Class Comparison: SSRIs and Serotonin [Norepinephrine](#) Reuptake Inhibitors (SNRIs) (Selected)

1.4.1.B.1.b) General Dosage Information

1) Extended-release [fluvoxamine](#) maleate has not been evaluated for use in pediatric patients and is not indicated for use in this population. In pediatric patients naive to [fluvoxamine](#), the lowest available dose of extended-release [fluvoxamine](#) may not be appropriate [22].

2.0] Pharmacokinetics

[Onset and Duration](#)

[Drug Concentration Levels](#)

[ADME](#)

2.1] Onset and Duration

A) Onset

1) [Fluvoxamine](#) Maleate

a) Initial Response

1) Obsessions: 3 to 10 weeks [432][433].

2) Depression: 2 to 3 weeks [434].

2.2] Drug Concentration Levels

A) [Fluvoxamine](#) Maleate

1j) Peak Concentration**a) Immediate-release, Age Differences**

1j) Adults, 5.7 nanogram/mL; children (6 to 11 years), 14.8 nanogram/mL; adolescents (12 to 17 years), 4.2 to 6.7 nanogram/mL [435].

a) In a multiple-dose study of immediate-release fluvoxamine maleate tablets in children age 6 to 11 years, adolescents age 12 to 17 years, and adults, peak concentrations were widely variable. Following oral administration of 100 mg twice daily, children exhibited a mean C_{max} of 14.8 nanogram/milliliter (ng/mL) compared to 4.2 ng/mL in adolescents. Following oral administration of 150 mg twice daily, adolescents exhibited a mean C_{max} of 6.7 ng/mL compared to 5.7 ng/mL in adults [435].

b) In a dose proportionality study, following administration of fluvoxamine maleate 100, 200, and 300 mg/day for 10 days in 30 healthy volunteers, the mean maximum plasma concentrations at steady state were 88, 283, and 546 nanograms/mL, respectively [435].

c) In a pharmacokinetics study, mean maximum plasma concentrations were 40% higher in elderly patients (66 to 73 years of age) than in younger subjects (19 to 35 years of age) following administration of immediate-release fluvoxamine 50 mg and 100 mg tablets [435].

d) Immediate-release, Gender Differences

1j) Children (6 to 11 years), females, 28.1 nanogram/milliliter; males, 9.1 nanogram/milliliter [435].

a) In a multiple-dose study of 100 mg immediate-release fluvoxamine maleate tablets administered orally twice daily in children age 6 to 11 years and adolescents age 12 to 17 years, female children exhibited a higher mean C_{max} compared to male children (28.1 ng/mL versus 9.1 ng/mL, respectively). Gender differences were not noted in adolescents [435].

b) Extended-release

1j) In a single-dose crossover study in 28 healthy volunteers, the mean C_{max} was 38% lower following administration of extended-release capsules compared with immediate-release tablets. In a dose proportionality study, following administration of fluvoxamine maleate extended-release capsules 100, 200, and 300 mg/day in 20 healthy volunteers, the mean maximum plasma concentrations were 47, 161, and 319 nanograms/mL, respectively. The C_{max} increased 5.7-fold following the 3-fold increase in dose from 100 to 300 mg [113].

2j) In a study of 28 healthy volunteers receiving extended-release fluvoxamine 100 mg, the C_{max} was increased by approximately 60% in females compared with males [113].

2j) Time to Peak Concentration

a) Immediate-release

1j) 3 to 8 hours [435]

a) In a dose proportionality study, following administration of 100, 200, and 300 milligrams/day for 10 days in 30 healthy volunteers, the maximum plasma concentrations at steady state were reached within 3 to 8 hours [435].

3j) Steady State

a) 7 to 10 days [113][435]

1j) Steady-state plasma concentrations were reached following 1 week of dosing with either immediate-release or extended release fluvoxamine maleate according to dose proportionality studies of 100 to 300 mg/day of either extended-release capsules (n=20), or immediate-release tablets (n=30) [113][435].

2j) In additional studies, steady-state plasma concentrations of fluvoxamine were attained in about 10 days of multiple dosing [436][434][437][438].

4j) Area Under the Curve

a) Immediate-release, Age Differences

1j) Adults, 59.4 nanogram x hour/milliliter; children (6 to 11 years), 155.1 nanogram x hour/milliliter; adolescents (12 to 17 years), 43.9 to 69.6 nanogram x hour/milliliter [435].

a) In a multiple-dose study of immediate-release fluvoxamine maleate tablets in children age 6 to 11 years, adolescents age 12 to 17 years, and adults, AUCs were widely variable. Following oral administration of 100 mg twice daily, children exhibited a mean AUC of 155.1 nanogram x hour/milliliter (ng x hr/mL) compared to 43.9 ng x hr/mL in adolescents. Following oral administration of 150 mg twice daily, adolescents exhibited a mean AUC of 69.6 ng x hr/mL compared to 59.4 ng x hr/mL in adults [435].

b) Immediate-release, Gender Differences

1j) Children (6 to 11 years), females, 293.5 nanogram x hour/milliliter; males, 95.8 nanogram x hour/milliliter [435].

a) In a multiple-dose study of 100 mg immediate-release fluvoxamine maleate tablets administered orally twice daily in children age 6 to 11 years and adolescents

age 12 to 17 years, female children exhibited a higher AUC compared to male children (293.5 ng x hr/mL versus 95.8 ng x hr/mL, respectively). Gender differences were not noted in adolescents [435].

c) Extended-release

1) In a multiple-dose proportionality study, following administration of fluvoxamine maleate extended-release capsules 100, 200, and 300 mg/day in 20 healthy volunteers, the AUC increased 5.7-fold following the 3-fold increase in dose from 100 to 300 mg [113].

2) In a study of healthy volunteers receiving extended-release fluvoxamine 100 mg, the AUC was increased by approximately 60% in females (n=13) compared with males (n=15) [113].

2.3] ADME

2.3.1] Absorption

A) Fluvoxamine Maleate

1) Bioavailability

a) Oral, immediate-release: 53% [435]; extended-release: 84% relative to immediate-release [113].

1) The absolute bioavailability of fluvoxamine maleate immediate-release tablets is 53% [435]. The bioavailability of fluvoxamine maleate extended-release capsules is 84% relative to immediate-release tablets [113].

2) Effects of Food

a) No significant effect [113][435].

1) Food causes the mean AUC and Cmax of fluvoxamine to increase only slightly and does not significantly affect the absorption of fluvoxamine maleate [113][435].

2.3.2] Distribution

A) Distribution Sites

1) Fluvoxamine Maleate

a) Protein Binding

1) 80% [113][435].

a) Fluvoxamine maleate is 80% bound to plasma protein, primarily albumin, over a concentration range of 20 to 2000 nanograms/mL [113][435].

B) Distribution Kinetics

1) Fluvoxamine Maleate

a) Volume of Distribution

1) 25 L/kg [113][435].

a) Fluvoxamine maleate exhibits extensive tissue distribution, with a mean apparent Vd of approximately 25 L/kg [113][435].

2.3.3] Metabolism

A) Metabolism Sites and Kinetics

1) Fluvoxamine Maleate

a) Liver, extensive [20][153]

1) Fluvoxamine is extensively metabolized in the liver [20][153][439][440] via oxidative demethylation and deamination [20][153].

B) Metabolites

1) Fluvoxamine Maleate

a) Fluvoxamine acid: active [20][153]

1) Nine mostly inactive metabolites of fluvoxamine maleate have been identified. One metabolite, fluvoxamine acid, has a weak effect (1 to 2 orders of magnitude less potent than the parent compound) on the inhibition of serotonin uptake [20][153].

C) Other

1) Fluvoxamine Maleate

a) Metabolic Enzymes and Transporters

1) Inhibitor of CYP1A2, CYP2C9, CYP2C19, CYP2D6, and CYP3A4

a) Based on several drug interaction studies in healthy volunteers and limited in vitro data for CYP3A4, fluvoxamine is an inhibitor of CYP1A2 (potent),

CYP2C9, CYP2C19, and CYP3A4. In vitro data suggest that fluvoxamine is also a relatively weak inhibitor of CYP2D6 [20][153].

2.3.4] Excretion

A) Kidney

1) Fluvoxamine Maleate

a) Renal Excretion (%)

1) 94% [113][435][439][440].

a) Following a dose of fluvoxamine maleate 5 mg orally, an average of 94% of drug-related products was recovered in the urine within 71 hours. Two percent is excreted unchanged in the urine [113][435].

b) The mean minimum concentrations were similar after 4 and 6 weeks of treatment with fluvoxamine maleate 50 mg twice daily (n=13) in renally impaired patients with creatinine clearance of 5 to 45 mL/minute, suggesting no accumulation of fluvoxamine in this group [113][435].

B) Total Body Clearance

1) Fluvoxamine Maleate

a) Hepatic Impairment

1) There was a 30% decrease in fluvoxamine clearance in patients with hepatic dysfunction compared with healthy subjects in a cross study [113][435].

b) Elderly

1) In elderly patients the clearance of fluvoxamine was reduced by 50% so initiation of therapy should be titrated slowly [435]

2.3.5] Elimination Half-life

A) Parent Compound

1) Fluvoxamine Maleate

a) Immediate-release, 15.6 hours [435]; extended-release, 16.3 hours [113].

1) Immediate-release

a) The mean plasma half-life of fluvoxamine at steady state following multiple dose oral administration of immediate-release tablets 100 mg/day in young, healthy volunteers was 15.6 hours [435].

b) In a study comparing administration of immediate-release fluvoxamine 50 mg and 100 mg to elderly patients (66 to 73 years of age) and younger subjects (19 to 35 years of age), the elimination half-life following multiple doses was 17.4 and 25.9 hours in elderly patients compared with 13.6 and 15.6 hours in younger subjects, respectively [435].

2) Extended-release

a) The mean plasma half-life of fluvoxamine following a single oral dose of a 100-mg extended release capsule in healthy volunteers was 16.3 hours [113].

3.0] Cautions

[Contraindications](#)

[Precautions](#)

[Adverse Reactions](#)

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

[Drug Interactions](#)

3.0.A] Black Box WARNING

Fluvoxamine Maleate

Oral (Capsule, Extended Release; 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 fluvoxamine maleate 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 [20][1].

Fluvoxamine maleate tablets are not approved for use in pediatric patients except for patients with obsessive compulsive disorder [20].

3.1] Contraindications

A) [Fluvoxamine](#) Maleate

- 1) Concomitant use with [alosectron](#), [pimozide](#), [thioridazine](#), [tizanidine](#) [40][22], or [ramelteon](#) [1]
- 2) Concomitant use of MAOIs, including [linezolid](#) or IV methylene blue, within 14 days of [fluvoxamine](#) discontinuation or use of [fluvoxamine](#) within 14 days of discontinuing an MAOI; increased risk of [serotonin syndrome](#) [20][1]

3.2] Precautions

A) [Fluvoxamine](#) Maleate

- 1) Black Box Warning: Increased risk of suicidal thinking and behavior in children, adolescents, and young adults with [major depressive disorder](#), especially during the first few months of therapy or following changes in dosage; monitoring recommended [40][1]
- 2) Black Box Warning: Not approved for use in pediatric patients, except for patients with [obsessive compulsive disorder](#) [20].
- 3) Beers Criteria: Avoid in older adults with a history of falls or fractures (unless safer alternatives are not available) as ataxia and impaired psychomotor performance may occur. If prescribed in older adults, use caution as SIADH or [hyponatremia](#) may develop or worsen. Monitor sodium levels when starting or changing doses [2].
- 4) Bleeding: Abnormal bleeding, including life-threatening hemorrhage, has been reported; [40][1] increased risk with concomitant use of NSAIDs, [aspirin](#), [warfarin](#), or other drugs that affect coagulation [1].
- 5) Concomitant Use: Avoid alcohol consumption [1].
- 6) Drug Discontinuation: Abrupt discontinuation may increase risk of serious discontinuation symptoms; monitoring and gradual dose reduction recommended [40][1].
- 7) Endocrine and Metabolic: [Hyponatremia](#), primarily due to SIADH, has been reported, including serious cases (serum sodium less than 110 mmol/L); increased risk in elderly, volume-depleted patients, or with concomitant use of diuretics; discontinue if symptomatic [hyponatremia](#) occurs [40][1].
- 8) Hepatic: Lower initial doses and monitoring recommended in patients with severe [hepatic impairment](#) [40][1].
- 9) Ophthalmologic: Pupillary dilation that occurs with antidepressants use may cause an angle closure attack in patients with anatomically narrow angles who do not have a patent [iridectomy](#) [1].
- 10) Psychiatric: Activation of [hypomania](#) or mania episode may occur; increased risk in patients with a history of mania or with [bipolar disorder](#) treated with antidepressant monotherapy; baseline screening recommended [40][1].
- 11) Neurologic: Seizures may occur during use, especially in patients with a history of seizure; avoid use in patients with unstable [epilepsy](#); monitoring recommended if [epilepsy](#) is controlled [40][1]; discontinue use with seizure or increase in seizure frequency [1].

12) **Serotonin Syndrome:** Serotonin syndrome has been reported, often with concurrent use with other serotonergic drugs (eg, triptans, tricyclic antidepressants, fentanyl, lithium, tramadol, buspirone, tryptophan, St John's wort), MAOIs (including methylene blue IV and linezolid), and other drugs that impair serotonin metabolism; monitoring recommended; discontinue use if suspected [20][1].

3.3] Adverse Reactions

3.3.1] Cardiovascular Effects

3.3.1.A] Fluvoxamine Maleate

3.3.1.A.1] Cardiorespiratory arrest

a) Cardiorespiratory arrest has been reported during postmarketing use of immediate-release or extended-release fluvoxamine maleate, although a causal relationship has not been established [22].

3.3.1.A.2] Electrocardiogram abnormal

a) Fluvoxamine maleate use was not associated with important changes in ECG variables during short-term, placebo-controlled trials involving patients with obsessive-compulsive disorder or depression [40][22].

b) Premature ventricular contractions (PVCs) not requiring therapy have been occasionally reported (Garnier et al, 1993).

c) In a pooled analysis of ECG data from several studies, fluvoxamine caused slight increases in the R-R, QT, and QTc intervals [48][49][50][51]. Fluvoxamine did not change T wave configurations as seen after tricyclic antidepressant administration [52].

d) In 25 healthy males, fluvoxamine 50 to 100 mg three times daily for 9 days produced a mean decrease in heart rate of 5 beats/minute compared with placebo [53].

3.3.1.A.3] Palpitations

a) Incidence: immediate-release, 3% [40]

b) Palpitations were reported in 3% patients with major depressive disorder or obsessive-compulsive disorder who were allocated to immediate-release fluvoxamine maleate during short-term premarketing clinical trials (n=892), compared with 2% of those allocated to placebo (n=778) [40].

3.3.1.A.4] Sudden cardiac death

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 its equivalent) had a 41% increased rate of sudden cardiac death (rate ratio, 1.41; 95% CI, 1.02 to 1.95) [47].

3.3.1.A.5] Ventricular tachycardia

a) Ventricular tachycardia, including torsades de pointes, has been reported during postmarketing use of immediate-release fluvoxamine maleate tablets, although a causal relationship has not been established [40].

3.3.2] Dermatologic Effects

3.3.2.A] **Fluvoxamine Maleate**

3.3.2.A.1] **Alopecia**

a) A case of patchy baldness was observed following 6 months of therapy with **fluvoxamine**. A 41-year-old male had taken the medication in varying dosages from 50 to 250 mg/day for treatment of **obsessive-compulsive disorder**. Three months following discontinuation of **fluvoxamine**, regrowth of fine white hair was noted over the alopecic patches [77].

3.3.2.A.2] **Rash**

a) In a placebo-controlled study involving pediatric patients with **obsessive-compulsive disorder**, rash was reported in 3.5% or more (2 or more of 57) patients treated with immediate-release **fluvoxamine maleate**. This was at least twice the rate found in placebo-treated patients [40].

3.3.2.A.3] **Stevens-Johnson syndrome**

a) **Stevens-Johnson syndrome** has been reported during postmarketing use of immediate-release or extended-release **fluvoxamine maleate**, although a causal relationship has not been established [40] [22].

3.3.2.A.4] **Sweating**

a) Incidence: immediate-release, 7%; extended-release, 7% [40][22]

b) In short-term, placebo-controlled clinical trials evaluating immediate-release **fluvoxamine maleate** (100 mg/day to 300 mg/day) for the treatment of **obsessive-compulsive disorder** (OCD) or depression, sweating was reported in 7% of **fluvoxamine maleate** patients (n=892) compared with 3% of placebo patients (n=778) [40].

c) In a 12-week, placebo-controlled clinical trial evaluating extended-release **fluvoxamine maleate** (100 to 300 mg once daily) for the treatment of **obsessive-compulsive disorder**, sweating was reported in 7% of **fluvoxamine maleate** patients (n=124) compared with less than 1% of placebo patients (n=124) [22].

3.3.2.A.5] **Toxic epidermal necrolysis**

a) **Toxic epidermal necrolysis** has been reported during postmarketing use of immediate-release **fluvoxamine maleate**, although a causal relationship has not been established [40].

b) A case of severe **toxic epidermal necrolysis** (TEN) was reported in a 16-year-old girl following treatment with **fluvoxamine**. The patient had been treated with **clomipramine** 100 mg/day and **clorazepate** 50 mg/day, and **metoclopramide** had been given once. After one week of **clomipramine**, it was withdrawn and replaced by **fluvoxamine** 100 mg/day. Within 8 days of **fluvoxamine**, the patient developed a widespread bullous eruption with mucous membrane involvement. Two days later, she showed epidermal detachment of the trunk, face, and proximal limbs involving 30% of the body surface area. This rapidly progressed to include 60% of body surface area. Histological examination of the skin showed total necrosis of the epidermis typical of TEN. Extensive epidemiologic data ruled out other drugs as causative agents. **Fluvoxamine** has been previously associated with a case of **Stevens-Johnson syndrome** [76].

3.3.3] **Endocrine/Metabolic Effects**

3.3.3.A] **Fluvoxamine Maleate**

3.3.3.A.1] Excessive thirst

- a)] There was a two-fold increase in the rate of thirst during studies of [obsessive-compulsive disorder](#) (OCD) treatment compared with studies of OCD and depression [40].
- b)] Polydipsia occurred in 3 women after taking [fluvoxamine](#) 100 mg/day. One patient developed polydipsia on the second day of treatment. She was also taking levosulpiride and [alprazolam](#). The symptoms disappeared on withdrawal of [fluvoxamine](#) but recurred when the drug was restarted 2 weeks later. The adverse effect disappeared when the drug was stopped 1 week later. Water ingestion also increased markedly in a 30-year-old woman with [dysthymia](#) and a 40-year-old woman with [panic disorder](#) and [agoraphobia](#) shortly after they started [fluvoxamine](#) treatment. Symptoms rapidly disappeared in these 2 women after the drug was discontinued [69].

3.3.3.A.2] Galactorrhea

- a)] [Galactorrhea](#) and [amenorrhea](#) associated with [fluvoxamine](#) were reported in a 38-year-old woman with refractory [bipolar affective disorder](#); this patient had been treated for over a decade with several psychotropic agents. The patient had been maintained for an undetermined length of time on [loxapine](#) 150 mg daily, [oxazepam](#) 30 mg three times daily, and zopiclone 7.5 mg at bedtime. [Fluvoxamine](#) was prescribed for depression, and the dose was titrated to 150 mg daily while the [loxapine](#) dosage was decreased to 75 mg daily. Six weeks after starting [fluvoxamine](#), she complained of [amenorrhea](#) followed soon by [galactorrhea](#). Thorough evaluation ruled out an underlying organic etiology; however, the serum prolactin level was 80 mcg/L (normal, 4 to 30 mcg/L). [Galactorrhea](#) resolved 3 weeks after stopping [fluvoxamine](#), and menstruation resumed a week later. The temporal relationship between [fluvoxamine](#) and the onset of [galactorrhea](#) and [amenorrhea](#) suggests a possible etiologic role for [fluvoxamine](#) [66]. 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 [67].

3.3.3.A.3] Hyperglycemia

- a)] A 60-year-old woman with well-controlled [insulin-dependent diabetes](#) developed [hyperglycemia](#) following [fluvoxamine](#) administration for the treatment of [major depression](#). Five days following initiation of [fluvoxamine](#) (100 mg/day) therapy, the woman's blood glycemia began to increase significantly without change in diet or compliance. Glycemia increased from 120 mg/dL at baseline to 210 mg/dL at days 19 and 21. [Hyperglycemia](#) persisted for 9 days before the patient discontinued [fluvoxamine](#) and the blood glycemia returned to baseline level. Twenty-two days later, [fluvoxamine](#) therapy was reinitiated and glycemia increased to the same range as the initial episode. [Fluvoxamine](#) was again stopped and glycemia returned to normal within 2 days [68].

3.3.3.A.4] Hyponatremia

- a)] [Hyponatremia](#) (serum sodium less than 110 mmol/L) has occurred in patients receiving [fluvoxamine](#) maleate, possibly as a result of SIADH. Symptoms included headache, difficulty concentrating, [memory impairment](#), confusion, weakness, and unsteadiness. Severe [hyponatremia](#) signs/symptoms have included hallucination, syncope, seizure, coma, respiratory arrest, and death. Patients at highest risk include the elderly, volume-depleted, or those taking diuretics. Consider drug discontinuation with symptomatic [hyponatremia](#) [40][22].
- b)] In a review of 25 published case reports of SSRI-induced SIADH, that includes one report with [fluvoxamine](#), the median age of patients was 75 years. Based on published reports, the onset of the SIADH was between 3 days and 4 months after starting therapy. Symptoms included confusion,

lethargy, dizziness, fatigue, anorexia, [delirium](#), and abdominal pain. 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 [64].

3.3.3.A.5] [Ineffective thermoregulation](#)

a) Three women developed diaphoresis, shivering, restlessness, anxiety, and subnormal body temperature, followed by low-grade fever, within 30 minutes of taking a first dose of [fluvoxamine](#) 25 mg in combination with a benzodiazepine (medazepam or ethyl loflazepate) in the evening. The women were being treated for either [panic disorder](#) or anxiety disorder, with associated depressive symptoms. Symptoms abated and disappeared by the next morning. One woman took a second dose and had the same experience. In all cases, symptoms did not reappear after discontinuation of [fluvoxamine](#) [70].

3.3.3.A.6] [Syndrome of inappropriate antidiuretic hormone secretion](#)

a) SIADH with [hyponatremia](#) (serum sodium less than 110 mmol/L) has occurred in patients receiving [fluvoxamine](#) maleate. Symptoms included headache, difficulty concentrating, [memory impairment](#), confusion, weakness, and unsteadiness. Severe [hyponatremia](#) signs/symptoms have included hallucination, syncope, seizure, coma, respiratory arrest, and death. Patients at highest risk include the elderly, volume-depleted, or those taking diuretics. Consider drug discontinuation with symptomatic [hyponatremia](#) [22][40].

b) In a review of 25 published case reports of SSRI-induced SIADH, that includes one report with [fluvoxamine](#), the median age of patients was 75 years. Based on these published reports, the onset of the SIADH was between 3 days and 4 months after starting therapy. Symptoms included confusion, lethargy, dizziness, fatigue, anorexia, [delirium](#), and abdominal pain. 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 [64].

c) A patient treated with [fluvoxamine](#) developed SIADH, which presented as profound confusion. Drug withdrawal resulted in rapid resolution of the CNS and biochemical abnormalities [65].

3.3.3.A.7] [Weight loss](#)

a) Incidence: immediate-release, at least 1%; extended-release, 2% [40][22]

- b) Weight loss was reported in at least 1% of patients with [major depressive disorder](#) or [obsessive-compulsive disorder](#) (OCD) who took immediate-release [fluvoxamine](#) maleate during premarketing clinical trials. There was a two-fold increase in the rate of weight loss in studies of OCD treatment compared with studies of OCD and depression [40].
- c) In a 12-week, placebo-controlled clinical trial evaluating extended-release [fluvoxamine](#) maleate (100 to 300 mg once daily) for the treatment of [obsessive-compulsive disorder](#), weight loss was reported in 2% of [fluvoxamine](#) maleate patients (n=124) compared with less than 1% of placebo patients (n=124) [22].
- d) Decreased appetite and weight loss have occurred in children taking SSRIs, including [fluvoxamine](#) maleate. Regular monitoring of growth is recommended. Weight loss was more frequent in pediatric OCD patients (2 or more of 57) taking immediate-release [fluvoxamine](#) maleate than in patients taking placebo [40][22].

3.3.4] Gastrointestinal Effects

3.3.4.A] [Fluvoxamine](#) Maleate

3.3.4.A.1] Constipation

- a) Incidence: immediate-release, 10%; extended-release, 4% [40][22]
- b) In short-term, placebo-controlled clinical trials evaluating immediate-release [fluvoxamine](#) maleate (100 mg/day to 300 mg/day) for the treatment of [obsessive-compulsive disorder](#) (OCD) or depression, constipation was reported in 10% of [fluvoxamine](#) maleate patients (n=892) compared with 8% of placebo patients (n=778) [40].
- c) In a 12-week, placebo-controlled clinical trial evaluating extended-release [fluvoxamine](#) maleate (100 to 300 mg once daily) for the treatment of [obsessive-compulsive disorder](#), constipation was reported in 4% of [fluvoxamine](#) maleate patients (n=124) compared with less than 1% of placebo patients (n=124) [22].
- d) Constipation was reported by 18% of fluvoxamine-treated patients (n=222) from pooled data of 10 double-blind, placebo-controlled studies comparing [fluvoxamine](#) and [imipramine](#). Constipation was reported by 20% and 7% of patients treated with [imipramine](#) and placebo, respectively [51].

3.3.4.A.2] Diarrhea

- a) Incidence: immediate-release, 11%; extended-release, 18% [40][22]
- b) In short-term, placebo-controlled clinical trials evaluating immediate-release [fluvoxamine](#) maleate (100 mg/day to 300 mg/day) for the treatment of [obsessive-compulsive disorder](#) (OCD) or depression, diarrhea was reported in 11% of [fluvoxamine](#) maleate patients (n=892) compared with 7% of placebo patients (n=778) [40].
- c) In a 12-week, placebo-controlled clinical trial evaluating extended-release [fluvoxamine](#) maleate (100 to 300 mg once daily) for the treatment of [obsessive-compulsive disorder](#), diarrhea was reported in 18% of [fluvoxamine](#) maleate patients (n=124) compared with 8% of placebo patients (n=124) [22].

3.3.4.A.3] [Dysphagia](#)

- a) Incidence: immediate-release, 2% [40]
- b) In short-term, placebo-controlled clinical trials evaluating immediate-release [fluvoxamine](#) maleate (100 mg/day to 300 mg/day) for the treatment of [obsessive-compulsive disorder](#) (OCD) or depression, [dysphagia](#) was reported in 2% of [fluvoxamine](#) maleate patients (n=892) compared with 1% of placebo patients (n=778). There was a two-fold decrease in the rate of [dysphagia](#) in studies of OCD treatment compared with studies of OCD and depression [40].

3.3.4.A.4] Flatulence

- a) Incidence: immediate-release, 4% [40]
- b) In short-term, placebo-controlled clinical trials evaluating immediate-release [fluvoxamine](#) maleate (100 mg/day to 300 mg/day) for the treatment of [obsessive-compulsive disorder](#) (OCD) or depression, flatulence was reported in 4% of [fluvoxamine](#) maleate patients (n=892) compared with 3% of placebo patients (n=778) [40].

3.3.4.A.5] Gastrointestinal hemorrhage

See Drug Consult reference: Concomitant Use of SSRIs and NSAIDs - Increased Risk of [Gastrointestinal Bleeding](#)

3.3.4.A.6] Indigestion

- a) Incidence: immediate-release, 10%; extended-release, 8% [40][22]
- b) In short-term, placebo-controlled clinical trials evaluating immediate-release [fluvoxamine](#) maleate (100 mg/day to 300 mg/day) for the treatment of [obsessive-compulsive disorder](#) (OCD) or depression, [dyspepsia](#) was reported in 10% of [fluvoxamine](#) maleate patients (n=892) compared with 5% of placebo patients (n=778) [40].
- c) In a 12-week, placebo-controlled clinical trial evaluating extended-release [fluvoxamine](#) maleate (100 to 300 mg once daily) for the treatment of [obsessive-compulsive disorder](#), [dyspepsia](#) was reported in 8% of [fluvoxamine](#) maleate patients (n=124) compared with 5% of placebo patients (n=124) [22].

3.3.4.A.7] Loss of appetite

- a) Incidence: immediate-release, 6%; extended-release, 13% [40][22]
- b) In short-term, placebo-controlled clinical trials evaluating immediate-release [fluvoxamine](#) maleate (100 mg/day to 300 mg/day) for the treatment of [obsessive-compulsive disorder](#) (OCD) or depression, anorexia was reported in 6% of [fluvoxamine](#) maleate patients (n=892) compared with 2% of placebo patients (n=778) [40].
- c) In a 12-week, placebo-controlled clinical trial evaluating extended-release [fluvoxamine](#) maleate (100 to 300 mg once daily) for the treatment of [obsessive-compulsive disorder](#), anorexia was reported in 13% of [fluvoxamine](#) maleate patients (n=124) compared with 5% of placebo patients (n=124) [22].
- d) Anorexia was reported by 15% of patients receiving [fluvoxamine](#), according to the pooled results of 10 placebo-controlled, double-blind studies comparing [fluvoxamine](#) and [imipramine](#) [51].

3.3.4.A.8] Nausea

- a) Incidence: immediate-release, 40%; extended-release, 34% [40][22]
- b) In short-term, placebo-controlled clinical trials evaluating immediate-release [fluvoxamine](#) maleate (100 mg/day to 300 mg/day) for the treatment of [obsessive-compulsive disorder](#) (OCD) or depression, nausea was reported in 40% of [fluvoxamine](#) maleate patients (n=892) compared with 14% of placebo patients (n=778). There was an approximate 25% decrease in the rate of nausea in studies of OCD treatment compared with studies of OCD and depression [40].
- c) In a 12-week, placebo-controlled clinical trial evaluating extended-release [fluvoxamine](#) maleate (100 to 300 mg once daily) for the treatment of [obsessive-compulsive disorder](#), nausea was reported in 34% of [fluvoxamine](#) maleate patients (n=124) compared with 13% of placebo patients (n=124) [22].
- d) 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; 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 [71].

e) Approximately 12.7% of patients with depression receiving [fluvoxamine](#) reported nausea as an adverse effect during an open, large-scale study of over 5000 patients. Nausea was the stated reason for withdrawing from this study in 5.6% of all patients [63].

f) Event monitoring in Great Britain of [fluvoxamine](#) use in 10,401 patients revealed the most commonly reported individual event to be nausea and vomiting (13%) [62].

3.3.4.A.9] [Pancreatitis](#)

a) [Pancreatitis](#) has been reported during postmarketing use of immediate-release [fluvoxamine](#) maleate tablets, although a causal relationship has not been established [40].

3.3.4.A.10] [Taste sense altered](#)

a) Incidence: immediate-release, 3%; extended-release, 2% [40][22]

b) In short-term, placebo-controlled clinical trials evaluating immediate-release [fluvoxamine](#) maleate (100 mg/day to 300 mg/day) for the treatment of [obsessive-compulsive disorder](#) (OCD) or depression, taste perversion was reported in 3% of [fluvoxamine](#) maleate patients (n=892) compared with 1% of placebo patients (n=778) [40].

c) In a 12-week, placebo-controlled clinical trial evaluating extended-release [fluvoxamine](#) maleate (100 to 300 mg once daily) for the treatment of [obsessive-compulsive disorder](#), taste perversion was reported in 2% of [fluvoxamine](#) maleate patients (n=124) compared with less than 1% of placebo patients (n=124) [22].

3.3.4.A.11] [Vomiting](#)

a) Incidence: immediate-release, 5%; extended-release, 6% [40][22]

b) In short-term, placebo-controlled clinical trials evaluating immediate-release [fluvoxamine](#) maleate (100 mg/day to 300 mg/day) for the treatment of [obsessive-compulsive disorder](#) (OCD) or depression, vomiting was reported in 5% of [fluvoxamine](#) maleate patients (n=892) compared with 2% of placebo patients (n=778) [40].

c) In a 12-week, placebo-controlled clinical trial evaluating extended-release [fluvoxamine](#) maleate (100 to 300 mg once daily) for the treatment of [obsessive-compulsive disorder](#), vomiting was reported in 6% of [fluvoxamine](#) maleate patients (n=124) compared with 2% of placebo patients (n=124) [22].

d) 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; 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 [71].

e) Vomiting was reported by 3.6% of patients and led to the discontinuation of therapy in 2.8% of all patients in a open, large-scale study of over 5000 patients with depression [63].

f) Event monitoring in Great Britain of [fluvoxamine](#) use in 10,401 patients revealed the most commonly reported individual event to be nausea and vomiting (13%) [62].

3.3.4.A.12] [Xerostomia](#)

a) Incidence: immediate-release, 14%; extended-release, 10% [40][22]

b) In short-term, placebo-controlled clinical trials evaluating immediate-release [fluvoxamine](#) maleate (100 mg/day to 300 mg/day) for the treatment of [obsessive-compulsive disorder](#) (OCD) or depression, dry mouth was reported in 14% of [fluvoxamine](#) maleate patients (n=892) compared with 10% of placebo patients (n=778) [40].

c) In a 12-week, placebo-controlled clinical trial evaluating extended-release [fluvoxamine](#) maleate (100 to 300 mg once daily) for the treatment of [obsessive-compulsive disorder](#), dry mouth was reported in 10% of [fluvoxamine](#) maleate patients (n=124) compared with 9% of placebo patients (n=124) [22].

d) From pooled data of 10 double-blind, placebo-controlled studies comparing [fluvoxamine](#) and [imipramine](#), dry mouth was experienced by 26% of the patients treated with [fluvoxamine](#) (n=222), which was significantly less than the incidence of 51% in patients who were receiving [imipramine](#) (n=221). Twenty-six percent of patients receiving placebo also complained of dry mouth [51].

e) During an open, large-scale study of over 5000 patients with depression, dry mouth was reported by 3.7% of patients but led to the discontinuation of therapy in only 0.8% of all patients [63].

f) [Fluvoxamine](#) failed to demonstrate any significant differences in salivary flow when compared to placebo. The study administered single doses of [fluvoxamine](#) 50, 75, and 100 mg to 17 healthy volunteers [72].

3.3.5] Hematologic Effects

3.3.5.A] [Fluvoxamine](#) Maleate

3.3.5.A.1] [Agranulocytosis](#)

a) [Agranulocytosis](#) has been reported during postmarketing use of immediate-release [fluvoxamine](#) maleate tablets, although a causal relationship has not been established [40].

3.3.5.A.2] Hemorrhage, Abnormal

a) General Information

1) Increased risk of [gastrointestinal bleeding](#) due to interference with serotonin reuptake [22].

2) Bleeding events include ecchymoses, [hematomas](#), [epistaxis](#), [petechiae](#), [gastrointestinal bleeding](#), and life-threatening hemorrhages [22].

3) Risk may be increased by the concomitant use of drugs that affect coagulation (eg, NSAIDs, [aspirin](#), [warfarin](#)) [22].

4) SSRIs reduce uptake of serotonin by [platelets](#); therefore, reduction in granular storage of serotonin is observed [44].

5) Serotonin-mediated [platelet](#) aggregation may be decreased [44].

6) Many cases occur in patients taking higher doses and is more common in patients with underlying diseases [44].

b) Prevention and Management

- 1)) Use caution when coadministering drugs that affect coagulation with [fluvoxamine](#) [22].
- 2)) Monitor patients receiving concurrent [warfarin](#) therapy when [fluvoxamine](#) is started or discontinued [22].
- 3)) Consider discontinuation of [fluvoxamine](#) 2 weeks prior to surgery (particularly, breast or orthopedic surgery) in patients in a stable phase of depression that are at a high risk of bleeding. Gradual tapering of treatment is recommended to minimize discontinuation syndrome. Restart therapy as soon as possible when there is no longer perioperative bleeding risk [45].
- 4)) Use of an antidepressant agent that is less likely to or does not increase the clinical risk of bleeding (eg, [bupropion](#), [mirtazapine](#)) may be considered [45].
- 5)) Take into account the type of surgery, type of antidepressant, risk of suicide, severity of depression, risk factors for bleeding, and potential for discontinuation syndrome when determining management plan [45]
- 6)) 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 [44].

c)) Adult Clinical Trials

- 1)) [Facelift surgery](#), [CABG](#) surgery (oral route): No significant relationship between serotonergic antidepressant use and a risk of perioperative bleeding in 4 studies (review article) [45]
- 2)) Orthopedic, spinal, breast, or [CABG](#) surgery (oral route): Some increased risk of bleeding associated with serotonergic antidepressant use in 6 studies; clinical significance unclear (review article) [45]

d)) Adult Case Reports

- 1)) A 33-year-old woman began taking [paroxetine](#) 40 mg daily for panic attacks and noted spontaneous bruising on her arms and legs and excessive menstrual bleeding within 2 weeks. No gynecologic or hematologic abnormalities were identified. [Vitamin C](#) added to [paroxetine](#) stopped bleeding in 3 weeks; discontinuation of [vitamin C](#) resulted in recurrent bleeding. Her medication was switched to [fluvoxamine](#) which also caused bleeding that resolved with [vitamin C](#) [46].

3.3.6] Hepatic Effects

3.3.6.A] [Fluvoxamine](#) Maleate

3.3.6.A.1] [Hepatitis](#)

- a)) [Hepatitis](#) has been reported during postmarketing use of immediate-release [fluvoxamine](#) maleate tablets, although a causal relationship has not been established [40].

3.3.6.A.2] Liver function tests abnormal

a) A 57-year-old man experienced a 3-fold increase in [gamma glutamyl transferase \(GGT\)](#) of 176 international units/L over baseline (50 international units/L) after 3 weeks of [fluvoxamine](#) maleate 100 mg twice daily. An enlarged liver with evidence of [fatty changes](#) was observed on abdominal ultrasound and examination. [GGT](#) levels returned to near baseline levels 5 weeks after discontinuing therapy [73].

3.3.7] Immunologic Effects

3.3.7.A] [Fluvoxamine](#) Maleate

3.3.7.A.1] [Anaphylaxis](#)

a) [Anaphylactic reaction](#) has been reported during postmarketing use of immediate-release or extended-release [fluvoxamine](#) maleate, although a causal relationship has not been established [40] [22].

3.3.8] Musculoskeletal Effects

3.3.8.A] [Fluvoxamine](#) Maleate

3.3.8.A.1] Fracture of bone

a) In a population-based, randomized, 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 [fluvoxamine](#), compared with those who did not use an SSRI (n=4871; mean age of 65.7 years). Daily SSRI use was associated with a significant 2.1-fold increased risk of fragility fracture (95% confidence interval (CI), 1.3 to 3.4). Daily SSRI users who were recurrent (ie, treated with SSRIs at baseline and at 5-year follow-up) had a significant 2.1-fold increased risk of fragility fracture (95% CI, 1.1 to 4.0). Fractures were reported at the following sites: forearm (40%), ankle and foot (21%), hip (13%), rib (13%), femur (9%), and back (4%). None were reported at the skull, toes, or fingers [79].

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](#), or [sertraline](#)) compared to those who were not exposed to antidepressants. Current SSRI use was associated with an increased risk of nonvertebral fracture (adjusted hazard ratio (HR), 2.35; 95% confidence interval (CI), 1.32 to 4.18) compared with no antidepressant use. Current SSRI use was also associated with an increased risk of nonvertebral fracture (adjusted HR, 2.07; 95% CI, 1.23 to 3.5) compared with past antidepressant use (n=1217). In addition, duration of SSRI use showed a 9% increase in fracture risk per extra month on an SSRI (95% CI, 3% to 16%; p for trend=0.004). Fractures of the hip (most frequent), wrist, humerus, and pelvis were reported [78].

3.3.8.A.3] Myalgia

a) Incidence: extended-release, 5% [22]

b) In a 12-week, placebo-controlled clinical trial evaluating extended-release [fluvoxamine](#) maleate (100 to 300 mg once daily) for the treatment of [obsessive-compulsive disorder](#), myalgia was reported in 5% of [fluvoxamine](#) maleate patients (n=124) compared with 2% of placebo patients (n=124) [22].

c) In short-term, placebo-controlled clinical trials evaluating immediate-release [fluvoxamine](#) maleate (100 mg/day to 300 mg/day) for the treatment of OCD, myalgia was reported at a rate that was two-fold higher than the rate reported in OCD and depression trials [40].

3.3.9] Neurologic Effects

3.3.9.A] [Fluvoxamine](#) Maleate

3.3.9.A.1] Asthenia

a) Incidence: immediate-release, 14%; extended-release, 26% [40][22]

b) In short-term, placebo-controlled clinical trials evaluating immediate-release [fluvoxamine](#) maleate (100 mg/day to 300 mg/day) for the treatment of [obsessive-compulsive disorder](#) (OCD) or depression, asthenia was reported in 14% of [fluvoxamine](#) maleate patients (n=892) compared with 6% of placebo patients (n=778). There was a two-fold increase in the rate of asthenia in studies of OCD treatment compared with studies of OCD and depression [40].

c) In a 12-week, placebo-controlled clinical trial evaluating extended-release [fluvoxamine](#) maleate (100 to 300 mg once daily) for the treatment of [obsessive-compulsive disorder](#), asthenia was reported in 26% of [fluvoxamine](#) maleate patients (n=124) compared with 8% of placebo patients (n=124) [22].

3.3.9.A.2] Dizziness

a) Incidence: immediate-release, 11%; extended-release, 12% [40][22]

b) In short-term, placebo-controlled clinical trials evaluating immediate-release [fluvoxamine](#) maleate (100 mg/day to 300 mg/day) for the treatment of [obsessive-compulsive disorder](#) (OCD) or depression, dizziness was reported in 11% of [fluvoxamine](#) maleate patients (n=892) compared with 6% of placebo patients (n=778) [40].

c) In a 12-week, placebo-controlled clinical trial evaluating extended-release [fluvoxamine](#) maleate (100 to 300 mg once daily) for the treatment of [obsessive-compulsive disorder](#), dizziness was reported in 12% of [fluvoxamine](#) maleate patients (n=124) compared with 10% of placebo patients (n=124) [22].

d) Event monitoring in Great Britain of [fluvoxamine](#) use in 10,401 patients revealed the most common category of adverse events to be neuropsychiatric. Dizziness was reported in 3.3% of patients [62].

e) In an open study of more than 5000 patients with depression, dizziness was reported by 4.5% of patients [63].

f) Dizziness was reported in 14% of patients who received [fluvoxamine](#) (n=222) during 10 double-blind, placebo-controlled studies comparing [fluvoxamine](#) and [imipramine](#) in patients with depression [51].

3.3.9.A.3] [Electroencephalogram](#) abnormal

a) EEG profiles of patients being treated with [fluvoxamine](#) showed concomitant increases of slow and fast activities and a decrease in alpha activity indicating sedative qualities. Single doses of [fluvoxamine](#) 75 mg were administered to 10 healthy volunteers. The EEG studies showed that [fluvoxamine](#) induced less augmentation of slow activity than [imipramine](#), indicating fewer sedative properties with [fluvoxamine](#) [54].

3.3.9.A.4] Extrapyramidal sign

a) Incidence: 0.1% to 1% [40][22]

b) Extrapyramidal syndrome was reported in 0.1% to 1% of patients with [major depressive disorder](#) or [obsessive-compulsive disorder](#) who took immediate-release [fluvoxamine](#) maleate during premarketing clinical trials [40][22].

- c) Dystonic reactions, [parkinsonism](#), [akathisia](#), and [dyskinesias](#) have been described, with the earliest onset noted at 5 days [55] and latest onset at 4 months [56].
- d) Extrapyramidal reactions (EPR) have been reported with 1 or more SSRIs. The majority of case reports involved [fluoxetine](#); however, all of the SSRIs were implicated in at least 1 EPR. Duration of symptoms with treatment was usually a few days. Symptoms occurred weekly for the first 4 weeks of treatment and periodically thereafter. For most cases, treatment was limited to reducing the dose or stopping the SSRI [57][58].
- e) In a limited number of case reports, [propranolol](#) and/or benzodiazepines were used to treat SSRI-induced [akathisia](#); the dose of [propranolol](#) ranged from 40 to 90 mg daily [58].
- f) In case reports, dystonic reactions responded to an unspecified dose of intramuscular trihexyphenidyl or [diphenhydramine](#) 50 mg [58][59].
- g) Possible mechanisms by which SSRIs cause extrapyramidal reactions (EPR) include: (1) central serotonergic activity which inhibits dopaminergic activity; and (2) concurrent use of an SSRI and antipsychotic may cause EPRs by a pharmacokinetic interaction, a pharmacodynamic interaction, or a combination of the two [57].
- h) Three days after starting concomitant [fluvoxamine](#) and [metoclopramide](#), a 14-year-old boy developed acute [dystonia](#) of the extensor muscles of the neck, back, and upper extremities; jaw rigidity; [horizontal nystagmus](#); [dysarthria](#); and uncontrolled movement of the tongue. He was treated with [fluvoxamine](#) 50 mg/day and [metoclopramide](#) 10 mg 3 times daily. Treatment with intramuscular [biperiden](#) 5 mg completely relieved symptoms within 30 minutes. Previous treatment with [metoclopramide](#) did NOT produce [dystonia](#) [60].
- i) A 71-year-old woman developed involuntary movements of the head, neck, and extremities, especially the arms, 5 days after she began taking [fluvoxamine](#) 50 mg daily for depression. Upon examination in the emergency department, the movements occurred at rest and were NOT suppressible; they were described as dystonic contractures and myoclonic jerks. Treatment consisted of IV [clonazepam](#) 1 mg which resulted in improvement within 10 minutes; 2 hours later, myoclonus recurred and responded to oral [clonazepam](#) 2 mg. [Fluvoxamine](#) was stopped and myoclonus resolved. One week later, this woman was rechallenged with [fluvoxamine](#) 50 mg daily which resulted in a similar reaction 11 days later. The abnormal movements resolved after administering oral [clonazepam](#) 2 mg. After stopping [fluvoxamine](#), the movements disappeared and did NOT recur during 6 months of follow-up. Of note, this woman was also taking [diltiazem](#), which inhibits the cytochrome P450 enzyme 1A2 (the enzyme responsible for metabolizing [fluvoxamine](#)). This may have resulted in increased [fluvoxamine](#) bioavailability [55].
- j) About 4 months after starting [fluvoxamine](#) 100 mg daily, a 38-year-old woman complained of periauricular pain and headache which progressed to tightening of jaw muscles and teeth clenching over the next month. She also had difficulty chewing solid foods. Upon reduction of the [fluvoxamine](#) dose to 50 mg, her complaints lessened but did NOT completely resolve until she stopped [fluvoxamine](#). This patient did NOT have a history of previous psychiatric illnesses or [dystonias](#) [56].

3.3.9.A.5] Headache

- a) Incidence: immediate-release, 22%; extended-release, 32% [40][22]
- b) In short-term, placebo-controlled clinical trials evaluating immediate-release [fluvoxamine](#) maleate (100 mg/day to 300 mg/day) for the treatment of [obsessive-compulsive disorder](#) (OCD) or depression, headache was reported in 22% of [fluvoxamine](#) maleate patients (n=892) compared with 20% of placebo patients (n=778) [40].
- c) In a 12-week, placebo-controlled clinical trial evaluating extended-release [fluvoxamine](#) maleate (100 to 300 mg once daily) for the treatment of [obsessive-compulsive disorder](#), headache was reported in 32% of [fluvoxamine](#) maleate patients (n=124) compared with 31% of placebo patients (n=124) [22].

- d) Event monitoring in Great Britain of [fluvoxamine](#) use in 10,401 patients revealed the most common category of adverse events to be neuropsychiatric. Headache was reported in 3.9% of patients [62].
- e) In an open study of more than 5000 patients with depression, headache was reported by 5% of patients, causing withdrawal from the study in 2.7% [63].
- f) Headache was reported in 22% of patients who received [fluvoxamine](#) (n=222) during 10 double-blind, placebo-controlled studies comparing [fluvoxamine](#) and [imipramine](#) in patients with depression [51].

3.3.9.A.6] Hyperactive behavior

- a) Incidence: immediate-release, 1% or greater [40]
- b) Hyperkinesia was reported in at least 1% of patients with [major depressive disorder](#) or OCD who took immediate-release [fluvoxamine](#) maleate during premarketing clinical trials [40].
- c) In a placebo-controlled study involving pediatric patients with [obsessive-compulsive disorder](#), hyperkinesia was reported in 3.5% or more (2 or more of 57) patients treated with immediate-release [fluvoxamine](#) maleate, and was more frequent than in placebo-treated patients [40].

3.3.9.A.7] Insomnia

- a) Incidence: immediate-release, 21%; extended-release, 35% [40][22]
- b) In short-term, placebo-controlled clinical trials evaluating immediate-release [fluvoxamine](#) maleate (100 mg/day to 300 mg/day) for the treatment of [obsessive-compulsive disorder](#) (OCD) or depression, insomnia was reported in 21% of [fluvoxamine](#) maleate patients (n=892) compared with 10% of placebo patients (n=778) [40].
- c) In a 12-week, placebo-controlled clinical trial evaluating extended-release [fluvoxamine](#) maleate (100 to 300 mg once daily) for the treatment of [obsessive-compulsive disorder](#), insomnia was reported in 35% of [fluvoxamine](#) maleate patients (n=124) compared with 20% of placebo patients (n=124) [22].
- d) Event monitoring in Great Britain of [fluvoxamine](#) use in 10,401 patients revealed the most common category of adverse events to be neuropsychiatric. Insomnia was reported in 2.4% of patients [62].
- e) Insomnia was reported in 15% of patients who received [fluvoxamine](#) (n=222) during 10 double-blind, placebo-controlled studies comparing [fluvoxamine](#) and [imipramine](#) in patients with depression [51].

3.3.9.A.8] Myoclonus

- a) Incidence: immediate-release, 0.1% to 1%; extended-release, 2% [40][22]
- b) There was a two-fold increase in the rate of myoclonus/twitch in studies of [obsessive-compulsive disorder](#) (OCD) treatment compared with studies of OCD and depression. Myoclonus was reported in at least 1% and twitching was reported in 0.1% to 1% of patients with [major depressive disorder](#) or OCD who took immediate-release [fluvoxamine](#) maleate during premarketing clinical trials [40].
- c) In a 12-week, placebo-controlled clinical trial evaluating extended-release [fluvoxamine](#) maleate (100 to 300 mg once daily) for the treatment of [obsessive-compulsive disorder](#), twitching was reported in 2% of [fluvoxamine](#) maleate patients (n=124) compared with 0% of placebo patients (n=124) [22].
- d) A 71-year-old woman developed involuntary movements of the head, neck, and extremities, especially the arms, 5 days after she began taking [fluvoxamine](#) 50 mg daily for depression. Upon examination in the emergency department, the movements occurred at rest and were NOT suppressible; they were described as dystonic contractures and myoclonic jerks. Treatment consisted of IV [clonazepam](#) 1 mg which resulted in improvement within 10 minutes; 2 hours later, myoclonus recurred and responded to oral [clonazepam](#) 2 mg. [Fluvoxamine](#) was stopped and myoclonus resolved. One week later, this woman was rechallenged with [fluvoxamine](#) 50 mg daily which resulted in a similar reaction 11 days later. The abnormal movements resolved after administering oral [clonazepam](#) 2 mg.

After stopping [fluvoxamine](#), the movements disappeared and did NOT recur during 6 months of follow-up. Of note, this woman was also taking [diltiazem](#), which inhibits the cytochrome P450 enzyme 1A2 (the enzyme responsible for metabolizing [fluvoxamine](#)). This may have resulted in increased [fluvoxamine](#) bioavailability [55].

3.3.9.A.9] Seizure

a) Incidence: 0.2% [40][22]

b) Seizures occurred in 0.2% of patients treated with immediate-release [fluvoxamine](#) maleate during premarketing trials. Cautious administration is recommended in patients with controlled [epilepsy](#) or a history of convulsions. Avoid treatment in unstable [epilepsy](#). Discontinue [fluvoxamine](#) maleate if seizures occur or increase in frequency [40][22].

c) A 49-year-old male who had been seizure-free for 10 years with [anticonvulsant therapy](#) experienced a generalized seizure 3 days after beginning [fluvoxamine](#) therapy, 150 mg at bedtime. Following an increase in dose of the [anticonvulsant therapy](#), the patient did not experience any more seizures [61].

3.3.9.A.10] Sleep disorder

a) [Fluvoxamine](#) 100 to 150 mg tended to increase rapid eye movement (REM) sleep latency, increase stage 3 sleep, and shorten REM time in a placebo-controlled trial of healthy volunteers. The overall quality of sleep deteriorated, and subjects complained of feeling worse in the mornings [51].

3.3.9.A.11] Somnolence

a) Incidence: immediate-release, 22%; extended-release, 27% [40][22]

b) In short-term, placebo-controlled clinical trials evaluating immediate-release [fluvoxamine](#) maleate (100 mg/day to 300 mg/day) for the treatment of [obsessive-compulsive disorder](#) (OCD) or depression, somnolence was reported in 22% of [fluvoxamine](#) maleate patients (n=892) compared with 8% of placebo patients (n=778) [40].

c) In a 12-week, placebo-controlled clinical trial evaluating extended-release [fluvoxamine](#) maleate (100 to 300 mg once daily) for the treatment of [obsessive-compulsive disorder](#), somnolence was reported in 27% of [fluvoxamine](#) maleate patients (n=124) compared with 11% of placebo patients (n=124) [22].

d) In an open study of more than 5000 patients with depression, somnolence was reported by 3.8% of patients [63].

e) Somnolence was reported in 26% of patients who received [fluvoxamine](#) (n=222) during 10 double-blind, placebo-controlled studies comparing [fluvoxamine](#) and [imipramine](#) in patients with depression [51].

3.3.9.A.12] Tremor

a) Incidence: immediate-release, 5%; extended-release, 6% [40][22]

b) In short-term, placebo-controlled clinical trials evaluating immediate-release [fluvoxamine](#) maleate (100 mg/day to 300 mg/day) for the treatment of [obsessive-compulsive disorder](#) (OCD) or depression, tremor was reported in 5% of [fluvoxamine](#) maleate patients (n=892) compared with 1% of placebo patients (n=778) [40].

c) In a 12-week, placebo-controlled clinical trial evaluating extended-release [fluvoxamine](#) maleate (100 to 300 mg once daily) for the treatment of [obsessive-compulsive disorder](#), tremor was reported in 6% of [fluvoxamine](#) maleate patients (n=124) compared with 0% of placebo patients (n=124) [22].

3.3.10] Ophthalmic Effects

3.3.10.A] Fluvoxamine Maleate**3.3.10.A.1] Blurred vision**

a) Incidence: 2% to 3% [1][40]

b) Adult Clinical Trials

1) **Obsessive-compulsive disorder** or depression (oral route): 3% vs 2% with placebo [40]

2) **Obsessive-compulsive disorder** (oral route): 2% vs 1% with placebo [1]

3.3.10.A.2] Cataract

a) Adult Case Reports

1) Bilateral white cataracts occurred in a 19-year-old woman after 7 months of **fluvoxamine** 150 mg/day, preceded by **quetiapine** 75 mg/day for unknown duration. The patient's visual acuity in both eyes had been deteriorating for 3 weeks before examination and continued to decrease over the next week. White mature **bilateral cataracts** were present and there were no other abnormalities. **Phacoemulsification** with **posterior chamber intraocular lens** implantation was performed in both eyes, and visual acuity was restored to 20/20 bilaterally [75].

3.3.10.A.3] Mydriasis

a) General Information

1) Pupillary dilation that occurs with antidepressants may cause an angle closure attack in patients with anatomically narrow angles without a patent **iridectomy** [1].

3.3.10.A.4] Raised intraocular pressure

a) Adult Case Reports

1) Aggravation of **glaucoma** and mydriasis that resolved after discontinuation of **fluvoxamine** was reported in a 66-year-old woman treated with **timolol** twice daily for **narrow-angle glaucoma**. She developed severe orbital pain, blurred vision, increased ocular pressure, mydriasis, and a closed angle 2 months after initiation of **fluvoxamine** treatment. She was treated with intravenous glycerol, **acetazolamide**, and **pilocarpine**. Within 2 days of discontinuation of **fluvoxamine**, normalization of intraocular pressure and resolution of orbital pain and blurred vision occurred [74].

3.3.12] Psychiatric Effects**3.3.12.A] Fluvoxamine Maleate****3.3.12.A.1] Agitation**

a) Incidence: immediate-release, 2%; extended-release, 2% [40][22]

b) In short-term, placebo-controlled clinical trials evaluating immediate-release **fluvoxamine** maleate (100 mg/day to 300 mg/day) for the treatment of **obsessive-compulsive disorder** (OCD) or depression, agitation was reported in 2% of **fluvoxamine** maleate patients (n=892) compared with 1% of placebo

patients (n=778). There was a two-fold increase in the rate of agitation in studies of OCD treatment compared with studies of OCD and depression[40].

c) In a 12-week, placebo-controlled clinical trial evaluating extended-release [fluvoxamine](#) maleate (100 to 300 mg once daily) for the treatment of [obsessive-compulsive disorder](#), agitation was reported in 2% of [fluvoxamine](#) maleate patients (n=124) compared with less than 1% of placebo patients (n=124) [22].

d) Severe agitation was reported in an 11-year-old boy following the ingestion of one therapeutic (50 mg) [fluvoxamine](#) tablet [81].

e) A 68-year-old male experienced severe agitation and restlessness within one week of beginning [fluvoxamine](#) therapy, 50 mg daily. The [akathisia](#) began to subside gradually following discontinuation of the [fluvoxamine](#) and administration of [diazepam](#) (Chong & Cheong, 1999).

f) Agitation was noted in 16% of patients taking [fluvoxamine](#) therapeutically [51].

3.3.12.A.2] Anxiety

a) Incidence: immediate-release, 5%; extended-release, 6% [40][22]

b) In short-term, placebo-controlled clinical trials evaluating immediate-release [fluvoxamine](#) maleate (100 mg/day to 300 mg/day) for the treatment of [obsessive-compulsive disorder](#) (OCD) or depression, anxiety was reported in 5% of [fluvoxamine](#) maleate patients (n=892) compared with 3% of placebo patients (n=778). There was a two-fold increase in the rate of anxiety in studies of OCD treatment compared with studies of OCD and depression [40].

c) In a 12-week, placebo-controlled clinical trial evaluating extended-release [fluvoxamine](#) maleate (100 to 300 mg once daily) for the treatment of [obsessive-compulsive disorder](#), anxiety was reported in 6% of [fluvoxamine](#) maleate patients (n=124) compared with 2% of placebo patients (n=124) [22].

d) Event monitoring in Great Britain of [fluvoxamine](#) use in 10,401 patients revealed the most common category of adverse events to be neuropsychiatric. Anxiety was reported in 2.6% of patients [62].

3.3.12.A.3] Depression, worsening

a) 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 patients being treated for other psychiatric and nonpsychiatric disorders. 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. The dose should be tapered off, avoiding abrupt discontinuation whenever possible. Patients and their caregivers should be provided with the Medication Guide that is available for this drug [40][22][87].

3.3.12.A.4] Feeling nervous

a) Incidence: immediate-release, 12% [40]

b) In short-term, placebo-controlled clinical trials evaluating immediate-release [fluvoxamine](#) maleate (100 mg/day to 300 mg/day) for the treatment of [obsessive-compulsive disorder](#) (OCD) or depression, nervousness was reported in 12% of [fluvoxamine](#) maleate patients (n=892) compared with 5% of placebo patients (n=778) [40].

3.3.12.A.5] Frontal lobe syndrome

a) A patient developed a [frontal lobe syndrome](#) (apathy, indifference) while taking moderate doses of [fluvoxamine](#) 150 mg/day and sulpiride, a [dopamine](#) (D-2) antagonist, at 400 mg/day. It was theorized

that serotonergic agents may cause this syndrome via reduction of frontal blood flow and that dopamine-blocking agents may modulate this effect [88].

b) Apathy, indifference, loss of initiative, and disinhibition were reported in association with [fluvoxamine](#) treatment of 2 patients with [panic disorder](#). The effects appeared to be dose-related and disappeared rapidly when the dose of [fluvoxamine](#), which has a short elimination half-life, was reduced. Patients' behavior seemed to resemble that of people with frontal lobe dysfunction [89].

3.3.12.A.6] Hypomania

a) Incidence: 1% or greater [40][22]

b) Mania or [hypomania](#) was reported in at least 1% of patients with primarily depression who took [fluvoxamine](#) maleate during premarketing clinical trials [40][22].

c) During an 8-week, placebo-controlled study of [fluvoxamine](#) for [obsessive-compulsive disorder](#) (OCD), 5 of 20 patients became manic (2) or hypomanic (3). This is inconsistent with prior experience with other serotonin reuptake inhibitors. The rate of [hypomania](#) associated with [fluvoxamine](#) when treating [major depression](#) is 0.4%, that for [clomipramine](#) when treating OCD is 0.4%, and that for [fluoxetine](#) in the treatment of depression is 0.98%. The high percentage (25%) in this study may reflect the presence of bipolar type II patients in the sample as these patients show a greater frequency of cycling [83].

3.3.12.A.7] Mania

a) Incidence: 1% to 4% [40][22]

b) Mania or [hypomania](#) was reported in 1% of patients with primarily depression who took [fluvoxamine](#) maleate during premarketing clinical trials. Manic reactions were reported in 4% of pediatric patients with [obsessive-compulsive disorder](#) who were given [fluvoxamine](#) maleate (n=57) during a ten-week study, compared with no manic reactions in patients who received placebo (n=63). Caution is advised when [fluvoxamine](#) maleate is used in patients with a history of mania [40][22].

c) Mania occurred in 3 patients who were treated with a combination of [fluvoxamine](#) and [lithium](#). Dosage of [fluvoxamine](#) was 100 to 200 mg/day and [lithium](#) levels were low, ie, 0.5, 0.55, 0.6 mmol/L. This may represent a "switch" from depression into mania induced by [fluvoxamine](#) [82].

d) During an 8-week, placebo-controlled study of [fluvoxamine](#) for [obsessive-compulsive disorder](#) (OCD), 5 of 20 patients became manic (2) or hypomanic (3). This is inconsistent with prior experience with other serotonin reuptake inhibitors. The rate of [hypomania](#) associated with [fluvoxamine](#) when treating [major depression](#) is 0.4%, that for [clomipramine](#) when treating OCD is 0.4%, and that for [fluoxetine](#) in the treatment of depression is 0.98%. The high percentage (25%) in this study may reflect the presence of bipolar type II patients in the sample as these patients show a greater frequency of cycling [83].

3.3.12.A.8] Psychotic disorder

a) Acute exacerbation of schizophrenic symptoms (hallucinations, attacks of anger) occurred in a 53-year-old woman with [chronic schizophrenia](#) since age 30 when [fluvoxamine](#) 150 mg/day was added to her treatment program for depression. After discontinuation of [fluvoxamine](#) and increase of [perphenazine](#) (from 16 to 32 mg/day), the patient was free of psychotic symptoms [84].

b) A 17-year-old male with mild [mental retardation](#) experienced an acute psychotic reaction resulting in hospitalization for 6 days following a single dose of [fluvoxamine](#) 50 mg for depression and anxiety symptoms. The subject experienced agitation, insomnia, auditory and visual hallucinations, fearful mood, [paranoid delusions](#), and episodes of catatonia within 24 hours of taking [fluvoxamine](#). Forty-eight hours after the [fluvoxamine](#) dose the subject was hospitalized with an unremarkable physical examination, negative drug screen, and normal laboratories. He was treated with [haloperidol](#) 2

mg, [lorazepam](#) 1 mg, and [chlorpromazine](#) 50 mg. Psychotic symptoms improved within 72 hours of admission and after an additional 72 hours of observation, the subject was discharged on no medication. Medical history was negative for past psychotic presentations and substance abuse history [85].

3.3.12.A.9] Suicidal thoughts

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 [fluvoxamine](#) (n=9690; 4182 person-years), suicide occurred at an event rate of 0.95/1000 person-years (95% confidence interval (CI), 0.26 to 2.44) and suicide attempts occurred at a rate of 8.37/1000 person-years (95% CI, 5.83 to 11.64). Based on data among treatment-naive patients alone (no antidepressant use in the past 3 years; n=4032; 1858 person-years), suicide occurred at a rate of 1.08/1000 person-years (95% CI, 0.13 to 3.88) and suicide attempts occurred at a rate of 5.92/1000 person-years (95% CI, 2.96 to 10.59). Following an extensive propensity score adjustment in comparison with [fluoxetine](#) hydrochloride, [fluvoxamine](#) had an overall hazard ratio of 1.35 (95% CI, 0.55 to 3.35). Most events were reported within the first 6 months after start of therapy [80].

b) A causal role for antidepressants in inducing suicidality has been established in children, adolescents, and young adults (up to 24 years old). Anyone considering the use of antidepressants in a child, adolescent, or young adult must balance this risk with the clinical need. Families and caregivers should be encouraged to observe the patient carefully for emerging symptoms and unexpected behavior. This causal role in children and adolescents was determined from pooled analyses of 24 short-term, placebo-controlled trials of 9 antidepressants (SSRIs and others) which included over 4400 patients with [major depressive disorder](#), [obsessive-compulsive disorder](#) (OCD), or other psychiatric disorders. The causal role in adults was determined from pooled analyses of 295 short-term, placebo-controlled trials of 11 antidepressants which included over 77,000 patients with [major depressive disorder](#) or other psychiatric disorders. The risk of suicidal thinking and behavior was increased in children, adolescents, and young adults up to 24 years old. This increased risk did not exist in adults over 24 years old, and the risk was lower in adults over 65 years old. The risk was highest in patients with [major depressive disorder](#), but there were signs of risk emerging from trials in other psychiatric indications, such as OCD and [social anxiety disorder](#). No suicides occurred in the pediatric trials. The risk of suicidality during longer-term use (ie, beyond several months) is not known [40][22][86].

c) Management

1) Adult and pediatric patients being treated with antidepressants for [major depressive disorder](#) who experience symptoms of anxiety, agitation, panic attacks, insomnia, irritability, hostility, aggressiveness, impulsivity, [akathisia](#) (psychomotor restlessness), [hypomania](#), or mania may be at risk of [suicidal ideation](#) and behavior (suicidality). This same concern applies to patients being treated for other psychiatric and nonpsychiatric disorders. 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. The dose should be tapered off, avoiding abrupt discontinuation whenever possible. Patients and their caregivers should be provided with the Medication Guide that is available for this drug [40][22][87][86].

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 [fluvoxamine](#) (n=9690; 4182 person-years), suicide occurred at an event rate of 0.95/1000 person-years (95% confidence interval (CI), 0.26 to 2.44) and suicide attempts occurred at a rate of 8.37/1000 person-years (95% CI, 5.83 to 11.64). Based on data among treatment-naïve patients alone (no antidepressant use in the past 3 years; n=4032; 1858 person-years), suicide occurred at a rate of 1.08/1000 person-years (95% CI, 0.13 to 3.88) and suicide attempts occurred at a rate of 5.92/1000 person-years (95% CI, 2.96 to 10.59). Following an extensive propensity score adjustment in comparison with [fluoxetine](#) hydrochloride, [fluvoxamine](#) had an overall hazard ratio of 1.35 (95% CI, 0.55 to 3.35). Most events were reported within the first 6 months after start of therapy [80].

3.3.13] Renal Effects

3.3.13.A] [Fluvoxamine Maleate](#)

3.3.13.A.1] [Acute renal failure](#)

a) [Acute renal failure](#) has been reported during postmarketing use of immediate-release [fluvoxamine](#) maleate tablets, although a causal relationship has not been established [40].

3.3.13.A.2] [Urinary retention](#)

a) Incidence: immediate-release, 1% [40]

b) In short-term, placebo-controlled clinical trials evaluating immediate-release [fluvoxamine](#) maleate (100 mg/day to 300 mg/day) for the treatment of [obsessive-compulsive disorder](#) (OCD) or depression, urinary retention was reported in 1% of [fluvoxamine](#) maleate patients (n=892) compared with 0% of placebo patients (n=778). There was a two-fold increase in the rate of urinary retention in studies of OCD treatment compared with studies of OCD and depression [40].

3.3.14] Reproductive Effects

3.3.14.A] [Fluvoxamine](#)

3.3.14.A.1] [Sexual dysfunction](#)

See Drug Consult reference: Drug-Induced Sexual Dysfunction

3.3.14.B] [Fluvoxamine Maleate](#)

3.3.14.B.1] [Abnormal ejaculation](#)

a) Incidence: immediate-release, 8%; extended-release, 10% [40][22]

b) In short-term, placebo-controlled clinical trials evaluating immediate-release [fluvoxamine](#) maleate (100 mg/day to 300 mg/day) for the treatment of [obsessive-compulsive disorder](#) (OCD) or depression, abnormal ejaculation (mostly delayed ejaculation) was reported in 8% of male [fluvoxamine](#) maleate patients compared with 1% of placebo patients. There was a two-fold increase in the rate of abnormal ejaculation (mostly delayed ejaculation) in studies of OCD treatment compared with studies of OCD and depression [40].

c) In a 12-week, placebo-controlled clinical trial evaluating extended-release [fluvoxamine](#) maleate (100 to 300 mg once daily) for the treatment of [obsessive-compulsive disorder](#), abnormal ejaculation

was reported in 10% of [fluvoxamine](#) maleate patients (n=124) compared with 0% of placebo patients (n=124) [22].

d) [Cyproheptadine](#), 1 mg per 25 mg of [fluvoxamine](#) taken 2 hours prior to intercourse was effective in reversing ejaculatory failure secondary to [fluvoxamine](#) in a 63-year-old man with recurrent [unipolar depression](#). Eventually, 150 mg [fluvoxamine](#) per day was effective in controlling the patient's affective symptoms and 6 mg of [cyproheptadine](#) was effective in preventing ejaculatory failure [92].

3.3.14.B.2] [Amenorrhea](#)

a) [Amenorrhea](#) has been listed in postmarketing reports of immediate-release [fluvoxamine](#) maleate use, although a causal relationship has not been established [40].

b) [Galactorrhea](#) and [amenorrhea](#) associated with [fluvoxamine](#) were reported in a 38-year-old woman with refractory [bipolar affective disorder](#); this patient had been treated for over a decade with several psychotropic agents. The patient had been maintained for an undetermined length of time on [loxapine](#) 150 mg daily, [oxazepam](#) 30 mg three times daily, and zopiclone 7.5 mg at bedtime. [Fluvoxamine](#) was prescribed for depression, and the dose was titrated to 150 mg daily while the [loxapine](#) dosage was decreased to 75 mg daily. Six weeks after starting [fluvoxamine](#), she complained of [amenorrhea](#) followed soon by [galactorrhea](#). Thorough evaluation ruled out an underlying organic etiology; however, the serum prolactin level was 80 mcg/L (normal, 4 to 30 mcg/L). [Galactorrhea](#) resolved 3 weeks after stopping [fluvoxamine](#), and menstruation resumed a week later. The temporal relationship between [fluvoxamine](#) and the onset of [galactorrhea](#) and [amenorrhea](#) suggests a possible etiologic role for [fluvoxamine](#) [66].

3.3.14.B.3] [Dysmenorrhea](#)

a) In a placebo-controlled study involving pediatric patients with [obsessive-compulsive disorder](#), [dysmenorrhea](#) was reported in 3.5% or more (2 or more of 57) patients treated with immediate-release [fluvoxamine](#) maleate, which was more frequent than in placebo-treated patients [40].

3.3.14.B.4] [Erectile dysfunction](#)

a) Incidence: immediate-release, 2% [40]

b) In short-term, placebo-controlled clinical trials evaluating immediate-release [fluvoxamine](#) maleate (100 mg/day to 300 mg/day) for the treatment of [obsessive-compulsive disorder](#) (OCD) or depression, impotence was reported in 2% of male [fluvoxamine](#) maleate patients compared with 1% of male placebo patients. There was a two-fold increase in the rate of impotence in studies of OCD treatment compared with studies of OCD and depression [40].

3.3.14.B.5] [Increased libido](#)

a) A 65-year-old female experienced increased sexual desire after 1 week of treatment with [fluvoxamine](#) 25 mg twice daily, medazepam 5 mg twice daily, and flunitrazepam 2 mg once daily for the treatment of depression and insomnia. Her depressive symptoms dramatically improved; however, sexual desire increased daily over the second week of therapy. [Fluvoxamine](#) was discontinued and treatment with sulpiride 100 mg twice daily, [amoxapine](#) 10 mg twice daily, medazepam 5 mg twice daily, and flunitrazepam 2 mg once daily were initiated. Symptoms of increased sexual desire disappeared and did not recur. The subject's past sexual history included cessation of her sexual relationship with her husband for 10 years prior to this event (Okada & Ikajima, 2000).

3.3.14.B.6] [Orgasm incapacity](#)

a) Incidence: immediate-release, 2%; extended-release, 5% [40][22]

b) In short-term, placebo-controlled clinical trials evaluating immediate-release [fluvoxamine](#) maleate (100 mg/day to 300 mg/day) for the treatment of [obsessive-compulsive disorder](#) (OCD) or depression, [anorgasmia](#) was reported in 2% of [fluvoxamine](#) maleate patients (n=892) compared with 0% of placebo patients (n=778). There was a two-fold increase in the rate of [anorgasmia](#) (in males) in studies of OCD treatment compared with studies of OCD and depression [40].

c) In a 12-week, placebo-controlled clinical trial evaluating extended-release [fluvoxamine](#) maleate (100 to 300 mg once daily) for the treatment of [obsessive-compulsive disorder](#), [anorgasmia](#) was reported in 5% of [fluvoxamine](#) maleate patients (n=124) compared with 0% of placebo patients (n=124) [22].

d) A 22-year-old woman who had been taking [fluvoxamine](#) for 2 months experienced [anorgasmia](#) which was unresponsive to treatment with [cyproheptadine](#) 8 and 12 mg; therefore, a reduction in [fluvoxamine](#) dosage was tried. Decreasing the weekend dose to 150 or 200 mg did NOT result in normal sexual function; a reduction in dose to [fluvoxamine](#) 200 mg daily resulted in a return of obsessive symptoms. In this patient, a partial drug holiday resulted in normal sexual function [91].

3.3.14.B.7] Reduced libido

a) Incidence: immediate-release, 2%; extended-release, 6% [40][22]

b) In short-term, placebo-controlled clinical trials evaluating immediate-release [fluvoxamine](#) maleate (100 mg/day to 300 mg/day) for the treatment of [obsessive-compulsive disorder](#) (OCD) or depression, decreased libido was reported in 2% of [fluvoxamine](#) maleate patients (n=892) compared with 1% of placebo patients (n=778). There was a two-fold increase in the rate of decreased libido in studies of OCD treatment compared with studies of OCD and depression [40].

c) In a 12-week, placebo-controlled clinical trial evaluating extended-release [fluvoxamine](#) maleate (100 to 300 mg once daily) for the treatment of [obsessive-compulsive disorder](#), reduced libido was reported in 6% of [fluvoxamine](#) maleate patients (n=124) compared with 2% of placebo patients (n=124) [22].

3.3.14.B.8] Sexual dysfunction

a) Incidence: extended-release, 4% (males) [22]

b) In a 12-week, placebo-controlled clinical trial evaluating extended-release [fluvoxamine](#) maleate (100 to 300 mg once daily) for the treatment of [obsessive-compulsive disorder](#), abnormal sexual function was reported in 4% of males assigned to [fluvoxamine](#) maleate compared with 3% of males assigned to placebo [22].

c) Of 20 healthy volunteers enrolled in a phenotyping study using [fluvoxamine](#), 7 (35%) reported sexual dysfunction after 4 weeks of [fluvoxamine](#) treatment. [Fluvoxamine](#) 100 mg daily on Friday and Saturday followed by 300 mg daily Sunday through Thursday resulted in normal sexual function with adequate control of depression and obsessive-compulsive symptoms. In humans, it is postulated that serotonin has an inhibitory effect on sexual function by direct effects on the central, spinal, or peripheral receptors [90].

3.3.15] Respiratory Effects

3.3.15.A] [Fluvoxamine](#) Maleate

3.3.15.A.1] [Pharyngitis](#)

a) Incidence: extended-release, 6% [22]

b) In a 12-week, placebo-controlled clinical trial evaluating extended-release [fluvoxamine](#) maleate (100 to 300 mg once daily) for the treatment of [obsessive-compulsive disorder](#), [pharyngitis](#) was

reported in 6% of [fluvoxamine](#) maleate patients (n=124) compared with less than 1% of placebo patients (n=124) [22].

c) In short-term, placebo-controlled clinical trials evaluating immediate-release [fluvoxamine](#) maleate (100 mg/day to 300 mg/day) for the treatment of [obsessive-compulsive disorder](#) (OCD), [pharyngitis](#) was reported at a rate that was two-fold higher than the rate reported in OCD and depression trials [40].

3.3.15.A.2] Upper respiratory infection

a) Incidence: immediate-release, 9% [40]

b) In short-term, placebo-controlled clinical trials evaluating immediate-release [fluvoxamine](#) maleate (100 mg/day to 300 mg/day) for the treatment of [obsessive-compulsive disorder](#) (OCD) or depression, [upper respiratory infection](#) was reported in 9% of [fluvoxamine](#) maleate patients (n=892) compared with 5% of placebo patients (n=778) [40].

3.3.15.A.3] Yawning

a) Incidence: immediate-release, 2%; extended-release, 2% [40][22]

b) In short-term, placebo-controlled clinical trials evaluating immediate-release [fluvoxamine](#) maleate (100 mg/day to 300 mg/day) for the treatment of [obsessive-compulsive disorder](#) (OCD) or depression, yawning was reported in 2% of [fluvoxamine](#) maleate patients (n=892) compared with 0% of placebo patients (n=778) [40].

c) In a 12-week, placebo-controlled clinical trial evaluating extended-release [fluvoxamine](#) maleate (100 to 300 mg once daily) for the treatment of [obsessive-compulsive disorder](#), yawning was reported in 2% of [fluvoxamine](#) maleate patients (n=124) compared with 0% of placebo patients (n=124) [22].

3.3.16] Other

3.3.16.A] Fluvoxamine Maleate

3.3.16.A.1] Accidental injury

a) Incidence: extended-release, 5% [22]

b) In a 12-week, placebo-controlled clinical trial evaluating extended-release [fluvoxamine](#) maleate (100 to 300 mg once daily) for the treatment of [obsessive-compulsive disorder](#), accidental injury was reported in 5% of [fluvoxamine](#) maleate patients (n=124) compared with 3% of placebo patients (n=124) [22].

3.3.16.A.2] Neuroleptic malignant syndrome

a) While most reports of [neuroleptic malignant syndrome](#) (NMS) involved concomitant administration of [fluvoxamine](#) maleate and an antipsychotic drug, a small number of NMS cases have been associated with the administration of [fluvoxamine](#) maleate alone. Symptoms included [hyperthermia](#), muscle rigidity, autonomic instability, changes in vital signs, and mental status changes [40][22].

b) [Neuroleptic malignant syndrome](#) has been described, with the earliest onset noted at 5 days [55], and latest onset at 4 months [56]. Duration of symptoms with treatment is usually a few days [57][58].

3.3.16.A.3] Serotonin syndrome

a) [Serotonin syndrome](#), which may include mental status changes (eg, agitation, hallucination, and coma), autonomic instability (eg, [tachycardia](#), [hyperthermia](#), and labile blood pressure), neuromuscular aberrations, and gastrointestinal symptoms (eg, nausea, vomiting, and diarrhea),

may occur with [fluvoxamine](#) maleate. This syndrome could be life-threatening. Risk is increased with concomitant use of SSRIs, serotonin [norepinephrine](#) reuptake inhibitors (SNRI), triptans, and MAOIs (contraindicated). If concomitant use with SSRIs, SNRIs, or a triptan is warranted, increased monitoring is advised [40][22].

b) [Serotonin syndrome](#) has been described with administration of [fluvoxamine](#). Symptoms include anxiety, coma, confusion, diaphoresis, disorientation, hyperreflexia, [hypertension](#), [hyperthermia](#), myoclonus, rigidity, seizures, and tremor. Incidence is rare (less than 0.1%). In severe cases, hospitalization has been required for treatment [81].

c) An 11-year-old boy developed [serotonin syndrome](#) (SS) 1 hour after receiving [fluvoxamine](#) 50 mg for [attention deficit disorder](#). He was also receiving [perphenazine](#) and [bentropine](#), which had been used for 2 years. Symptoms of SS included agitation, unresponsiveness to verbal or painful stimuli, fluctuating blood pressure and heart rate, jaw myoclonus, shivering, fever to 103.5 degrees Fahrenheit, and hyperreflexia with rigidity of the lower extremities. Initial treatment consisted of [diazepam](#) 10 mg and [lorazepam](#) 21 mg in incremental intravenous doses. Due to a rise in temperature, he was paralyzed with rocuronium 50 mg and intubated; sedation and pharmacologic paralysis were continued for 24 hours. Full recovery occurred 48 hours after hospitalization [81].

3.3.16.A.4] Withdrawal sign or symptom

a) Withdrawal symptoms including [dysphoric mood](#), irritability, agitation, dizziness, [sensory disturbances](#) (eg, paresthesias, including electric shock sensations), anxiety, confusion, headache, lethargy, emotional lability, insomnia, and [hypomania](#) have occurred when immediate-release [fluvoxamine](#) maleate was discontinued, primarily if discontinuation is abrupt. These events may be serious, although they are usually self-limiting. A gradual reduction in dose is recommended and, if intolerable symptoms develop, a temporary resumption of therapy with the prescribed dose may be warranted, followed by a more gradual reduction [40][22].

b) On the fourth day following the abrupt discontinuation of [fluvoxamine](#) (200 mg/day), a 12-year-old boy experienced nausea, poor concentration, light-headedness, fatigue, headache, gait instability, and insomnia. [Fluvoxamine](#) was restarted at the same dose and the patient's discontinuation symptoms resolved within 2 days. A second 12-year-old boy developed discontinuation symptoms of headache, poor concentration, irritability, dizziness, fatigue, and shock-like sensation in the brain 5 days after stopping [fluvoxamine](#) 200 mg/day. Reinstitution of [fluvoxamine](#) at the former dose resulted in resolution of withdrawal symptoms in 3 days (Diler & Avci, 2002).

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: Unknown

4) Clinical Management

a) Although human and animal studies of [fluvoxamine](#) use during pregnancy did not reveal substantial [teratogenicity](#) [426], nonteratogenic effects ([pulmonary hypertension](#) of the newborn (PPHN) and clinical findings consistent with [serotonin syndrome](#)) and increased special or intensive unit care of the infant were demonstrated following maternal use of [fluvoxamine](#) during the third trimester of pregnancy [420][113][425]. One small study indicated no long-term effects on cognitive ability were demonstrated but did show evidence of an increased risk for social-behavioral abnormalities at 2 to 6 years of age in children exposed to serotonin-reuptake inhibitors (SSRIs) or serotonin–norepinephrine reuptake inhibitors in utero who developed [neonatal abstinence syndrome](#) (NAS) at birth [424]. A study of prospectively collected data suggests antenatal use of SSRI antidepressants is associated with QTc interval prolongation in exposed neonates [423]. One study revealed that women who discontinued antidepressant medication during pregnancy had a greater likelihood of [relapse](#) compared with those who continued antidepressant therapy throughout the pregnancy [420][113]. Therefore, when deciding whether to treat a pregnant woman with [fluvoxamine](#) during the third trimester, evaluate the potential [risk to the fetus](#) and the potential benefit to the mother. Consider tapering the [fluvoxamine](#) dose during the third trimester of pregnancy [420][113].

5) Literature Reports

a) A nested case-controlled study showed that [fluvoxamine](#), [sertraline](#), [fluoxetine](#), [citalopram](#), 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](#). [422].

b) A study of prospectively collected data suggests antenatal use of selective serotonin-reuptake inhibitor (SSRI) antidepressants is associated with QTc interval prolongation in exposed neonates. Between January 2000 and December 2005, researchers compared 52 neonates exposed to SSRI antidepressants ([paroxetine](#) (n=25), [citalopram](#) (n=13), [fluoxetine](#) (n=12), [fluvoxamine](#) (n=1), and [venlafaxine](#) (n=1)) in the immediate antenatal period to 52 matched neonates with no exposure. Prolonged QTc is defined as an interval of greater than 460 milliseconds (msec) (the widely used upper limit cited by authorities in both pediatric cardiology and neonatology). A pediatric cardiologist blinded to drug exposure, interpreted all [electrocardiograms](#) (ECGs) using standard

statistical analyses. ECG recordings revealed markedly prolonged mean QTc intervals in exposed neonates compared to unexposed neonates (mean; 409 +/- 42 msec versus 392 +/- 29 msec, $p=0.02$). The mean uncorrected QT interval was 7.5% longer among exposed neonates (mean; 280 +/- 31 msec versus 261 +/- 25 msec, p less than 0.001). Ten percent ($n=5$) of exposed neonates had a notable increase in QTc interval prolongation (greater than 460 msec) compared to none of the unexposed neonates. The longest QTc interval observed was 543 msec [423].

c) Neonates exposed to [fluvoxamine](#) and other SSRIs late in the third trimester have developed complications, including respiratory distress, seizures, vomiting, tremor, and irritability that were consistent with either SSRI toxicity or a possible drug discontinuation syndrome. In some cases, clinical findings were consistent with [serotonin syndrome](#) [420][113].

d) 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; $p=0.068$) [424].

e) In a case control study of women who delivered infants with [pulmonary hypertension](#) of the newborn (PPHN; $n=377$) and women who delivered healthy infants ($n=836$), the risk for developing PPHN was approximately six-fold higher in infants exposed to SSRIs after week 20 of gestation compared with infants not exposed to SSRIs during gestation. This study demonstrates a potential increased risk of PPHN, associated with considerable neonatal morbidity and mortality, in infants exposed to SSRIs later in the pregnancy. In the general population, PPHN occurs in 1 to 2 per 1000 live births [420][113].

f) In a prospective longitudinal study of 201 women with a history of [major depression](#) and no signs of depression at the beginning of pregnancy, there was a greater likelihood of [relapse](#) of [major depression](#) in those who discontinued antidepressant drugs during pregnancy compared with those who continued antidepressant drugs throughout the pregnancy [420][113].

g) A population-based study of 1782 pregnant women exposed to SSRIs found no increased risk of adverse perinatal outcome except for treatment in the neonatal intensive or special care unit, particularly with third trimester exposure. Using 1996 to 2001 data derived from a government project involving 4 birth or medication registries in Finland, women who had at least one purchase (a 3-month supply) of an SSRI during the period of one month before pregnancy and the day pregnancy ended were compared with 1782 controls with no reimbursed drug purchases during the same peripartum period. The mean age of both cohorts was 30 years (+/- 7). There were more than twice as many smokers and six times as many pregnancies induced by artificial reproductive techniques in the SSRI group compared to controls (p less than 0.001), and mean length of gestation

and birth weight were lower (p less than 0.001) in the SSRI group. Malformations, however, were not more common in the SSRI group ($p = 0.4$). Purchases of SSRIs (citalopram, fluoxetine, paroxetine, sertraline and fluvoxamine) were more common in the first trimester than later in pregnancy, with 65 women purchasing fluvoxamine during the first trimester, 23 during the second trimester, 27 during the third, and 10 throughout pregnancy. When compared with first trimester exposure, treatment in a special or intensive care unit was more common for the infants exposed during the third trimester (11.2% and 15.7%, respectively; $p = 0.009$). Even after adjusting for confounding variables, this difference remained statistically significant (OR 1.6; 95% CI 1.1-2.2) [425].

h) In a cohort study ($n=267$), the pregnancy outcome did not differ between women treated with sertraline ($n=147$), paroxetine ($n=97$), or fluvoxamine ($n=26$) versus controls. Rates of major malformations, stillbirth, and spontaneous and elective abortions were similar between the 2 groups as were the mean birth rate and gestational age. Nine major malformations were detected in infants exposed to a selective serotonin reuptake inhibitor (SSRI) and in control infants. Of the 49 women who were treated throughout pregnancy with an SSRI, there were also no differences in outcome compared to women treated only during the first trimester. The majority of women took sertraline 50 mg/day, paroxetine 30 mg/day, and fluvoxamine 50 mg/day [426].

i) A cohort study of prospectively collected data demonstrated an increased risk of autism spectrum disorder (ASD) in children whose mothers used antidepressants during the second or third trimesters of pregnancy; the risk was even greater with second or third trimester exposure to SSRIs. Thirty-one infants who were exposed to antidepressants during the second or third trimester were diagnosed with ASD. After adjusting for potential confounders, second or third trimester exposure to antidepressants was associated with a significant 87% increased risk of ASD, while first trimester exposure or use of antidepressants in the year before pregnancy was not associated with any such risk. Use of SSRIs during the second or third trimester was associated with a significant more than 2-fold increased risk of ASD (22 exposed infants), while other classes of antidepressants were not associated with an increased risk. Even after restricting the sample size to those children whose mothers had a history of depression and used antidepressants during the second or third trimester, the risk of ASD still persisted. In addition, use of more than 1 class of antidepressants during the second or third trimester was associated with a significant more than 4-fold increased risk of ASD [427].

j) Treatment with fluvoxamine 200 mg/day and quetiapine 400 mg/day in a 33-year-old woman during her second pregnancy resulted in an uneventful pregnancy and the birth of a healthy female infant. The patient was being treated with fluvoxamine and quetiapine when she was diagnosed with a severe postpartum psychotic depression after the birth of her first child; multiple attempts at reducing her medication led to relapse. After being informed of the risks-benefits of fluvoxamine/quetiapine exposure during pregnancy, the patient decided to go forward with a second pregnancy while maintaining her drug regimen of fluvoxamine and quetiapine with the addition of folate 5 mg/day throughout the pregnancy. The patient gained 9 kg with no symptoms of psychiatric instability. Routine biochemical tests were within the normal range and 5 echographic reports found no fetal abnormalities. The presence of an intrauterine myoma led to an elective caesarean-section. A healthy female infant weighing 2600 g and measuring 49 cm in length was delivered, with Apgar scores of 9 and 10 at 1 minute and 5 minutes, respectively [428].

B)) Breastfeeding

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

2) Micromedex 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) The American Academy of Pediatrics considers antidepressants to be drugs worthy of concern in the nursing infant, particularly during long-term use [429]. The long-term effects of exposure to SSRIs via breastmilk on the cognitive development of the infant have not been determined. Although [fluvoxamine](#) appeared in the breastmilk of two nursing mothers, the drug was not observed in the plasma of either infant and both developed normally with no adverse effects [430]. Similarly, in a case report of a nursing woman being treated with [fluvoxamine/quetiapine](#), the nursing infant received breastmilk supplemented with formula for 3 months and showed no developmental abnormalities [428]. Because [fluvoxamine](#) is secreted in human breastmilk and there is potential for serious adverse effects in the nursing infant, a decision should be made whether to discontinue the drug or discontinue nursing, taking into consideration the potential [risk to the fetus](#) as well as the potential benefit to the mother [420][113][430].

4) Literature Reports

a) Treatment with [fluvoxamine](#) 200 mg/day and [quetiapine](#) 400 mg/day in a 33-year-old woman during her second pregnancy resulted in an uneventful pregnancy and the birth of a healthy female infant weighing 2600 g and measuring 49 cm in length with Apgar scores of 9 and 10 at 1 minute and 5 minutes, respectively. The patient chose to breastfeed; however, formula was required to supplement her breast milk due to insufficient milk production. In the 3 months that the infant received breast milk supplemented with formula, no adverse effects were detected and the infant continues to develop normally [428].

b) In a study of 2 mother-infant pairs, there were no adverse effects from [fluvoxamine](#) found in either nursing infant. The infants were 26 months and 0.75 months of age at the time of the study, which involved collecting venous blood samples and breastmilk over a 24 hour dosing interval. Assuming a milk intake for both infants of 0.15 L/kg/day, the infant dose calculated as a percentage of the weight-adjusted maternal dose were 1.38% (26 month old infant) and 0.8% (0.75 month old infant). The milk to plasma ratios were 1.34 and 1.21, respectively. [Fluvoxamine](#) was not detected in the plasma of either infant. The 26-month-old infant had a Denver developmental assessment with a quotient of 115, indicating that the infant achieved the anticipated milestones. The 0.75-month-old infant was too young to have a meaningful Denver assessment, so a detailed pediatric examination was performed and found no abnormalities. Both mothers reported that the health and progress of their infants was satisfactory [430].

5) Drug Levels in Breastmilk**a) [Fluvoxamine](#) Maleate****1) Parent Drug****a) Percent Adult Dose in Breastmilk**

1)) In a study of 2 mother-infant pairs, the infant dose calculated as a percentage of the weight adjusted maternal dose were 0.8% (0.75 month old infant) and 1.38% (26 month old infant). These values assume an average milk intake of 0.15 liters/kilogram (L/kg) per day [430].

b)) Milk to Maternal Plasma Ratio

1)) In a study of 2 mother-infant pairs, the milk to maternal plasma ratio were 1.21 (0.75 month old infant) and 1.34 (26 month old infant) [430].

c)) Time to Peak Concentration in Milk

1)) In a study of 2 mother-infant pairs, the time after dose at which maximum fluvoxamine concentrations were achieved in breast milk were 2.1 hours (0.75 month old infant) and 4.2 hours (26 month old infant) [430].

3.5] Drug Interactions

3.5.1] Drug-Drug Combinations

3.5.1.A] [Abciximab](#)

1)) Interaction Effect: increased risk of bleeding

2)) Summary: Exercise caution when coadministering a SSRI and an antiplatelet agent as this may increase the risk of bleeding events[139][138].[137]. Bleeding events reported have included [epistaxis](#), ecchymosis, [hematoma](#), [petechiae](#), and life-threatening hemorrhages. Monitor patient for signs of increased bleeding when [fluvoxamine](#) is administered with an antiplatelet agent concomitantly [137].

3)) Severity: major

4)) Onset: unspecified

5)) Substantiation: theoretical

6)) Clinical Management: When [fluvoxamine](#) and an antiplatelet agent are given concurrently, monitor patient for signs of increased bleeding[137].

7)) Probable Mechanism: unknown

8)) Literature Reports

a)) In a retrospective study of patients over 50 years of age with the diagnosis of acute [myocardial infarction](#) (N=27,058), SSRI use with any antiplatelet therapy significantly increased the risk of bleeding by 1.42-fold compared with [aspirin](#) use alone. Therapy with [aspirin](#), [clopidogrel](#), and an SSRI significantly increased risk by 2.35-fold compared with [aspirin](#) use alone and by 1.57-fold compared with [clopidogrel](#) and [aspirin](#) combination therapy [138].

b)) In a systematic review and meta-analysis of 22 observational studies, SSRI use was associated with a significant 1.55 fold increase in risk of [upper gastrointestinal bleeding](#) (UGIB). Concomitant use of SSRIs and antiplatelet drugs was associated with a 2.48-fold increase in risk of UGIB (3 studies) [139].

3.5.1.B] Aceclofenac

- 1) Interaction Effect: an increased risk of bleeding
- 2) Summary: Caution is recommended with the concomitant use of NSAIDs and antidepressants, including SSRIs due to an increased risk of [intracranial hemorrhage](#)[367] and [gastrointestinal bleeding](#) [371][372][368][369]. Bleeding events have included [epistaxis](#), ecchymosis, [hematoma](#), [petechiae](#), and life-threatening hemorrhages [374][373][375][376]. When an SSRI and an NSAID are given concurrently, monitor the patient for signs of increased bleeding.
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: established
- 6) Clinical Management: Use caution if NSAIDs and SSRIs are coadministered. Concomitant use of NSAIDs and SSRIs may cause an increased risk of [intracranial hemorrhage](#)[367] and [gastrointestinal bleeding](#) [368][369]. When an SSRI and an NSAID are given concurrently, monitor the patient for signs of increased bleeding.
- 7) Probable Mechanism: depletion of [platelet](#) serotonin by SSRI; additive effects
- 8) Literature Reports

a) Concomitant use of NSAIDs and antidepressants, including tricyclic antidepressants, SSRIs, serotonin-norepinephrine reuptake inhibitors, and MAOIs, resulted in a 60% increased risk of [intracranial hemorrhage](#) within 30 days of concomitant use compared with antidepressant use alone. There was no significant difference between the antidepressant drug classes and the increased risk; however, there was an increased risk associated with male patients compared with female patients [367].

b) 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. Combined use of an SSRI and NSAIDs or low-dose [aspirin](#) increased the risk to 12.2 and 5.2 times, 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 [370].

c) Two metaanalyses of incidents of upper GI bleed due to SSRIs, NSAIDs, and their combination found that SSRIs increased the risk by 1.73 [371] to 2.36 times [372], NSAIDs by 2.55 times [371], and the combination of SSRIs and NSAIDs by 4.02 [371] to 6.33 times [372].

d) The release of serotonin by [platelets](#) is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs and NSAIDs have been associated with an increased risk of bleeding [373].

3.5.1.C] Acemetacin

- 1) Interaction Effect: an increased risk of bleeding
- 2) Summary: Caution is recommended with the concomitant use of NSAIDs and antidepressants, including SSRIs due to an increased risk of [intracranial hemorrhage](#)[367] and [gastrointestinal bleeding](#) [371][372][368][369]. Bleeding events have included [epistaxis](#), ecchymosis, [hematoma](#), [petechiae](#), and life-threatening hemorrhages [374][373][375][376]. When an SSRI and an NSAID are given concurrently, monitor the patient for signs of increased bleeding.

- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: established
- 6) Clinical Management: Use caution if NSAIDs and SSRIs are coadministered. Concomitant use of NSAIDs and SSRIs may cause an increased risk of [intracranial hemorrhage](#)[367] and [gastrointestinal bleeding](#) [368][369]. When an SSRI and an NSAID are given concurrently, monitor the patient for signs of increased bleeding.
- 7) Probable Mechanism: depletion of [platelet](#) serotonin by SSRI; additive effects
- 8) Literature Reports

a) Concomitant use of NSAIDs and antidepressants, including tricyclic antidepressants, SSRIs, serotonin-norepinephrine reuptake inhibitors, and MAOIs, resulted in a 60% increased risk of [intracranial hemorrhage](#) within 30 days of concomitant use compared with antidepressant use alone. There was no significant difference between the antidepressant drug classes and the increased risk; however, there was an increased risk associated with male patients compared with female patients [367].

b) 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. Combined use of an SSRI and NSAIDs or low-dose [aspirin](#) increased the risk to 12.2 and 5.2 times, 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 [370].

c) Two metaanalyses of incidents of upper GI bleed due to SSRIs, NSAIDs, and their combination found that SSRIs increased the risk by 1.73 [371] to 2.36 times [372], NSAIDs by 2.55 times [371], and the combination of SSRIs and NSAIDs by 4.02 [371] to 6.33 times [372].

d) The release of serotonin by [platelets](#) is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs and NSAIDs have been associated with an increased risk of bleeding [373].

3.5.1.D] Acenocoumarol

- 1) Interaction Effect: an increased risk of bleeding
- 2) Summary: The release of serotonin by [platelets](#) is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs and anticoagulants has been associated with an increased risk of bleeding[114][115][113]. 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](#). In patients receiving [warfarin](#) and [fluvoxamine](#) concomitantly for 2 weeks, [warfarin](#) plasma concentrations increased by 98% and prothrombin times were prolonged. [Fluvoxamine](#) appears to inhibit several cytochrome P450 isoenzymes which may include 1A2 and 2C9 isozymes, which are responsible for [warfarin](#) metabolism [115][113].
- 3) Severity: major
- 4) Onset: delayed
- 5) Substantiation: probable
- 6) Clinical Management: When [fluvoxamine](#) 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 [fluvoxamine](#) therapy is initiated or discontinued. Periodically reassess the prothrombin time ratio and INR in patients receiving [fluvoxamine](#) and [anticoagulant therapy](#)[113].

7J) Probable Mechanism: unknown

8J) Literature Reports

aJ) 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 [114].

bJ) 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 [115].

cJ) A hospitalized 80-year-old female was started on intravenous [heparin](#) and oral [warfarin](#) therapy due to an [embolic stroke](#) secondary to [atrial fibrillation](#) and [mitral stenosis](#). Her [warfarin](#) dose was maintained at 1 mg daily, with her INR between 2.5 and 3. [Fluvoxamine](#) 25 mg daily was started for depression, and her [warfarin](#) dose was increased to 1.5 mg daily 3 days later due to worsening of the left [hemiparesis](#). Three days later, her INR was 9.96, and a repeat INR to rule out laboratory error was 11.3. [Warfarin](#) was discontinued, fresh frozen plasma was given, and [fluvoxamine](#) was discontinued. Six days later, [warfarin](#) was again started at 1 mg daily, and the INR increased over 4 days to 11.8. The elevated INR was attributed to the persisting effect of [fluvoxamine](#). She was eventually stabilized on [warfarin](#) 1 mg daily with INR values between 2 and 2.5 [116].

3.5.1.EJ Agomelatine

1J) Interaction Effect: increased agomelatine exposure

2J) Summary: Concomitant use of agomelatine (a CYP1A2 substrate) with a strong CYP1A2 inhibitor is contraindicated[236][237].

3J) Severity: contraindicated

4J) Onset: unspecified

5J) Substantiation: theoretical

- 6) Clinical Management: Concomitant use of agomelatine, a CYP1A2 substrate, with a strong CYP1A2 inhibitor is contraindicated[236][237].
- 7) Probable Mechanism: inhibition of CYP1A2-mediated metabolism of agomelatine

3.5.1.F] 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[243]. 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](#) [118].
- 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 [242].

3.5.1.G] Alosetron

- 1) Interaction Effect: increased [alosectron](#) exposure and increased side effects
- 2) Summary: [Fluvoxamine](#) is a potent inhibitor of the CYP1A2-mediated metabolism of [alosectron](#). In a [pharmacokinetic study](#) of 40 healthy female subjects, [fluvoxamine](#) increased mean [alosectron](#) AUC by 6-fold and prolonged [alosectron](#) half-life by 3-fold. Concomitant use of [fluvoxamine](#) and [alosectron](#) is contraindicated due to the increased risk of serious bowel side effects, including [ischemic colitis](#)[330][1].
- 3) Severity: contraindicated
- 4) Onset: unspecified
- 5) Substantiation: established

- 6J) Clinical Management: Concomitant use of [aloseptron](#) and [fluvoxamine](#) is contraindicated[330][1]
- 7J) Probable Mechanism: inhibition by [fluvoxamine](#) of CYP1A2-mediated [aloseptron](#) metabolism
- 8J) Literature Reports

aJ) [Fluvoxamine](#) inhibits the CYP1A2-mediated metabolism of [aloseptron](#). In a [pharmacokinetic study](#) involving 40 healthy female subjects, participants received an escalating dose of [fluvoxamine](#) 50 to 200 mg daily for 16 days. On the final day, participants also received a single 1 mg dose of [aloseptron](#). The area under the concentration-time curve (AUC) and half-life of [aloseptron](#) increased 6-fold and 3-fold, respectively [330].

3.5.1.HJ [Alprazolam](#)

- 1J) Interaction Effect: elevated plasma [alprazolam](#) levels and an increased risk of side effects (CNS depression)
- 2J) Summary: [Fluvoxamine](#) coadministration (100 mg daily) with [alprazolam](#) 1 mg four times daily resulted in a 2-fold increase in [alprazolam](#) steady-state plasma concentrations, area under the concentration-time curve (AUC), maximum concentration (C_{max}), and half-life. Elevated plasma levels of [alprazolam](#) were associated with impaired psychomotor performance and memory. This effect may be even more pronounced with higher [fluvoxamine](#) doses (300 mg daily)[202].
- 3J) Severity: moderate
- 4J) Onset: delayed
- 5J) Substantiation: theoretical
- 6J) Clinical Management: If [alprazolam](#) is given to a patient already on [fluvoxamine](#), the initial [alprazolam](#) dose should be reduced by 50% due to the possibility of significant [alprazolam](#) accumulation. Monitor for signs of [alprazolam](#) intoxication (eg, sedation, dizziness, ataxia, weakness, decreased cognition or motor performance) or consider switching to a benzodiazepine eliminated by glucuronidation (eg, [lorazepam](#), [oxazepam](#), [temazepam](#)).
- 7J) Probable Mechanism: inhibition by [fluvoxamine](#) of cytochrome P4503A4-mediated [alprazolam](#) metabolism

3.5.1.IJ [Amiodarone](#)

- 1J) Interaction Effect: increased [amiodarone](#) and [fluvoxamine](#) exposure
- 2J) Summary: If [fluvoxamine](#) (a CYP3A4 inhibitor and a CYP1A2 substrate) is used concomitantly with [amiodarone](#), a CYP1A2 inhibitor, a CYP3A4 inhibitor and substrate[379], the exposure of [amiodarone](#) and [fluvoxamine](#) may be increased. If coadministration is required, additional monitoring and dose adjustment may be warranted. [Amiodarone](#) has a long and variable half-life. Potential drug interaction may occur even after [amiodarone](#) is discontinued [379].
- 3J) Severity: major
- 4J) Onset: unspecified
- 5J) Substantiation: theoretical
- 6J) Clinical Management: If [fluvoxamine](#) (a CYP3A4 inhibitor and a CYP1A2 substrate) is used concomitantly with [amiodarone](#), a CYP1A2 inhibitor, a CYP3A4 inhibitor and substrate[379], the exposure of [amiodarone](#) and [fluvoxamine](#) may be increased. If coadministration is required, additional monitoring and dose adjustment may be warranted.
- 7J) Probable Mechanism: inhibition of CYP3A4-mediated metabolism of [amiodarone](#) and inhibition of CYP1A2-mediated metabolism of [fluvoxamine](#)

3.5.1.JJ [Amitriptyline](#)

- 1J) Interaction Effect: [amitriptyline](#) toxicity (dry mouth, urinary retention, sedation)

- 2) Summary: Coadministration of [fluvoxamine](#) and [amitriptyline](#) was found to significantly increase plasma levels of [amitriptyline](#)[222]. A bidirectional effect was suggested in which [fluvoxamine](#) increased [amitriptyline](#) concentrations (by interfering with N-demethylation) and [amitriptyline](#) increased [fluvoxamine](#) levels [223].
- 3) Severity: moderate
- 4) Onset: delayed
- 5) Substantiation: probable
- 6) Clinical Management: Monitor patients for signs of [amitriptyline](#) and [fluvoxamine](#) toxicity; lower doses of one or both agents may be required with concomitant therapy.
- 7) Probable Mechanism: decreased [amitriptyline](#) metabolism
- 8) Literature Reports

a) [Fluvoxamine](#) has been shown to significantly increase plasma levels of [amitriptyline](#) and [clomipramine](#) and to mildly increase levels of their metabolites [nortriptyline](#) and desmethyldomipramine, respectively. This may be due to competitive inhibition of oxidative metabolism in the liver [220].

b) Metabolism of tricyclic antidepressants coadministered with [fluvoxamine](#) was studied in eight depressed patients (one patient received [amitriptyline](#)) [221]. [Fluvoxamine](#) was found to interfere with N-demethylation of [amitriptyline](#). The combination of [fluvoxamine](#) and [amitriptyline](#) led to increased plasma levels of [amitriptyline](#) and decreased concentrations of [amitriptyline's](#) N-demethylated metabolite, [nortriptyline](#). In addition, plasma levels of [fluvoxamine](#) were increased.

3.5.1.K] [Amoxapine](#)

- 1) Interaction Effect: increased risk of [serotonin syndrome](#) ([hypertension](#), [hyperthermia](#), myoclonus, mental status changes)
- 2) Summary: Both [amoxapine](#)[119] and [fluvoxamine](#), a selective serotonin reuptake inhibitor, affect the serotonergic neurotransmitter systems. [Fluvoxamine](#) is also a weak CYP2D6 inhibitor in vitro. Therefore, caution is advised with concomitant administration of [amoxapine](#) and [fluvoxamine](#), as it may result in additive serotonergic effects and/or may increase the risk of serious adverse effects, including [serotonin syndrome](#). If coadministration is required, appropriate monitoring may be warranted [40]. Symptoms of [serotonin syndrome](#) include neuromuscular abnormalities, autonomic hyperactivity, and mental status changes. [Serotonin syndrome](#) can be life-threatening. If [serotonin syndrome](#) develops, discontinue the offending agents and provide supportive care and other therapy as necessary [120]. Monitoring of TCA plasma levels and a dose reduction of the TCA (eg, [amoxapine](#)) may be required when used concomitantly with a CYP2D6 inhibitor, such as [fluvoxamine](#) [40][119].
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Use caution with concomitant administration of [amoxapine](#) and [fluvoxamine](#), as it may result in additive serotonergic effects or inhibition of CYP2D6-mediated tricyclic antidepressant (TCA) metabolism by [fluvoxamine](#), and may increase the risk of serious adverse effects, including [serotonin syndrome](#). If coadministration is required, appropriate monitoring may be warranted. If [serotonin syndrome](#) develops, discontinue the offending agents and provide supportive care and other therapy as necessary[40]. Monitoring of TCA plasma levels and a dose reduction of the TCA (eg, [amoxapine](#)) may be required when used concomitantly with a CYP2D6 inhibitor, such as [fluvoxamine](#) [40][119].
- 7) Probable Mechanism: additive serotonergic effect; inhibition of CYP2D6-mediated [amoxapine](#) metabolism by [fluvoxamine](#)

3.5.1.L] Amphetamine

- 1) Interaction Effect: increased [amphetamine](#) exposure and increased risk of [serotonin syndrome](#)
- 2) Summary: Coadministration of an [amphetamine](#) and a serotonergic agent that inhibits CYP2D6 may result in increased [amphetamine](#) exposure and additional risk for [serotonin syndrome](#). If concomitant use of an [amphetamine](#) and such an agent is clinically required, initiate with lower doses and monitor patients carefully, especially during treatment initiation and dosage adjustment. Discontinue both drugs if [serotonin syndrome](#) is suspected[377].
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Coadministration of an [amphetamine](#) and another serotonergic agent may result in [serotonin syndrome](#), because both drugs affect the serotonergic neurotransmitter system. Additionally, coadministration of an [amphetamine](#) with a CYP2D6 inhibitor may increase [amphetamine](#) exposure, because [amphetamines](#) and their derivatives are metabolized to some degree by CYP2D6. An increase in [amphetamine](#) exposure may further increase risk of [serotonin syndrome](#). If concomitant use of an [amphetamine](#) and a serotonergic agent that inhibits CYP2D6 is clinically required, initiate with lower doses and monitor patients carefully, especially during treatment initiation and dosage adjustment. Discontinue both drugs if [serotonin syndrome](#) is suspected[377].
- 7) Probable Mechanism: inhibition of CYP2D6-mediated metabolism of [amphetamine](#); additive serotonergic effects

3.5.1.M] Amitriptyline Guacil

- 1) Interaction Effect: an increased risk of bleeding
- 2) Summary: Caution is recommended with the concomitant use of NSAIDs and antidepressants, including SSRIs due to an increased risk of [intracranial hemorrhage](#)[367] and [gastrointestinal bleeding](#) [371][372][368][369]. Bleeding events have included [epistaxis](#), ecchymosis, [hematoma](#), [petechiae](#), and life-threatening hemorrhages [374][373][375][376]. When an SSRI and an NSAID are given concurrently, monitor the patient for signs of increased bleeding.
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: established
- 6) Clinical Management: Use caution if NSAIDs and SSRIs are coadministered. Concomitant use of NSAIDs and SSRIs may cause an increased risk of [intracranial hemorrhage](#)[367] and [gastrointestinal bleeding](#) [368][369]. When an SSRI and an NSAID are given concurrently, monitor the patient for signs of increased bleeding.
- 7) Probable Mechanism: depletion of [platelet](#) serotonin by SSRI; additive effects
- 8) Literature Reports

a) Concomitant use of NSAIDs and antidepressants, including tricyclic antidepressants, SSRIs, serotonin-norepinephrine reuptake inhibitors, and MAOIs, resulted in a 60% increased risk of [intracranial hemorrhage](#) within 30 days of concomitant use compared with antidepressant use alone. There was no significant difference between the antidepressant drug classes and the increased risk; however, there was an increased risk associated with male patients compared with female patients [367].

b) 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. Combined use of an SSRI and NSAIDs or low-dose [aspirin](#) increased the risk to 12.2 and 5.2 times, 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 [370].

c) Two metaanalyses of incidents of upper GI bleed due to SSRIs, NSAIDs, and their combination found that SSRIs increased the risk by 1.73 [371] to 2.36 times [372], NSAIDs by 2.55 times [371], and the combination of SSRIs and NSAIDs by 4.02 [371] to 6.33 times [372].

d) The release of serotonin by [platelets](#) is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs and NSAIDs have been associated with an increased risk of bleeding [373].

3.5.1.N] [Anagrelide](#)

1) Interaction Effect: increased [anagrelide](#) exposure and increased risk of bleeding

2) Summary: Caution is advised with coadministration of [anagrelide](#) (a CYP1A2 substrate) and [fluvoxamine](#) (a CYP1A2 inhibitor) as this may increase [anagrelide](#) plasma concentrations. Coadministration of [anagrelide](#) and another drug that may increase the risk of bleeding, such as [fluvoxamine](#), should also be undertaken with caution. If concurrent use is required, monitor patients for bleeding[403].

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Caution is advised with coadministration of [anagrelide](#) (a CYP1A2 substrate) and [fluvoxamine](#) (a CYP1A2 inhibitor) as this may increase [anagrelide](#) plasma concentrations. Coadministration of [anagrelide](#) and another drug that may increase the risk of bleeding, such as [fluvoxamine](#), should also be undertaken with caution. If concurrent use is required, monitor patients for bleeding[403].

7) Probable Mechanism: inhibition of CYP1A2-mediated [anagrelide](#) metabolism; additive effects on hemostasis

3.5.1.O] [Ancrod](#)

1) Interaction Effect: an increased risk of bleeding

2) Summary: The release of serotonin by [platelets](#) is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs and anticoagulants has been associated with an increased risk of bleeding[114][115][113]. 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](#). In patients receiving [warfarin](#) and [fluvoxamine](#) concomitantly for 2 weeks, [warfarin](#) plasma concentrations increased by 98% and prothrombin times were prolonged. [Fluvoxamine](#) appears to inhibit several cytochrome P450 isoenzymes which may include 1A2 and 2C9 isozymes, which are responsible for [warfarin](#) metabolism [115][113].

3) Severity: major

4) Onset: delayed

5) Substantiation: probable

6) Clinical Management: When [fluvoxamine](#) 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 [fluvoxamine](#) therapy is initiated or

discontinued. Periodically reassess the prothrombin time ratio and INR in patients receiving [fluvoxamine](#) and [anticoagulant therapy](#)[113].

7) Probable Mechanism: unknown

8) Literature Reports

a) According to a retrospective cohort study (n=234), there was an increased risk of clinically relevant bleeding (hospital admission due to bleeding) in patients receiving [warfarin](#) for [atrial fibrillation](#) during concomitant SSRI therapy or within 2 weeks following SSRI therapy termination. Patients with a mean age of 72 +/- 7 years receiving [warfarin](#) plus SSRI (n=117) were matched with randomly selected patients who received [warfarin](#) only (n=117). SSRI included [fluoxetine](#), [citalopram](#), [paroxetine](#), [sertraline](#), [fluvoxamine](#), or escitalopram. Nine patients experienced 11 bleeding episodes during 213.9 treatment years in the [warfarin](#) plus SSRI group, and 10 patients experienced 14 bleedings during 586.4 treatment years in the warfarin-only group. The corresponding total incidences of bleedings were 51.4 and 23.9 per 1000 treatment years, respectively. The hazard ratio for first bleedings during treatment with [warfarin](#) plus SSRI was 3.49 (95% CI; 1.37 to 8.91, p=0.009) compared with [warfarin](#) only. The SSRI implicated in patients experiencing bleeding at the time of concomitant administration were [sertraline](#) or [citalopram](#). The addition of an SSRI was not associated with a change in [warfarin](#) dose or INR (p=0.48 and p=0.31 respectively). The results of the study may be limited by earlier bleeding events, unknown patient adherence, and exclusion of [clopidogrel](#), dipyridamol, corticosteroids and anticoagulants other than [warfarin](#) in the model [114].

b) A population-based, case-controlled study of new coumarin users (acenocoumarol and phenprocoumon) with concomitant selective serotonin reuptake inhibitors (SSRIs) resulted in an increased risk of hospitalization due to nongastrointestinal bleeding. Using national pharmacy and hospitalization records, Netherlands researchers identified 1848 cases that were admitted for abnormal bleeding and compared them with 5818 control subjects also taking coumarins. Median duration of treatment in patients was 220 days (range, 1 to 4690 days). Patients on SSRIs showed greater risk for hospitalization for nongastrointestinal bleeding (adjusted odds ratio (OR) 1.7, 95% confidence interval (CI), 1.1 to 2.5), however, the rate of [gastrointestinal bleeding](#) (adjusted OR 0.8, 95% CI, 0.4 to 1.5) was not significantly different [115].

c) A hospitalized 80-year-old female was started on intravenous [heparin](#) and oral [warfarin](#) therapy due to an [embolic stroke](#) secondary to [atrial fibrillation](#) and [mitral stenosis](#). Her [warfarin](#) dose was maintained at 1 mg daily, with her INR between 2.5 and 3. [Fluvoxamine](#) 25 mg daily was started for depression, and her [warfarin](#) dose was increased to 1.5 mg daily 3 days later due to worsening of the left [hemiparesis](#). Three days later, her INR was 9.96, and a repeat INR to rule out laboratory error was 11.3. [Warfarin](#) was discontinued, fresh frozen plasma was given, and [fluvoxamine](#) was discontinued. Six days later, [warfarin](#) was again started at 1 mg daily, and the INR increased over 4 days to 11.8. The elevated INR was attributed to the persisting effect of [fluvoxamine](#). She was eventually stabilized on [warfarin](#) 1 mg daily with INR values between 2 and 2.5 [116].

3.5.1.P] [Anisindione](#)

1) Interaction Effect: an increased risk of bleeding

2) Summary: The release of serotonin by [platelets](#) is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs and anticoagulants has been associated with an increased risk of bleeding[114][115][113]. 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](#). In patients receiving [warfarin](#) and [fluvoxamine](#) concomitantly for 2 weeks, [warfarin](#) plasma concentrations increased by

98% and prothrombin times were prolonged. [Fluvoxamine](#) appears to inhibit several cytochrome P450 isoenzymes which may include 1A2 and 2C9 isozymes, which are responsible for [warfarin](#) metabolism [115][113].

3) Severity: major

4) Onset: delayed

5) Substantiation: probable

6) Clinical Management: When [fluvoxamine](#) 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 [fluvoxamine](#) therapy is initiated or discontinued. Periodically reassess the prothrombin time ratio and INR in patients receiving [fluvoxamine](#) and [anticoagulant therapy](#)[113].

7) Probable Mechanism: unknown

8) Literature Reports

a) According to a retrospective cohort study (n=234), there was an increased risk of clinically relevant bleeding (hospital admission due to bleeding) in patients receiving [warfarin](#) for [atrial fibrillation](#) during concomitant SSRI therapy or within 2 weeks following SSRI therapy termination. Patients with a mean age of 72 +/- 7 years receiving [warfarin](#) plus SSRI (n=117) were matched with randomly selected patients who received [warfarin](#) only (n=117). SSRI included [fluoxetine](#), [citalopram](#), [paroxetine](#), [sertraline](#), [fluvoxamine](#), or escitalopram. Nine patients experienced 11 bleeding episodes during 213.9 treatment years in the [warfarin](#) plus SSRI group, and 10 patients experienced 14 bleedings during 586.4 treatment years in the warfarin-only group. The corresponding total incidences of bleedings were 51.4 and 23.9 per 1000 treatment years, respectively. The hazard ratio for first bleedings during treatment with [warfarin](#) plus SSRI was 3.49 (95% CI; 1.37 to 8.91, p=0.009) compared with [warfarin](#) only. The SSRI implicated in patients experiencing bleeding at the time of concomitant administration were [sertraline](#) or [citalopram](#). The addition of an SSRI was not associated with a change in [warfarin](#) dose or INR (p=0.48 and p=0.31 respectively). The results of the study may be limited by earlier bleeding events, unknown patient adherence, and exclusion of [clopidogrel](#), dipyridamol, corticosteroids and anticoagulants other than [warfarin](#) in the model [114].

b) A population-based, case-controlled study of new coumarin users (acenocoumarol and phenprocoumon) with concomitant selective serotonin reuptake inhibitors (SSRIs) resulted in an increased risk of hospitalization due to nongastrointestinal bleeding. Using national pharmacy and hospitalization records, Netherlands researchers identified 1848 cases that were admitted for abnormal bleeding and compared them with 5818 control subjects also taking coumarins. Median duration of treatment in patients was 220 days (range, 1 to 4690 days). Patients on SSRIs showed greater risk for hospitalization for nongastrointestinal bleeding (adjusted odds ratio (OR) 1.7, 95% confidence interval (CI), 1.1 to 2.5), however, the rate of [gastrointestinal bleeding](#) (adjusted OR 0.8, 95% CI, 0.4 to 1.5) was not significantly different [115].

c) A hospitalized 80-year-old female was started on intravenous [heparin](#) and oral [warfarin](#) therapy due to an [embolic stroke](#) secondary to [atrial fibrillation](#) and [mitral stenosis](#). Her [warfarin](#) dose was maintained at 1 mg daily, with her INR between 2.5 and 3. [Fluvoxamine](#) 25 mg daily was started for depression, and her [warfarin](#) dose was increased to 1.5 mg daily 3 days later due to worsening of the left [hemiparesis](#). Three days later, her INR was 9.96, and a repeat INR to rule out laboratory error was 11.3. [Warfarin](#) was discontinued, fresh frozen plasma was given, and [fluvoxamine](#) was discontinued. Six days later, [warfarin](#) was again started at 1 mg daily, and the INR increased over 4 days to 11.8. The elevated INR was attributed to the persisting effect of [fluvoxamine](#). She was eventually stabilized on [warfarin](#) 1 mg daily with INR values between 2 and 2.5 [116].

3.5.1.Q] Antithrombin III Human

1) Interaction Effect: an increased risk of bleeding

2) Summary: The release of serotonin by [platelets](#) is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs and anticoagulants has been associated with an increased risk of bleeding[114][115][113]. 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](#). In patients receiving [warfarin](#) and [fluvoxamine](#) concomitantly for 2 weeks, [warfarin](#) plasma concentrations increased by 98% and prothrombin times were prolonged. [Fluvoxamine](#) appears to inhibit several cytochrome P450 isoenzymes which may include 1A2 and 2C9 isozymes, which are responsible for [warfarin](#) metabolism [115][113].

3) Severity: major

4) Onset: delayed

5) Substantiation: probable

6) Clinical Management: When [fluvoxamine](#) 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 [fluvoxamine](#) therapy is initiated or discontinued. Periodically reassess the prothrombin time ratio and INR in patients receiving [fluvoxamine](#) and [anticoagulant therapy](#)[113].

7) Probable Mechanism: unknown

8) Literature Reports

a) According to a retrospective cohort study (n=234), there was an increased risk of clinically relevant bleeding (hospital admission due to bleeding) in patients receiving [warfarin](#) for [atrial fibrillation](#) during concomitant SSRI therapy or within 2 weeks following SSRI therapy termination. Patients with a mean age of 72 +/- 7 years receiving [warfarin](#) plus SSRI (n=117) were matched with randomly selected patients who received [warfarin](#) only (n=117). SSRI included [fluoxetine](#), [citalopram](#), [paroxetine](#), [sertraline](#), [fluvoxamine](#), or escitalopram. Nine patients experienced 11 bleeding episodes during 213.9 treatment years in the [warfarin](#) plus SSRI group, and 10 patients experienced 14 bleedings during 586.4 treatment years in the warfarin-only group. The corresponding total incidences of bleedings were 51.4 and 23.9 per 1000 treatment years, respectively. The hazard ratio for first bleedings during treatment with [warfarin](#) plus SSRI was 3.49 (95% CI; 1.37 to 8.91, p=0.009) compared with [warfarin](#) only. The SSRI implicated in patients experiencing bleeding at the time of concomitant administration were [sertraline](#) or [citalopram](#). The addition of an SSRI was not associated with a change in [warfarin](#) dose or INR (p=0.48 and p=0.31 respectively). The results of the study may be limited by earlier bleeding events, unknown patient adherence, and exclusion of [clopidogrel](#), dipyridamol, corticosteroids and anticoagulants other than [warfarin](#) in the model [114].

b) A population-based, case-controlled study of new coumarin users (acenocoumarol and phenprocoumon) with concomitant selective serotonin reuptake inhibitors (SSRIs) resulted in an increased risk of hospitalization due to nongastrointestinal bleeding. Using national pharmacy and hospitalization records, Netherlands researchers identified 1848 cases that were admitted for abnormal bleeding and compared them with 5818 control subjects also taking coumarins. Median duration of treatment in patients was 220 days (range, 1 to 4690 days). Patients on SSRIs showed greater risk for hospitalization for nongastrointestinal bleeding (adjusted odds ratio (OR) 1.7, 95% confidence interval (CI), 1.1 to 2.5), however, the rate of [gastrointestinal bleeding](#) (adjusted OR 0.8, 95% CI, 0.4 to 1.5) was not significantly different [115].

c) A hospitalized 80-year-old female was started on intravenous [heparin](#) and oral [warfarin](#) therapy due to an [embolic stroke](#) secondary to [atrial fibrillation](#) and [mitral stenosis](#). Her [warfarin](#) dose was maintained at 1 mg daily, with her INR between 2.5 and 3. [Fluvoxamine](#) 25 mg daily was started for depression, and her [warfarin](#) dose was increased to 1.5 mg daily 3 days later due to worsening of the left [hemiparesis](#). Three days later, her INR was 9.96, and a repeat INR to rule out laboratory error was 11.3. [Warfarin](#) was discontinued, fresh frozen plasma was given, and [fluvoxamine](#) was discontinued. Six days later, [warfarin](#) was again started at 1 mg daily, and the INR increased over 4 days to 11.8. The elevated INR was attributed to the persisting effect of [fluvoxamine](#). She was eventually stabilized on [warfarin](#) 1 mg daily with INR values between 2 and 2.5 [116].

3.5.1.R] Apixaban

- 1) Interaction Effect: an increased risk of bleeding
- 2) Summary: Coadministration of apixaban, a factor Xa inhibitor, and drugs that affect hemostasis, such as SSRI therapy, increases the risk of bleeding. There is no established reversal therapy or antidote for apixaban-induced bleeding, and its [anticoagulation](#) effects usually persist for 24 hours after the last dose. Discontinue apixaban if active pathological bleeding occurs[289]. If concomitant apixaban and SSRI therapy is necessary, use caution and monitor the patient closely.
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Concomitant apixaban therapy with drugs that also affect hemostasis, such as an SSRI, increases the risk of bleeding. Discontinue apixaban if active pathological bleeding occurs. There is no established reversal therapy or antidote for apixaban-induced bleeding, and its [anticoagulation](#) effects usually persist for 24 hours after the last dose[289]. If concomitant apixaban and SSRI therapy is necessary, use caution and monitor the patient closely.
- 7) Probable Mechanism: additive effects on hemostasis

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[114][115][113]. 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](#). In patients receiving [warfarin](#) and [fluvoxamine](#) concomitantly for 2 weeks, [warfarin](#) plasma concentrations increased by 98% and prothrombin times were prolonged. [Fluvoxamine](#) appears to inhibit several cytochrome P450 isoenzymes which may include 1A2 and 2C9 isozymes, which are responsible for [warfarin](#) metabolism [115][113].
- 3) Severity: major
- 4) Onset: delayed
- 5) Substantiation: probable
- 6) Clinical Management: When [fluvoxamine](#) 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 [fluvoxamine](#) therapy is initiated or discontinued. Periodically reassess the prothrombin time ratio and INR in patients receiving [fluvoxamine](#) and [anticoagulant therapy](#)[113].
- 7) Probable Mechanism: unknown
- 8) Literature Reports

a) According to a retrospective cohort study (n=234), there was an increased risk of clinically relevant bleeding (hospital admission due to bleeding) in patients receiving [warfarin](#) for [atrial fibrillation](#) during concomitant SSRI therapy or within 2 weeks following SSRI therapy termination. Patients with a mean age of 72 +/- 7 years receiving [warfarin](#) plus SSRI (n=117) were matched with randomly selected patients who received [warfarin](#) only (n=117). SSRI included [fluoxetine](#), [citalopram](#), [paroxetine](#), [sertraline](#), [fluvoxamine](#), or escitalopram. Nine patients experienced 11 bleeding episodes during 213.9 treatment years in the [warfarin](#) plus SSRI group, and 10 patients experienced 14 bleedings during 586.4 treatment years in the warfarin-only group. The corresponding total incidences of bleedings were 51.4 and 23.9 per 1000 treatment years, respectively. The hazard ratio for first bleedings during treatment with [warfarin](#) plus SSRI was 3.49 (95% CI; 1.37 to 8.91, p=0.009) compared with [warfarin](#) only. The SSRI implicated in patients experiencing bleeding at the time of concomitant administration were [sertraline](#) or [citalopram](#). The addition of an SSRI was not associated with a change in [warfarin](#) dose or INR (p=0.48 and p=0.31 respectively). The results of the study may be limited by earlier bleeding events, unknown patient adherence, and exclusion of [clopidogrel](#), dipyridamol, corticosteroids and anticoagulants other than [warfarin](#) in the model [114].

b) A population-based, case-controlled study of new coumarin users (acenocoumarol and phenprocoumon) with concomitant selective serotonin reuptake inhibitors (SSRIs) resulted in an increased risk of hospitalization due to nongastrointestinal bleeding. Using national pharmacy and hospitalization records, Netherlands researchers identified 1848 cases that were admitted for abnormal bleeding and compared them with 5818 control subjects also taking coumarins. Median duration of treatment in patients was 220 days (range, 1 to 4690 days). Patients on SSRIs showed greater risk for hospitalization for nongastrointestinal bleeding (adjusted odds ratio (OR) 1.7, 95% confidence interval (CI), 1.1 to 2.5), however, the rate of [gastrointestinal bleeding](#) (adjusted OR 0.8, 95% CI, 0.4 to 1.5) was not significantly different [115].

c) A hospitalized 80-year-old female was started on intravenous [heparin](#) and oral [warfarin](#) therapy due to an [embolic stroke](#) secondary to [atrial fibrillation](#) and [mitral stenosis](#). Her [warfarin](#) dose was maintained at 1 mg daily, with her INR between 2.5 and 3. [Fluvoxamine](#) 25 mg daily was started for depression, and her [warfarin](#) dose was increased to 1.5 mg daily 3 days later due to worsening of the left [hemiparesis](#). Three days later, her INR was 9.96, and a repeat INR to rule out laboratory error was 11.3. [Warfarin](#) was discontinued, fresh frozen plasma was given, and [fluvoxamine](#) was discontinued. Six days later, [warfarin](#) was again started at 1 mg daily, and the INR increased over 4 days to 11.8. The elevated INR was attributed to the persisting effect of [fluvoxamine](#). She was eventually stabilized on [warfarin](#) 1 mg daily with INR values between 2 and 2.5 [116].

3.5.1.T] Asenapine

- 1) Interaction Effect: increased exposure to asenapine
- 2) Summary: Concomitant use of asenapine (a CYP1A2 substrate) with this drug (a strong CYP1A2 inhibitor) may result in increased exposure to asenapine. Reduce asenapine dosage based on clinical response if necessary[155].
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Concomitant use of asenapine (a CYP1A2 substrate) with this drug (a strong CYP1A2 inhibitor) may result in increased exposure to asenapine. Reduce asenapine dosage based on clinical response if necessary[155].
- 7) Probable Mechanism: inhibition of CYP1A2-mediated asenapine metabolism

8) Literature Reports

a) The C_{max} and AUC of asenapine increased by 13% and 29%, respectively, after a single 5-mg dose of asenapine in healthy volunteers administered [fluvoxamine](#) (a strong CYP1A2 inhibitor) 25 mg twice daily for 8 days. Furthermore, greater increases in asenapine exposure would be likely with full therapeutic doses of [fluvoxamine](#) [156].

3.5.1.U] [Aspirin](#)

1) Interaction Effect: an increased risk of bleeding

2) Summary: Caution is recommended with the concomitant use of NSAIDs and antidepressants, including SSRIs due to an increased risk of [intracranial hemorrhage](#)[367] and [gastrointestinal bleeding](#) [371][372][368][369]. Bleeding events have included [epistaxis](#), ecchymosis, [hematoma](#), [petechiae](#), and life-threatening hemorrhages [374][373][375][376]. When an SSRI and an NSAID are given concurrently, monitor the patient for signs of increased bleeding.

3) Severity: major

4) Onset: unspecified

5) Substantiation: established

6) Clinical Management: Use caution if NSAIDs and SSRIs are coadministered. Concomitant use of NSAIDs and SSRIs may cause an increased risk of [intracranial hemorrhage](#)[367] and [gastrointestinal bleeding](#) [368][369]. When an SSRI and an NSAID are given concurrently, monitor the patient for signs of increased bleeding.

7) Probable Mechanism: depletion of [platelet](#) serotonin by SSRI; additive effects

8) Literature Reports

a) Concomitant use of NSAIDs and antidepressants, including tricyclic antidepressants, SSRIs, serotonin-norepinephrine reuptake inhibitors, and MAOIs, resulted in a 60% increased risk of [intracranial hemorrhage](#) within 30 days of concomitant use compared with antidepressant use alone. There was no significant difference between the antidepressant drug classes and the increased risk; however, there was an increased risk associated with male patients compared with female patients [367].

b) 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. Combined use of an SSRI and NSAIDs or low-dose [aspirin](#) increased the risk to 12.2 and 5.2 times, 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 [370].

c) Two metaanalyses of incidents of upper GI bleed due to SSRIs, NSAIDs, and their combination found that SSRIs increased the risk by 1.73 [371] to 2.36 times [372], NSAIDs by 2.55 times [371], and the combination of SSRIs and NSAIDs by 4.02 [371] to 6.33 times [372].

d) The release of serotonin by [platelets](#) is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs and NSAIDs have been associated with an increased risk of bleeding [373].

3.5.1.V] [Astemizole](#)

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

- 2) Summary: [Fluvoxamine](#) should not be used in combination with [astemizole](#). [Fluvoxamine](#) appears to be a potent inhibitor of the cytochrome P450IIIA4 isozyme, the enzyme primarily responsible for metabolizing [astemizole](#). Inhibition of this enzyme may result in elevated [astemizole](#) concentrations; increased plasma concentrations of [astemizole](#) are associated with QT prolongation and [torsades de pointes](#), which can be fatal[203][204].
- 3) Severity: contraindicated
- 4) Onset: rapid
- 5) Substantiation: probable
- 6) Clinical Management: Concurrent use of [astemizole](#) and [fluvoxamine](#) is contraindicated.
- 7) Probable Mechanism: inhibition by [fluvoxamine](#) of [astemizole](#) metabolism

3.5.1.W] [Atorvastatin](#)

- 1) Interaction Effect: increased plasma concentrations of selected statins and increased risk for [myopathy](#) and [rhabdomyolysis](#)
- 2) Summary: Coadministration of [fluvoxamine](#) with selected statins may result in increased plasma levels of the statin drug and an increased risk for [myopathy](#). Monitor the patient and consider lowering the dosage of the statin drug[188].
- 3) Severity: moderate
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Coadministration of [fluvoxamine](#) with selected statins may result in increased plasma levels of the statin drug and an increased risk for [myopathy](#). Monitor the patient for unexplained muscle pain, tenderness, and weakness, and consider lowering the dosage of the statin drug[188].
- 7) Probable Mechanism: inhibition of CYP3A4-mediated statin metabolism

3.5.1.X] [Bemiparin](#)

- 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[114][115][113]. 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](#). In patients receiving [warfarin](#) and [fluvoxamine](#) concomitantly for 2 weeks, [warfarin](#) plasma concentrations increased by 98% and prothrombin times were prolonged. [Fluvoxamine](#) appears to inhibit several cytochrome P450 isoenzymes which may include 1A2 and 2C9 isozymes, which are responsible for [warfarin](#) metabolism [115][113].
- 3) Severity: major
- 4) Onset: delayed
- 5) Substantiation: probable
- 6) Clinical Management: When [fluvoxamine](#) 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 [fluvoxamine](#) therapy is initiated or discontinued. Periodically reassess the prothrombin time ratio and INR in patients receiving [fluvoxamine](#) and [anticoagulant therapy](#)[113].
- 7) Probable Mechanism: unknown
- 8) Literature Reports

- a) According to a retrospective cohort study (n=234), there was an increased risk of clinically relevant bleeding (hospital admission due to bleeding) in patients receiving [warfarin](#) for [atrial](#)

fibrillation during concomitant SSRI therapy or within 2 weeks following SSRI therapy termination. Patients with a mean age of 72 +/- 7 years receiving **warfarin** plus SSRI (n=117) were matched with randomly selected patients who received **warfarin** only (n=117). SSRI included **fluoxetine**, **citalopram**, **paroxetine**, **sertraline**, **fluvoxamine**, or escitalopram. Nine patients experienced 11 bleeding episodes during 213.9 treatment years in the **warfarin** plus SSRI group, and 10 patients experienced 14 bleedings during 586.4 treatment years in the warfarin-only group. The corresponding total incidences of bleedings were 51.4 and 23.9 per 1000 treatment years, respectively. The hazard ratio for first bleedings during treatment with **warfarin** plus SSRI was 3.49 (95% CI; 1.37 to 8.91, p=0.009) compared with **warfarin** only. The SSRI implicated in patients experiencing bleeding at the time of concomitant administration were **sertraline** or **citalopram**. The addition of an SSRI was not associated with a change in **warfarin** dose or INR (p=0.48 and p=0.31 respectively). The results of the study may be limited by earlier bleeding events, unknown patient adherence, and exclusion of **clopidogrel**, dipyridamol, corticosteroids and anticoagulants other than **warfarin** in the model [114].

b) A population-based, case-controlled study of new coumarin users (acenocoumarol and phenprocoumon) with concomitant selective serotonin reuptake inhibitors (SSRIs) resulted in an increased risk of hospitalization due to nongastrointestinal bleeding. Using national pharmacy and hospitalization records, Netherlands researchers identified 1848 cases that were admitted for abnormal bleeding and compared them with 5818 control subjects also taking coumarins. Median duration of treatment in patients was 220 days (range, 1 to 4690 days). Patients on SSRIs showed greater risk for hospitalization for nongastrointestinal bleeding (adjusted odds ratio (OR) 1.7, 95% confidence interval (CI), 1.1 to 2.5), however, the rate of **gastrointestinal bleeding** (adjusted OR 0.8, 95% CI, 0.4 to 1.5) was not significantly different [115].

c) A hospitalized 80-year-old female was started on intravenous **heparin** and oral **warfarin** therapy due to an **embolic stroke** secondary to **atrial fibrillation** and **mitral stenosis**. Her **warfarin** dose was maintained at 1 mg daily, with her INR between 2.5 and 3. **Fluvoxamine** 25 mg daily was started for depression, and her **warfarin** dose was increased to 1.5 mg daily 3 days later due to worsening of the left **hemiparesis**. Three days later, her INR was 9.96, and a repeat INR to rule out laboratory error was 11.3. **Warfarin** was discontinued, fresh frozen plasma was given, and **fluvoxamine** was discontinued. Six days later, **warfarin** was again started at 1 mg daily, and the INR increased over 4 days to 11.8. The elevated INR was attributed to the persisting effect of **fluvoxamine**. She was eventually stabilized on **warfarin** 1 mg daily with INR values between 2 and 2.5 [116].

3.5.1.Y] Bendamustine

1) Interaction Effect: increased bendamustine levels and decreased levels of active minor metabolites of bendamustine

2) Summary: Alternative treatments should be considered when concomitant use of bendamustine with a CYP1A2 inhibitor is necessary. Based on in vitro data, bendamustine is primarily metabolized via CYP1A2 into 2 active minor metabolites (M3 and M4). However, the cytotoxic efficacy is primarily due to the parent compound as the active metabolites have very low plasma concentrations. Concomitant administration of a strong CYP1A2 inhibitor, such as **fluvoxamine**, may result in increased bendamustine concentrations and decreased concentrations of the metabolites[154]. If used concomitantly, patients should be closely monitored for increased incidence of bendamustine adverse events (**myelosuppression**, infection, skin reactions) and doses should be adjusted appropriately.

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

- 6) Clinical Management: Consider alternative treatment when concomitant use of bendamustine with a strong CYP1A2 inhibitor, such as [fluvoxamine](#), is required. However, use caution if bendamustine and [fluvoxamine](#) are coadministered[154]. Monitor the patient for increased bendamustine adverse events ([myelosuppression](#), infection, skin reactions) and adjust doses as necessary.
- 7) Probable Mechanism: inhibition of the CYP1A2-mediated bendamustine metabolism

3.5.1.Z] [Benzphetamine](#)

- 1) Interaction Effect: increased [amphetamine](#) exposure and increased risk of [serotonin syndrome](#)
- 2) Summary: Coadministration of an [amphetamine](#) and a serotonergic agent that inhibits CYP2D6 may result in increased [amphetamine](#) exposure and additional risk for [serotonin syndrome](#). If concomitant use of an [amphetamine](#) and such an agent is clinically required, initiate with lower doses and monitor patients carefully, especially during treatment initiation and dosage adjustment. Discontinue both drugs if [serotonin syndrome](#) is suspected[377].
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Coadministration of an [amphetamine](#) and another serotonergic agent may result in [serotonin syndrome](#), because both drugs affect the serotonergic neurotransmitter system. Additionally, coadministration of an [amphetamine](#) with a CYP2D6 inhibitor may increase [amphetamine](#) exposure, because [amphetamines](#) and their derivatives are metabolized to some degree by CYP2D6. An increase in [amphetamine](#) exposure may further increase risk of [serotonin syndrome](#). If concomitant use of an [amphetamine](#) and a serotonergic agent that inhibits CYP2D6 is clinically required, initiate with lower doses and monitor patients carefully, especially during treatment initiation and dosage adjustment. Discontinue both drugs if [serotonin syndrome](#) is suspected[377].
- 7) Probable Mechanism: inhibition of CYP2D6-mediated metabolism of [amphetamine](#); additive serotonergic effects

3.5.1.AA] [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[114][115][113]. 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](#). In patients receiving [warfarin](#) and [fluvoxamine](#) concomitantly for 2 weeks, [warfarin](#) plasma concentrations increased by 98% and prothrombin times were prolonged. [Fluvoxamine](#) appears to inhibit several cytochrome P450 isoenzymes which may include 1A2 and 2C9 isozymes, which are responsible for [warfarin](#) metabolism [115][113].
- 3) Severity: major
- 4) Onset: delayed
- 5) Substantiation: probable
- 6) Clinical Management: When [fluvoxamine](#) 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 [fluvoxamine](#) therapy is initiated or discontinued. Periodically reassess the prothrombin time ratio and INR in patients receiving [fluvoxamine](#) and [anticoagulant therapy](#)[113].
- 7) Probable Mechanism: unknown
- 8) Literature Reports

a) According to a retrospective cohort study (n=234), there was an increased risk of clinically relevant bleeding (hospital admission due to bleeding) in patients receiving [warfarin](#) for [atrial fibrillation](#) during concomitant SSRI therapy or within 2 weeks following SSRI therapy termination. Patients with a mean age of 72 +/- 7 years receiving [warfarin](#) plus SSRI (n=117) were matched with randomly selected patients who received [warfarin](#) only (n=117). SSRI included [fluoxetine](#), [citalopram](#), [paroxetine](#), [sertraline](#), [fluvoxamine](#), or escitalopram. Nine patients experienced 11 bleeding episodes during 213.9 treatment years in the [warfarin](#) plus SSRI group, and 10 patients experienced 14 bleedings during 586.4 treatment years in the warfarin-only group. The corresponding total incidences of bleedings were 51.4 and 23.9 per 1000 treatment years, respectively. The hazard ratio for first bleedings during treatment with [warfarin](#) plus SSRI was 3.49 (95% CI; 1.37 to 8.91, p=0.009) compared with [warfarin](#) only. The SSRI implicated in patients experiencing bleeding at the time of concomitant administration were [sertraline](#) or [citalopram](#). The addition of an SSRI was not associated with a change in [warfarin](#) dose or INR (p=0.48 and p=0.31 respectively). The results of the study may be limited by earlier bleeding events, unknown patient adherence, and exclusion of [clopidogrel](#), dipyridamol, corticosteroids and anticoagulants other than [warfarin](#) in the model [114].

b) A population-based, case-controlled study of new coumarin users (acenocoumarol and phenprocoumon) with concomitant selective serotonin reuptake inhibitors (SSRIs) resulted in an increased risk of hospitalization due to nongastrointestinal bleeding. Using national pharmacy and hospitalization records, Netherlands researchers identified 1848 cases that were admitted for abnormal bleeding and compared them with 5818 control subjects also taking coumarins. Median duration of treatment in patients was 220 days (range, 1 to 4690 days). Patients on SSRIs showed greater risk for hospitalization for nongastrointestinal bleeding (adjusted odds ratio (OR) 1.7, 95% confidence interval (CI), 1.1 to 2.5), however, the rate of [gastrointestinal bleeding](#) (adjusted OR 0.8, 95% CI, 0.4 to 1.5) was not significantly different [115].

c) A hospitalized 80-year-old female was started on intravenous [heparin](#) and oral [warfarin](#) therapy due to an [embolic stroke](#) secondary to [atrial fibrillation](#) and [mitral stenosis](#). Her [warfarin](#) dose was maintained at 1 mg daily, with her INR between 2.5 and 3. [Fluvoxamine](#) 25 mg daily was started for depression, and her [warfarin](#) dose was increased to 1.5 mg daily 3 days later due to worsening of the left [hemiparesis](#). Three days later, her INR was 9.96, and a repeat INR to rule out laboratory error was 11.3. [Warfarin](#) was discontinued, fresh frozen plasma was given, and [fluvoxamine](#) was discontinued. Six days later, [warfarin](#) was again started at 1 mg daily, and the INR increased over 4 days to 11.8. The elevated INR was attributed to the persisting effect of [fluvoxamine](#). She was eventually stabilized on [warfarin](#) 1 mg daily with INR values between 2 and 2.5 [116].

3.5.1.AB] [Bromfenac](#)

1) Interaction Effect: an increased risk of bleeding

2) Summary: Caution is recommended with the concomitant use of NSAIDs and antidepressants, including SSRIs due to an increased risk of [intracranial hemorrhage](#)[367] and [gastrointestinal bleeding](#) [371][372][368][369]. Bleeding events have included [epistaxis](#), ecchymosis, [hematoma](#), [petechiae](#), and life-threatening hemorrhages [374][373][375][376]. When an SSRI and an NSAID are given concurrently, monitor the patient for signs of increased bleeding.

3) Severity: major

4) Onset: unspecified

5) Substantiation: established

6) Clinical Management: Use caution if NSAIDs and SSRIs are coadministered. Concomitant use of NSAIDs and SSRIs may cause an increased risk of [intracranial hemorrhage](#)[367] and [gastrointestinal](#)

[bleeding](#) [368][369]. When an SSRI and an NSAID are given concurrently, monitor the patient for signs of increased bleeding.

7) Probable Mechanism: depletion of [platelet](#) serotonin by SSRI; additive effects

8) Literature Reports

a) Concomitant use of NSAIDs and antidepressants, including tricyclic antidepressants, SSRIs, serotonin-norepinephrine reuptake inhibitors, and MAOIs, resulted in a 60% increased risk of [intracranial hemorrhage](#) within 30 days of concomitant use compared with antidepressant use alone. There was no significant difference between the antidepressant drug classes and the increased risk; however, there was an increased risk associated with male patients compared with female patients [367].

b) 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. Combined use of an SSRI and NSAIDs or low-dose [aspirin](#) increased the risk to 12.2 and 5.2 times, 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 [370].

c) Two metaanalyses of incidents of upper GI bleed due to SSRIs, NSAIDs, and their combination found that SSRIs increased the risk by 1.73 [371] to 2.36 times [372], NSAIDs by 2.55 times [371], and the combination of SSRIs and NSAIDs by 4.02 [371] to 6.33 times [372].

d) The release of serotonin by [platelets](#) is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs and NSAIDs have been associated with an increased risk of bleeding [373].

3.5.1.AC] Bromopride

1) Interaction Effect: increased risk of extrapyramidal reactions

2) Summary: Concomitant use of bromopride and other drugs that may cause extrapyramidal reactions is contraindicated[106].

3) Severity: contraindicated

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Concomitant use of bromopride and other drugs that may cause extrapyramidal reactions is contraindicated[106].

7) Probable Mechanism: additive extrapyramidal side effects

3.5.1.AD] Bufexamac

1) Interaction Effect: an increased risk of bleeding

2) Summary: Caution is recommended with the concomitant use of NSAIDs and antidepressants, including SSRIs due to an increased risk of [intracranial hemorrhage](#)[367] and [gastrointestinal bleeding](#) [371][372][368][369]. Bleeding events have included [epistaxis](#), ecchymosis, [hematoma](#), [petechiae](#), and life-threatening hemorrhages [374][373][375][376]. When an SSRI and an NSAID are given concurrently, monitor the patient for signs of increased bleeding.

3) Severity: major

4) Onset: unspecified

- 5) Substantiation: established
- 6) Clinical Management: Use caution if NSAIDs and SSRIs are coadministered. Concomitant use of NSAIDs and SSRIs may cause an increased risk of [intracranial hemorrhage](#)[367] and [gastrointestinal bleeding](#) [368][369]. When an SSRI and an NSAID are given concurrently, monitor the patient for signs of increased bleeding.
- 7) Probable Mechanism: depletion of [platelet](#) serotonin by SSRI; additive effects
- 8) Literature Reports

a) Concomitant use of NSAIDs and antidepressants, including tricyclic antidepressants, SSRIs, serotonin-norepinephrine reuptake inhibitors, and MAOIs, resulted in a 60% increased risk of [intracranial hemorrhage](#) within 30 days of concomitant use compared with antidepressant use alone. There was no significant difference between the antidepressant drug classes and the increased risk; however, there was an increased risk associated with male patients compared with female patients [367].

b) 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. Combined use of an SSRI and NSAIDs or low-dose [aspirin](#) increased the risk to 12.2 and 5.2 times, 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 [370].

c) Two metaanalyses of incidents of upper GI bleed due to SSRIs, NSAIDs, and their combination found that SSRIs increased the risk by 1.73 [371] to 2.36 times [372], NSAIDs by 2.55 times [371], and the combination of SSRIs and NSAIDs by 4.02 [371] to 6.33 times [372].

d) The release of serotonin by [platelets](#) is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs and NSAIDs have been associated with an increased risk of bleeding [373].

3.5.1.AE] [Buprenorphine](#)

- 1) Interaction Effect: increased risk of [serotonin syndrome](#)
- 2) Summary: Exercise caution with the concomitant use of [buprenorphine](#) and other agents that affect the serotonergic neurotransmitter system due to the potential of [serotonin syndrome](#). If concurrent use is required, monitor for [serotonin syndrome](#), particularly during treatment initiation and with dosage adjustments[212]
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Concomitant use of [buprenorphine](#) with other agents that affect the serotonergic neurotransmitter system should be undertaken with caution due to the potential of [serotonin syndrome](#). If concurrent use is required, monitor for [serotonin syndrome](#), particularly during treatment initiation and with dosage adjustments[212]
- 7) Probable Mechanism: additive serotonergic effects

3.5.1.AF] [Bupropion](#)

- 1) Interaction Effect: lower seizure threshold

- 2) Summary: Use extreme caution when prescribing [bupropion](#) with drugs that lower seizure threshold (eg, antipsychotics, antidepressants, [theophylline](#), systemic corticosteroids). Begin treatment with a low initial dose and increase dose gradually[366].
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Use extreme caution when prescribing [bupropion](#) with drugs that lower seizure threshold (eg, antipsychotics, antidepressants, [theophylline](#), systemic corticosteroids). Begin treatment with a low initial dose and increase dose gradually[366].
- 7) Probable Mechanism: unknown

3.5.1.AG] Cangrelor

- 1) Interaction Effect: increased risk of bleeding
- 2) Summary: Exercise caution when coadministering a SSRI and an antiplatelet agent as this may increase the risk of bleeding events[139][138].[137]. Bleeding events reported have included [epistaxis](#), ecchymosis, [hematoma](#), [petechiae](#), and life-threatening hemorrhages. Monitor patient for signs of increased bleeding when [fluvoxamine](#) is administered with an antiplatelet agent concomitantly [137].
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: When [fluvoxamine](#) and an antiplatelet agent are given concurrently, monitor patient for signs of increased bleeding[137].
- 7) Probable Mechanism: unknown
- 8) Literature Reports

a) In a retrospective study of patients over 50 years of age with the diagnosis of acute [myocardial infarction](#) (N=27,058), SSRI use with any antiplatelet therapy significantly increased the risk of bleeding by 1.42-fold compared with [aspirin](#) use alone. Therapy with [aspirin](#), [clopidogrel](#), and an SSRI significantly increased risk by 2.35-fold compared with [aspirin](#) use alone and by 1.57-fold compared with [clopidogrel](#) and [aspirin](#) combination therapy [138].

b) In a systematic review and meta-analysis of 22 observational studies, SSRI use was associated with a significant 1.55 fold increase in risk of [upper gastrointestinal bleeding](#) (UGIB). Concomitant use of SSRIs and antiplatelet drugs was associated with a 2.48-fold increase in risk of UGIB (3 studies) [139].

3.5.1.AH] Cannabis

- 1) Interaction Effect: manic symptoms
- 2) Summary: One case of mania following use of marijuana with [fluoxetine](#) therapy has been reported[174]. 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 [173].

3.5.1.AII Carbamazepine

- 1)) Interaction Effect: increased **carbamazepine** exposure
- 2)) Summary: The concomitant use of **carbamazepine** (a CYP3A4 substrate) and a CYP3A4 inhibitor may increase the exposure of **carbamazepine**. If **carbamazepine** is used concomitantly with a CYP3A4 inhibitor, closely monitor **carbamazepine** levels and adjust the **carbamazepine** dosage as required[244][245].
- 3)) Severity: moderate
- 4)) Onset: unspecified
- 5)) Substantiation: theoretical
- 6)) Clinical Management: If **carbamazepine** (a CYP3A4 substrate) is used concomitantly with a CYP3A4 inhibitor, closely monitor **carbamazepine** levels and adjust the **carbamazepine** dosage as required[244][245].
- 7)) Probable Mechanism: inhibition of CYP3A4-mediated metabolism of **carbamazepine**
- 8)) Literature Reports

a)) The addition of **fluvoxamine** to a constant dosage of **carbamazepine** in 3 patients caused an increase in **carbamazepine** levels, resulting in symptoms of toxicity [246]. However, no increase in **carbamazepine** levels in 8 epileptic patients who were given **fluvoxamine** 100 mg daily or **fluoxetine** 20 mg daily with **carbamazepine** for 3 weeks [247].

b)) Concomitant administration of **verapamil** 120 mg orally 3 times a day in patients receiving **carbamazepine** for refractory **partial epilepsy** was reported to result in **carbamazepine neurotoxicity** in all of 6 patients treated. Increase in free and total **carbamazepine** levels were observed in 5 patients (mean increases of 33% and 46%, respectively) associated with a concurrent decrease by 36% in the ratio of **carbamazepine**-10,11 epoxide to **carbamazepine**. Symptoms resolved after several days following withdrawal of **verapamil** in all patients. Rechallenge in 2 patients resulted in similar neurotoxic symptoms. Reductions in the dose of **carbamazepine** may be required when **verapamil** is administered and then increased when **verapamil** is withdrawn to avoid exacerbation of **epileptic seizures**. Seizure aggravation occurred in 1 patient in this series following abrupt withdrawal of **verapamil** [248].

c)) In a 24-year-old woman with **intractable epilepsy**, the patient's complex-partial seizures had been refractory to multiple anticonvulsants, partial temporal **lobectomy**, and **vagal nerve stimulation**; this resulted in intermittent hospitalization a mean of every 55 days for management of **complex partial status epilepticus**. **Verapamil** 180 mg/day was added to an anticonvulsant regimen composed of **carbamazepine** 600 mg twice daily in addition to **levetiracetam**, **topiramate**, and **clonazepam**. Baseline **carbamazepine** plasma concentration level was at the low end of the therapeutic range (4.2 mg/mL). At 1-month follow-up, **carbamazepine** plasma concentration

was 7.4 mg/L, and the patient reported subjective improvement in seizure control. Verapamil dose was titrated incrementally up to 480 mg daily, resulting in an increase in carbamazepine plasma concentration to 13.3 mg/L, without report of adverse effects and with an extension to approximately 4 months between hospital admissions [249].

d)) Cimetidine 400 mg 3 times daily significantly increased steady-state carbamazepine plasma levels by 17% after 2 days. However, carbamazepine levels decreased to pretreatment levels by the seventh day of cimetidine treatment. Carbamazepine side effects appeared in most patients within 24 hours following cimetidine initiation, but subsided over the next 48 to 72 hours. The investigators concluded that dosage adjustments appear unnecessary, but that patients should be warned of the appearance of carbamazepine side effects for the first 3 to 5 days after beginning cimetidine [250].

e)) A case of carbamazepine toxicity was reported in an elderly man receiving carbamazepine 200 mg 3 times daily, isoniazid 300 mg daily, and cimetidine 400 mg twice daily. Two days after initiating this drug combination, the patient developed nausea, vomiting, dizziness, and epigastric pain. Carbamazepine serum concentrations were elevated. Patients receiving this combination of therapy should have close monitoring of carbamazepine concentrations [251].

f)) Concomitant carbamazepine and diltiazem administration may produce elevated serum carbamazepine levels, resulting in neurotoxicity [252][253][254][255]. In a case report, diltiazem 60 mg 3 times daily elevated the carbamazepine level by 40% higher than baseline, resulting in clinical signs of carbamazepine toxicity. Nifedipine 20 mg 3 times daily did not produce any adverse effect [252]. In another case report, a patient with a stable carbamazepine dose (800 mg daily) and serum concentration (8.5 to 10.1 mg/L) was started on diltiazem 30 mg 3 times a day for atrial fibrillation. Approximately 2 weeks later, the patient was admitted to the hospital with mental slowing and speech difficulties. The serum carbamazepine level the next day was 15.5 mg/L. Carbamazepine was consequently reduced to 300 mg daily, which produced a serum level of 8.3 mg/L and resolution of the mental disturbances [253].

3.5.1.AJ] Celecoxib

1)) Interaction Effect: an increased risk of bleeding

2)) Summary: Caution is recommended with the concomitant use of NSAIDs and antidepressants, including SSRIs due to an increased risk of intracranial hemorrhage[367] and gastrointestinal bleeding [371][372][368][369]. Bleeding events have included epistaxis, ecchymosis, hematoma, petechiae, and life-threatening hemorrhages [374][373][375][376]. When an SSRI and an NSAID are given concurrently, monitor the patient for signs of increased bleeding.

3)) Severity: major

4)) Onset: unspecified

5)) Substantiation: established

6)) Clinical Management: Use caution if NSAIDs and SSRIs are coadministered. Concomitant use of NSAIDs and SSRIs may cause an increased risk of intracranial hemorrhage[367] and gastrointestinal bleeding [368][369]. When an SSRI and an NSAID are given concurrently, monitor the patient for signs of increased bleeding.

7)) Probable Mechanism: depletion of platelet serotonin by SSRI; additive effects

8)) Literature Reports

a)) Concomitant use of NSAIDs and antidepressants, including tricyclic antidepressants, SSRIs, serotonin-norepinephrine reuptake inhibitors, and MAOIs, resulted in a 60% increased risk of intracranial hemorrhage within 30 days of concomitant use compared with antidepressant

use alone. There was no significant difference between the antidepressant drug classes and the increased risk; however, there was an increased risk associated with male patients compared with female patients [367].

b)) 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. Combined use of an SSRI and NSAIDs or low-dose [aspirin](#) increased the risk to 12.2 and 5.2 times, 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 [370].

c)) Two metaanalyses of incidents of upper GI bleed due to SSRIs, NSAIDs, and their combination found that SSRIs increased the risk by 1.73 [371] to 2.36 times [372], NSAIDs by 2.55 times [371], and the combination of SSRIs and NSAIDs by 4.02 [371] to 6.33 times [372].

d)) The release of serotonin by [platelets](#) is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs and NSAIDs have been associated with an increased risk of bleeding [373].

3.5.1.AK] 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[114][115][113]. 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](#). In patients receiving [warfarin](#) and [fluvoxamine](#) concomitantly for 2 weeks, [warfarin](#) plasma concentrations increased by 98% and prothrombin times were prolonged. [Fluvoxamine](#) appears to inhibit several cytochrome P450 isoenzymes which may include 1A2 and 2C9 isozymes, which are responsible for [warfarin](#) metabolism [115][113].

3)) Severity: major

4)) Onset: delayed

5)) Substantiation: probable

6)) Clinical Management: When [fluvoxamine](#) 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 [fluvoxamine](#) therapy is initiated or discontinued. Periodically reassess the prothrombin time ratio and INR in patients receiving [fluvoxamine](#) and [anticoagulant therapy](#)[113].

7)) Probable Mechanism: unknown

8)) Literature Reports

a)) According to a retrospective cohort study (n=234), there was an increased risk of clinically relevant bleeding (hospital admission due to bleeding) in patients receiving [warfarin](#) for [atrial fibrillation](#) during concomitant SSRI therapy or within 2 weeks following SSRI therapy termination. Patients with a mean age of 72 +/- 7 years receiving [warfarin](#) plus SSRI (n=117) were matched with randomly selected patients who received [warfarin](#) only (n=117). SSRI included [fluoxetine](#), [citalopram](#), [paroxetine](#), [sertraline](#), [fluvoxamine](#), or escitalopram. Nine patients experienced 11 bleeding episodes during 213.9 treatment years in the [warfarin](#) plus SSRI

group, and 10 patients experienced 14 bleedings during 586.4 treatment years in the warfarin-only group. The corresponding total incidences of bleedings were 51.4 and 23.9 per 1000 treatment years, respectively. The hazard ratio for first bleedings during treatment with [warfarin](#) plus SSRI was 3.49 (95% CI; 1.37 to 8.91, $p=0.009$) compared with [warfarin](#) only. The SSRI implicated in patients experiencing bleeding at the time of concomitant administration were [sertraline](#) or [citalopram](#). The addition of an SSRI was not associated with a change in [warfarin](#) dose or INR ($p=0.48$ and $p=0.31$ respectively). The results of the study may be limited by earlier bleeding events, unknown patient adherence, and exclusion of [clopidogrel](#), dipyridamol, corticosteroids and anticoagulants other than [warfarin](#) in the model [114].

b) A population-based, case-controlled study of new coumarin users (acenocoumarol and phenprocoumon) with concomitant selective serotonin reuptake inhibitors (SSRIs) resulted in an increased risk of hospitalization due to nongastrointestinal bleeding. Using national pharmacy and hospitalization records, Netherlands researchers identified 1848 cases that were admitted for abnormal bleeding and compared them with 5818 control subjects also taking coumarins. Median duration of treatment in patients was 220 days (range, 1 to 4690 days). Patients on SSRIs showed greater risk for hospitalization for nongastrointestinal bleeding (adjusted odds ratio (OR) 1.7, 95% confidence interval (CI), 1.1 to 2.5), however, the rate of [gastrointestinal bleeding](#) (adjusted OR 0.8, 95% CI, 0.4 to 1.5) was not significantly different [115].

c) A hospitalized 80-year-old female was started on intravenous [heparin](#) and oral [warfarin](#) therapy due to an [embolic stroke](#) secondary to [atrial fibrillation](#) and [mitral stenosis](#). Her [warfarin](#) dose was maintained at 1 mg daily, with her INR between 2.5 and 3. [Fluvoxamine](#) 25 mg daily was started for depression, and her [warfarin](#) dose was increased to 1.5 mg daily 3 days later due to worsening of the left [hemiparesis](#). Three days later, her INR was 9.96, and a repeat INR to rule out laboratory error was 11.3. [Warfarin](#) was discontinued, fresh frozen plasma was given, and [fluvoxamine](#) was discontinued. Six days later, [warfarin](#) was again started at 1 mg daily, and the INR increased over 4 days to 11.8. The elevated INR was attributed to the persisting effect of [fluvoxamine](#). She was eventually stabilized on [warfarin](#) 1 mg daily with INR values between 2 and 2.5 [116].

3.5.1.AL] [Choline Salicylate](#)

1) Interaction Effect: an increased risk of bleeding

2) Summary: Caution is recommended with the concomitant use of NSAIDs and antidepressants, including SSRIs due to an increased risk of [intracranial hemorrhage](#)[367] and [gastrointestinal bleeding](#) [371][372][368][369]. Bleeding events have included [epistaxis](#), ecchymosis, [hematoma](#), [petechiae](#), and life-threatening hemorrhages [374][373][375][376]. When an SSRI and an NSAID are given concurrently, monitor the patient for signs of increased bleeding.

3) Severity: major

4) Onset: unspecified

5) Substantiation: established

6) Clinical Management: Use caution if NSAIDs and SSRIs are coadministered. Concomitant use of NSAIDs and SSRIs may cause an increased risk of [intracranial hemorrhage](#)[367] and [gastrointestinal bleeding](#) [368][369]. When an SSRI and an NSAID are given concurrently, monitor the patient for signs of increased bleeding.

7) Probable Mechanism: depletion of [platelet](#) serotonin by SSRI; additive effects

8) Literature Reports

a) Concomitant use of NSAIDs and antidepressants, including tricyclic antidepressants, SSRIs, serotonin-norepinephrine reuptake inhibitors, and MAOIs, resulted in a 60% increased risk of [intracranial hemorrhage](#) within 30 days of concomitant use compared with antidepressant

use alone. There was no significant difference between the antidepressant drug classes and the increased risk; however, there was an increased risk associated with male patients compared with female patients [367].

b)) 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. Combined use of an SSRI and NSAIDs or low-dose [aspirin](#) increased the risk to 12.2 and 5.2 times, 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 [370].

c)) Two metaanalyses of incidents of upper GI bleed due to SSRIs, NSAIDs, and their combination found that SSRIs increased the risk by 1.73 [371] to 2.36 times [372], NSAIDs by 2.55 times [371], and the combination of SSRIs and NSAIDs by 4.02 [371] to 6.33 times [372].

d)) The release of serotonin by [platelets](#) is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs and NSAIDs have been associated with an increased risk of bleeding [373].

3.5.1.AM] [Cilostazol](#)

1)) Interaction Effect: increased [cilostazol](#) exposure and increased risk of bleeding

2)) Summary: [Cilostazol](#) (a CYP2C19 substrate) exposure is increased with concomitant administration of [fluvoxamine](#) (a CYP2C19 inhibitor)[206]. Concomitant use of [cilostazol](#) (a CYP2C19 substrate) and [omeprazole](#) (a CYP2C19 inhibitor) resulted in increased plasma concentrations of [cilostazol](#) and one of its active metabolites [207]. Additionally, case-control and cohort studies have shown that coadministration of SSRIs and antiplatelet agents has been associated with an increased risk of bleeding due to additive effects on [platelets](#). Bleeding events reported have included [epistaxis](#), ecchymosis, [hematoma](#), [petechiae](#), and life-threatening hemorrhages [137]. If coadministration is required, consider reducing the [cilostazol](#) dose to 50 mg twice daily [206] and monitor patient for signs of increased bleeding [137].

3)) Severity: major

4)) Onset: unspecified

5)) Substantiation: probable

6)) Clinical Management: [Cilostazol](#) (a CYP2C19 substrate) exposure is increased with concomitant administration of [fluvoxamine](#) (a CYP2C19 inhibitor)[206]. Additionally, concomitant use of SSRIs and antiplatelet agents may increase the risk of bleeding due to additive effects on [platelets](#) [137]. If coadministration is required, consider reducing the [cilostazol](#) dose to 50 mg twice daily [206] and monitor patient for signs of increased bleeding [137].

7)) Probable Mechanism: inhibition of CYP2C19-mediated metabolism of [cilostazol](#); additive effects on [platelets](#)

8)) Literature Reports

a)) Concomitant use of [cilostazol](#), a CYP2C19 substrate, and [omeprazole](#), a CYP2C19 inhibitor, resulted in increased plasma concentrations of [cilostazol](#) and one of its active metabolites. Twenty healthy nonsmoking volunteers participated in a single-center, open-label study to evaluate the effect of [omeprazole](#) on the pharmacokinetics of a single dose of [cilostazol](#) 100 mg. Each study subject received [cilostazol](#) 100 mg on day 0 under fasting conditions. On days 7 through 18, [omeprazole](#) 40 mg was given each morning. Another single dose of [cilostazol](#) 100 mg was administered with [omeprazole](#) on day 14. After [omeprazole](#) administration, the Cmax of [cilostazol](#)

increased by 18% (from 782 mcg/L to 921 mcg/L) and the AUC increased by 26% (from 10,287 mcg/L/h to 13,033 mcg/L/hr). The mean C_{max} of OPC-13015, a pharmacologically active metabolite of [cilostazol](#), increased by 29% and the AUC increased by 69% in the presence of [omeprazole](#). Conversely, the C_{max} and AUC of OPC-13213, another pharmacologically active metabolite of [cilostazol](#), decreased by 22% and 31%, respectively. Although the changes in systemic exposure to [cilostazol](#) were well tolerated, the dose of [cilostazol](#) should be reduced to 50 mg twice daily when given concurrently with [omeprazole](#) [207].

3.5.1.AN] [Cisapride](#)

- 1) Interaction Effect: [cardiotoxicity](#) (QT prolongation, [torsades de pointes](#), [cardiac arrest](#))
- 2) Summary: [Fluvoxamine](#) should not be used in combination with [cisapride](#). Although there is no direct experience with this combination, [fluvoxamine](#) appears to be a potent inhibitor of the cytochrome P450 3A4 isozyme, the enzyme primarily responsible for the metabolism of [cisapride](#). Inhibition of this enzyme may result in elevated [cisapride](#) concentrations; increased plasma concentrations of [cisapride](#) are associated with QT prolongation and [torsades de pointes](#), which can be fatal[384].
- 3) Severity: contraindicated
- 4) Onset: rapid
- 5) Substantiation: probable
- 6) Clinical Management: Concurrent use of [fluvoxamine](#) and [cisapride](#) is contraindicated.
- 7) Probable Mechanism: inhibition of cytochrome P450 3A4-mediated [cisapride](#) metabolism

3.5.1.AO] [Citalopram](#)

- 1) Interaction Effect: increased [citalopram](#) exposure with risk of QT interval prolongation and increased risk of [serotonin syndrome](#)
- 2) Summary: [Fluvoxamine](#) is an SSRI and a potent CYP2C19 inhibitor[40] and [citalopram](#) is an SSRI and a CYP2C19 substrate associated with QT prolongation. In a [pharmacokinetic study](#), patients who received [citalopram](#) 40 mg/day for 21 days coadministered with [cimetidine](#) (another potent CYP2C19 inhibitor) 400 mg/day for 8 days experienced an increase in [citalopram](#) AUC and C_{max} of 43% and 39%, respectively [166]. Although the interaction between [citalopram](#) and [fluvoxamine](#) has not been studied specifically, concomitant use may result in increased [citalopram](#) exposure and an increased risk of QT prolongation. If coadministration with [fluvoxamine](#) is required, do not exceed [citalopram](#) doses of 20 mg/day, and additionally monitor for symptoms of [serotonin syndrome](#), including neuromuscular abnormalities, autonomic instability, and mental status changes, especially during treatment initiation and dose increases. [Serotonin syndrome](#) can be life-threatening. If [serotonin syndrome](#) develops, discontinue [citalopram](#) and [fluvoxamine](#) and initiate supportive care [166].
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: The concomitant use of [citalopram](#) with [fluvoxamine](#) may result in increased [citalopram](#) exposure and risk of QT prolongation. If coadministration of [citalopram](#) with [fluvoxamine](#) is required, do not exceed [citalopram](#) doses of 20 mg/day. Additionally, concurrent use of [citalopram](#) with [fluvoxamine](#) is not recommended because it may result in a life-threatening condition called [serotonin syndrome](#). If concomitant use is necessary, discuss the risks of [serotonin syndrome](#) with the patient and monitor closely for symptoms of [serotonin syndrome](#) (mental status changes, autonomic instability, neuromuscular symptoms, seizures, and gastrointestinal symptoms), especially during treatment initiation and dose increases. If [serotonin syndrome](#) develops, discontinue [citalopram](#) and [fluvoxamine](#) and initiate supportive care[166].

7J) Probable Mechanism: inhibition of CYP2C19-mediated [citalopram](#) metabolism by [fluvoxamine](#); additive serotonergic effects

3.5.1.APJ Clobazam

1J) Interaction Effect: increased [fluvoxamine](#) plasma concentrations; increased exposure to the active metabolite of clobazam

2J) Summary: Concurrent use of clobazam (a CYP2C19 substrate and CYP2D6 inhibitor[282]) and [fluvoxamine](#) (a strong CYP2C19 inhibitor and CYP2D6 substrate [22]) may result in increased plasma concentrations of both [fluvoxamine](#) and N-desmethyloclobazam, the active metabolite of clobazam. Coadministration of clobazam with a single dose of [dextromethorphan](#) (another CYP2D6 substrate) resulted in an increase of [dextromethorphan](#) AUC and Cmax by 90% and 59%, respectively. A similar increase in [fluvoxamine](#) concentrations may be expected. If used concomitantly, dosage reductions of clobazam and [fluvoxamine](#) may be necessary [282][22].

3J) Severity: moderate

4J) Onset: unspecified

5J) Substantiation: theoretical

6J) Clinical Management: The concomitant use of clobazam and [fluvoxamine](#) may cause increased plasma concentrations of both [fluvoxamine](#) and N-desmethyloclobazam, the active metabolite of clobazam. If concomitant use is required, dose reductions may be warranted for clobazam and [fluvoxamine](#)[282][40].

7J) Probable Mechanism: inhibition of CYP2D6-mediated [fluvoxamine](#) metabolism by clobazam; inhibition of CYP2C19-mediated clobazam metabolism by [fluvoxamine](#)

3.5.1.AQJ Clomipramine

1J) Interaction Effect: [clomiPRAMINE](#) toxicity (dry mouth, urinary retention, sedation)

2J) Summary: Coadministration of [fluvoxamine](#) and [clomiPRAMINE](#) was found to significantly increase plasma levels of [clomiPRAMINE](#)[229]. A bidirectional effect was suggested in which [fluvoxamine](#) increased [clomiPRAMINE](#) concentrations (by interfering with N-demethylation) and [clomiPRAMINE](#) increased [fluvoxamine](#) levels [230].

3J) Severity: moderate

4J) Onset: delayed

5J) Substantiation: probable

6J) Clinical Management: Monitor patients for signs of [clomiPRAMINE](#) and [fluvoxamine](#) toxicity; lower doses of one or both agents may be required with concomitant therapy.

7J) Probable Mechanism: decreased [clomiPRAMINE](#) metabolism

8J) Literature Reports

aJ) [Fluvoxamine](#) has been shown to significantly increase plasma levels of [amitriptyline](#) and [clomiPRAMINE](#) and to mildly increase levels of their metabolites [nortriptyline](#) and desmethyloclopiPRAMINE, respectively. This may be due to competitive inhibition of oxidative metabolism in the liver [227].

bJ) Metabolism of tricyclic antidepressants coadministered with [fluvoxamine](#) was studied in eight depressed patients (four patients received [clomiPRAMINE](#)). [Fluvoxamine](#) was found to interfere with N-demethylation and 8-hydroxylation of [clomiPRAMINE](#). The combination of [fluvoxamine](#) and [clomiPRAMINE](#) led to increased plasma levels of [clomiPRAMINE](#) and decreased concentrations of [clomiPRAMINE](#)'s N-demethylated metabolite, desmethyloclopiPRAMINE. In addition, plasma levels of [fluvoxamine](#) were increased [228].

3.5.1.AR] Clonixin

- 1) Interaction Effect: an increased risk of bleeding
- 2) Summary: Caution is recommended with the concomitant use of NSAIDs and antidepressants, including SSRIs due to an increased risk of [intracranial hemorrhage](#)[367] and [gastrointestinal bleeding](#) [371][372][368][369]. Bleeding events have included [epistaxis](#), ecchymosis, [hematoma](#), [petechiae](#), and life-threatening hemorrhages [374][373][375][376]. When an SSRI and an NSAID are given concurrently, monitor the patient for signs of increased bleeding.
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: established
- 6) Clinical Management: Use caution if NSAIDs and SSRIs are coadministered. Concomitant use of NSAIDs and SSRIs may cause an increased risk of [intracranial hemorrhage](#)[367] and [gastrointestinal bleeding](#) [368][369]. When an SSRI and an NSAID are given concurrently, monitor the patient for signs of increased bleeding.
- 7) Probable Mechanism: depletion of [platelet](#) serotonin by SSRI; additive effects
- 8) Literature Reports

a) Concomitant use of NSAIDs and antidepressants, including tricyclic antidepressants, SSRIs, serotonin-norepinephrine reuptake inhibitors, and MAOIs, resulted in a 60% increased risk of [intracranial hemorrhage](#) within 30 days of concomitant use compared with antidepressant use alone. There was no significant difference between the antidepressant drug classes and the increased risk; however, there was an increased risk associated with male patients compared with female patients [367].

b) 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. Combined use of an SSRI and NSAIDs or low-dose [aspirin](#) increased the risk to 12.2 and 5.2 times, 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 [370].

c) Two metaanalyses of incidents of upper GI bleed due to SSRIs, NSAIDs, and their combination found that SSRIs increased the risk by 1.73 [371] to 2.36 times [372], NSAIDs by 2.55 times [371], and the combination of SSRIs and NSAIDs by 4.02 [371] to 6.33 times [372].

d) The release of serotonin by [platelets](#) is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs and NSAIDs have been associated with an increased risk of bleeding [373].

3.5.1.AS] Clopidogrel

- 1) Interaction Effect: reduction in clinical efficacy of [clopidogrel](#) and reduced [platelet](#) inhibition; increased risk of bleeding
- 2) Summary: [Clopidogrel](#) is metabolized to its active metabolite by CYP2C19. Concomitant use of [clopidogrel](#) and [fluvoxamine](#) (strong CYP2C19 inhibitor) has the potential for reduced [clopidogrel](#) active metabolite concentrations and reduced [platelet](#) inhibition[121]. Additionally, concomitant use may increase the risk of bleeding, as the release of serotonin by [platelets](#) is important for maintaining

hemostasis. Case reports and epidemiological studies have shown that use of SSRIs and serotonin-norepinephrine reuptake inhibitors (SNRIs), including [fluvoxamine](#), is associated with [gastrointestinal bleeding](#). Bleeding events reported with SSRIs and SNRIs include cases of ecchymoses, [hematomas](#), [epistaxis](#), and [petechiae](#); life-threatening hemorrhages have also occurred [1]. Consider avoiding concomitant use.

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Concomitant use of [clopidogrel](#) and [fluvoxamine](#) has the potential for reduced [clopidogrel](#) active metabolite concentrations and reduced [platelet](#) inhibition. Concomitant use may also increase the risk of bleeding[121]. Consider avoiding concomitant use.

7) Probable Mechanism: inhibition of CYP2C19-mediated [clopidogrel](#) metabolism to its active metabolite by [fluvoxamine](#); unknown

3.5.1.AT] Clorgyline

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

2) Summary: Concurrent administration or overlapping therapy with [fluvoxamine](#) and a monoamine oxidase (MAO) inhibitor may result in CNS toxicity or [serotonin syndrome](#), a hyperserotonergic state characterized by symptoms such as restlessness, myoclonus, changes in mental status, hyperreflexia, diaphoresis, shivering, and tremor. Serious, even fatal, reactions have been reported with concomitant use of serotonin specific reuptake inhibitors and MAO inhibitors[298][299][300][301]. Concomitant use is not recommended.

3) Severity: major

4) Onset: rapid

5) Substantiation: probable

6) Clinical Management: Concurrent use of [fluvoxamine](#) and a MAO inhibitor should be avoided. Wait at least two weeks after discontinuing an MAO inhibitor before initiating therapy with [fluvoxamine](#). Wait at least two weeks after discontinuing [fluvoxamine](#) before initiating therapy with a MAO inhibitor.

7) Probable Mechanism: serotonin reuptake inhibition

8) Literature Reports

a) Concomitant use of serotonin specific reuptake inhibitors and monoamine oxidase inhibitors can produce a toxic reaction known as [serotonin syndrome](#) [294]. [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) A 26-year old woman who had been taking [isocarboxazid](#) for eight weeks stopped taking the drug for 11 days before beginning therapy with [sertraline](#). After a single 100 mg [sertraline](#) dose, the patient became restless and developed leg twitches. The patient was later admitted to the emergency room with diaphoresis, [tachycardia](#), hyperreflexia, and various neuromuscular disturbances. After treatment with [diazepam](#) and [propranolol](#) the patient did not improve. The patient was then given two 4 mg doses of [cyproheptadine](#) an hour apart, with notable improvement in symptoms after the second dose [295].

c) A drug interaction occurred in a 61-year old woman whose regimen of [sertraline](#) 100 mg twice daily was added to a regimen of [lithium](#), [phenelzine](#), [thioridazine](#), and [doxepin](#). Three hours after taking the first [sertraline](#) dose, the patient was found in a semicomatose state, with elevated body temperature, increased pulse, increased respiration rate, and a blood pressure of 140/110

mm Hg. After transportation to the hospital, the patient was misdiagnosed as having [neuroleptic malignant syndrome](#) (NMS) which was later changed to [serotonin syndrome](#) due to a reaction between [sertraline](#) and [phenelzine](#). The authors suggest that monoamine oxidase inhibitor (MAOI) therapy should be discontinued for at least two weeks before initiation of therapy with a selective serotonin reuptake inhibitor (SSRI) and that before starting a MAOI, SSRI therapy should be discontinued for at least 5 half-lives of the parent drug and any active metabolites [296].

d) Two cases reports suggested a possible interaction between [fluoxetine](#) and [selegiline](#) [297]. 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.AU] [Clozapine](#)

1) Interaction Effect: increased [clozapine](#) exposure

2) Summary: The concomitant use of [clozapine](#) (a CYP1A2 substrate) with a potent CYP1A2 inhibitor may increase the exposure of [clozapine](#) and lead to increased adverse events. If coadministered, reduce the [clozapine](#) dose to one-third of the original dose during concomitant administration with strong CYP1A2 inhibitors. Once coadministration with a strong CYP1A2 inhibitor is discontinued, increase the [clozapine](#) dose back to its original dose based on clinical response[192].

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: The concomitant use of [clozapine](#) (a CYP1A2 substrate) with a potent CYP1A2 inhibitor may increase the exposure of [clozapine](#) and lead to an increase in adverse events. If used concomitantly, reduce the [clozapine](#) dose to one-third of the original dose during concomitant administration with strong CYP1A2 inhibitors. If coadministration with a strong CYP1A2 inhibitor is discontinued, increase the [clozapine](#) dose back to its original strength based on clinical response[192].

7) Probable Mechanism: inhibition of CYP1A2-mediated metabolism of [clozapine](#)

8) Literature Reports

a) Therapeutic drug monitoring data showed higher [clozapine](#) concentration/dose ratios in 3 of 4 patients when concurrent [fluvoxamine](#) was used compared with [clozapine](#) alone. In 2 of these patients, [clozapine](#) concentrations were 5 to 10 times higher when [fluvoxamine](#) was coadministered. One patient experienced adverse effects, including sedation and [urinary incontinence](#). Inhibition of the CYP1A2 enzyme by [fluvoxamine](#) was thought to be the mechanism in this drug interaction [193].

b) [Fluvoxamine](#) significantly increased serum levels of [clozapine](#) in 16 patients with [schizophrenia](#). [Clozapine](#) 2.5 to 3 mg/kg/day was given for 14 days, then [fluvoxamine](#) 50 mg daily was added for 14 days. Serum concentrations of [clozapine](#) and 2 metabolites were measured on days 1, 7, and 14. The increase in [clozapine](#) serum concentration was approximately 3-fold when given with [fluvoxamine](#) compared with [clozapine](#) alone [194].

c) Two patients experienced the onset of extrapyramidal symptoms (EPS) when [fluvoxamine](#) was added to an existing regimen that included [clozapine](#). The first patient, a 46-year-old man, was stabilized on [clozapine](#) 400 mg daily for more than a year when [fluvoxamine](#) 25 mg daily was started. No signs of EPS were present before [fluvoxamine](#) therapy, and the [clozapine](#) plasma level

was 686.2 nanograms/milliliter (ng/mL). Four days after [fluvoxamine](#) was initiated, the patient experienced rigidity and an Extrapyramidal Symptom Rating Scale (ESRS) score of 6. Three weeks later, the ESRS had increased to 8 and the [clozapine](#) level was 817.9 ng/mL. [Fluvoxamine](#) was discontinued, and 3 weeks later the ESRS score and [clozapine](#) level decreased to 1 and 686.8 ng/mL, respectively. The second patient, a 46-year-old woman, was maintained on [clozapine](#) 600 mg daily for more than 2 years with a plasma level of 1292.5 ng/mL and no signs of EPS. [Fluvoxamine](#) was started at 25 mg daily and 6 days later she developed moderate [akathisia](#) and tremors (ESRS of 7). Three weeks and 6 weeks into combination therapy, her [clozapine](#) plasma levels were 1438.2 ng/mL and 1548.9 ng/mL, respectively. The ESRS increased to 9, but the patient preferred the combination therapy due to the efficacy in alleviating psychotic symptoms [195].

d) One study presented 2 case reports in which addition of an SSRI to [clozapine](#) therapy resulted in exacerbation of psychotic symptoms. The first patient, a 26-year-old woman with [schizophrenia](#), had been taking [clozapine](#) 175 mg per day. Other medications included [propranolol](#) for [tachycardia](#) and trihexyphenidyl for [hypersalivation](#). After marked improvement in psychotic symptoms but continued compulsive behavior, [sertraline](#) 50 mg/day was added. Within 4 weeks, the patient's obsessive-compulsive symptoms and psychotic symptoms worsened. Plasma [clozapine](#) concentrations increased from 325 nanograms/milliliter (ng/mL) before [sertraline](#) therapy to 695 ng/mL after [sertraline](#) therapy. The second patient, a 24-year-old woman with [schizophrenia](#), was placed on a regimen of [clozapine](#) 500 mg/day, which was later increased to 600 mg/day. After [fluvoxamine](#) 50 mg/day was started as adjunctive treatment, the patient's [clozapine](#) level rose from 1146 ng/mL before [fluvoxamine](#) treatment to 2750 ng/mL after 28 days of [fluvoxamine](#) treatment. During this time the patient's compulsive symptoms remained unchanged, but psychotic symptoms worsened. The authors postulated that the worsening of psychotic symptoms could be due to SSRI inhibition of [clozapine](#) metabolism by cytochrome P450 isozymes or an imbalance of the serotonergic and dopaminergic blockade caused by coadministration the 2 drugs [196].

3.5.1.AV] [Cyclobenzaprine](#)

- 1) Interaction Effect: increased risk of [serotonin syndrome](#)
- 2) Summary: [Serotonin syndrome](#), a life-threatening condition, has occurred with coadministration of [cyclobenzaprine](#) and other drugs, such as SSRIs. If concurrent use is necessary, monitor patients closely for [serotonin syndrome](#), especially during treatment initiation and dose increases. Symptoms of [serotonin syndrome](#) include neuromuscular abnormalities (eg, hyperreflexia, tremor, and ataxia), autonomic instability (eg, [tachycardia](#), diaphoresis, and [hyperthermia](#)), gastrointestinal symptoms (eg, nausea, vomiting, diarrhea), or mental status changes (eg, agitation and confusion). Discontinue both drugs immediately if these symptoms occur and initiate supportive therapy[234][235].
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Coadministration of [cyclobenzaprine](#) with an SSRI may result in a life-threatening condition called [serotonin syndrome](#). If concurrent use is necessary, monitor patients closely for [serotonin syndrome](#), especially during treatment initiation and dose increases. Symptoms of [serotonin syndrome](#) include neuromuscular abnormalities (eg, hyperreflexia, tremor, and ataxia), autonomic instability (eg, [tachycardia](#), diaphoresis, and [hyperthermia](#)), gastrointestinal symptoms (eg, nausea, vomiting, diarrhea), or mental status changes (eg, agitation and confusion). Discontinue both drugs immediately if these symptoms occur and initiate supportive therapy[234][235].
- 7) Probable Mechanism: additive serotonergic effects

3.5.1.AW] Cyclosporine

- 1) Interaction Effect: an increased risk of [cycloSPORINE](#) toxicity (renal dysfunction, [cholestasis](#), paresthesias)
- 2) Summary: [Fluvoxamine](#) was reported to increase [cycloSPORINE](#) trough serum levels in a 62-year-old female. Fluvoxamine is an inhibitor of cytochrome P450 3A4 enzymes, which are required for [cycloSPORINE](#) metabolism[398].
- 3) Severity: moderate
- 4) Onset: delayed
- 5) Substantiation: probable
- 6) Clinical Management: Closely monitor [cycloSPORINE](#) serum concentrations when [fluvoxamine](#) therapy is initiated, altered, or discontinued.
- 7) Probable Mechanism: inhibition of cytochrome P450 3A4 enzymes by [fluvoxamine](#) decreases [cycloSPORINE](#) metabolism
- 8) Literature Reports

a) A 62-year-old female received a cadaveric renal [allograft](#) nine years prior to initiating [fluvoxamine](#) therapy for depression. Her baseline [cycloSPORINE](#) trough level ranged from 200 ng/mL to 250 ng/mL, and serum [creatinine](#) was 1.5 mg/dL. Medications included [cycloSPORINE](#) 300 mg daily, [prednisone](#), [atenolol](#), [levothyroxine](#), [bumetanide](#), [rocaltrol](#), and [omeprazole](#). [Fluvoxamine](#) 100 mg daily was started for symptoms of depression, and two weeks later the patient complained of shivering and exhibited a fine tremor. [CycloSPORINE](#) trough level was 380 ng/mL and serum [creatinine](#) had increased to 1.9 mg/dL. [CycloSPORINE](#) dosage was decreased to 200 mg daily, and both the [cycloSPORINE](#) trough level and serum [creatinine](#) returned to their baseline values [397].

3.5.1.AX] 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[114][115][113]. 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](#). In patients receiving [warfarin](#) and [fluvoxamine](#) concomitantly for 2 weeks, [warfarin](#) plasma concentrations increased by 98% and prothrombin times were prolonged. [Fluvoxamine](#) appears to inhibit several cytochrome P450 isoenzymes which may include 1A2 and 2C9 isozymes, which are responsible for [warfarin](#) metabolism [115][113].
- 3) Severity: major
- 4) Onset: delayed
- 5) Substantiation: probable
- 6) Clinical Management: When [fluvoxamine](#) 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 [fluvoxamine](#) therapy is initiated or discontinued. Periodically reassess the prothrombin time ratio and INR in patients receiving [fluvoxamine](#) and [anticoagulant therapy](#)[113].
- 7) Probable Mechanism: unknown
- 8) Literature Reports

a) According to a retrospective cohort study (n=234), there was an increased risk of clinically relevant bleeding (hospital admission due to bleeding) in patients receiving [warfarin](#) for [atrial fibrillation](#) during concomitant SSRI therapy or within 2 weeks following SSRI therapy termination. Patients with a mean age of 72 +/- 7 years receiving [warfarin](#) plus SSRI (n=117) were matched with randomly selected patients who received [warfarin](#) only (n=117). SSRI included [fluoxetine](#), [citalopram](#), [paroxetine](#), [sertraline](#), [fluvoxamine](#), or escitalopram. Nine patients experienced 11 bleeding episodes during 213.9 treatment years in the [warfarin](#) plus SSRI group, and 10 patients experienced 14 bleedings during 586.4 treatment years in the warfarin-only group. The corresponding total incidences of bleedings were 51.4 and 23.9 per 1000 treatment years, respectively. The hazard ratio for first bleedings during treatment with [warfarin](#) plus SSRI was 3.49 (95% CI; 1.37 to 8.91, p=0.009) compared with [warfarin](#) only. The SSRI implicated in patients experiencing bleeding at the time of concomitant administration were [sertraline](#) or [citalopram](#). The addition of an SSRI was not associated with a change in [warfarin](#) dose or INR (p=0.48 and p=0.31 respectively). The results of the study may be limited by earlier bleeding events, unknown patient adherence, and exclusion of [clopidogrel](#), dipyridamol, corticosteroids and anticoagulants other than [warfarin](#) in the model [114].

b) A population-based, case-controlled study of new coumarin users (acenocoumarol and phenprocoumon) with concomitant selective serotonin reuptake inhibitors (SSRIs) resulted in an increased risk of hospitalization due to nongastrointestinal bleeding. Using national pharmacy and hospitalization records, Netherlands researchers identified 1848 cases that were admitted for abnormal bleeding and compared them with 5818 control subjects also taking coumarins. Median duration of treatment in patients was 220 days (range, 1 to 4690 days). Patients on SSRIs showed greater risk for hospitalization for nongastrointestinal bleeding (adjusted odds ratio (OR) 1.7, 95% confidence interval (CI), 1.1 to 2.5), however, the rate of [gastrointestinal bleeding](#) (adjusted OR 0.8, 95% CI, 0.4 to 1.5) was not significantly different [115].

c) A hospitalized 80-year-old female was started on intravenous [heparin](#) and oral [warfarin](#) therapy due to an [embolic stroke](#) secondary to [atrial fibrillation](#) and [mitral stenosis](#). Her [warfarin](#) dose was maintained at 1 mg daily, with her INR between 2.5 and 3. [Fluvoxamine](#) 25 mg daily was started for depression, and her [warfarin](#) dose was increased to 1.5 mg daily 3 days later due to worsening of the left [hemiparesis](#). Three days later, her INR was 9.96, and a repeat INR to rule out laboratory error was 11.3. [Warfarin](#) was discontinued, fresh frozen plasma was given, and [fluvoxamine](#) was discontinued. Six days later, [warfarin](#) was again started at 1 mg daily, and the INR increased over 4 days to 11.8. The elevated INR was attributed to the persisting effect of [fluvoxamine](#). She was eventually stabilized on [warfarin](#) 1 mg daily with INR values between 2 and 2.5 [116].

3.5.1.AY] [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[114][115][113]. 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](#). In patients receiving [warfarin](#) and [fluvoxamine](#) concomitantly for 2 weeks, [warfarin](#) plasma concentrations increased by 98% and prothrombin times were prolonged. [Fluvoxamine](#) appears to inhibit several cytochrome P450 isoenzymes which may include 1A2 and 2C9 isozymes, which are responsible for [warfarin](#) metabolism [115][113].

3) Severity: major

4) Onset: delayed

5) Substantiation: probable

6) Clinical Management: When [fluvoxamine](#) 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 [fluvoxamine](#) therapy is initiated or discontinued. Periodically reassess the prothrombin time ratio and INR in patients receiving [fluvoxamine](#) and [anticoagulant therapy](#)[113].

7) Probable Mechanism: unknown

8) Literature Reports

a) According to a retrospective cohort study (n=234), there was an increased risk of clinically relevant bleeding (hospital admission due to bleeding) in patients receiving [warfarin](#) for [atrial fibrillation](#) during concomitant SSRI therapy or within 2 weeks following SSRI therapy termination. Patients with a mean age of 72 +/- 7 years receiving [warfarin](#) plus SSRI (n=117) were matched with randomly selected patients who received [warfarin](#) only (n=117). SSRI included [fluoxetine](#), [citalopram](#), [paroxetine](#), [sertraline](#), [fluvoxamine](#), or escitalopram. Nine patients experienced 11 bleeding episodes during 213.9 treatment years in the [warfarin](#) plus SSRI group, and 10 patients experienced 14 bleedings during 586.4 treatment years in the warfarin-only group. The corresponding total incidences of bleedings were 51.4 and 23.9 per 1000 treatment years, respectively. The hazard ratio for first bleedings during treatment with [warfarin](#) plus SSRI was 3.49 (95% CI; 1.37 to 8.91, p=0.009) compared with [warfarin](#) only. The SSRI implicated in patients experiencing bleeding at the time of concomitant administration were [sertraline](#) or [citalopram](#). The addition of an SSRI was not associated with a change in [warfarin](#) dose or INR (p=0.48 and p=0.31 respectively). The results of the study may be limited by earlier bleeding events, unknown patient adherence, and exclusion of [clopidogrel](#), dipyridamol, corticosteroids and anticoagulants other than [warfarin](#) in the model [114].

b) A population-based, case-controlled study of new coumarin users (acenocoumarol and phenprocoumon) with concomitant selective serotonin reuptake inhibitors (SSRIs) resulted in an increased risk of hospitalization due to nongastrointestinal bleeding. Using national pharmacy and hospitalization records, Netherlands researchers identified 1848 cases that were admitted for abnormal bleeding and compared them with 5818 control subjects also taking coumarins. Median duration of treatment in patients was 220 days (range, 1 to 4690 days). Patients on SSRIs showed greater risk for hospitalization for nongastrointestinal bleeding (adjusted odds ratio (OR) 1.7, 95% confidence interval (CI), 1.1 to 2.5), however, the rate of [gastrointestinal bleeding](#) (adjusted OR 0.8, 95% CI, 0.4 to 1.5) was not significantly different [115].

c) A hospitalized 80-year-old female was started on intravenous [heparin](#) and oral [warfarin](#) therapy due to an [embolic stroke](#) secondary to [atrial fibrillation](#) and [mitral stenosis](#). Her [warfarin](#) dose was maintained at 1 mg daily, with her INR between 2.5 and 3. [Fluvoxamine](#) 25 mg daily was started for depression, and her [warfarin](#) dose was increased to 1.5 mg daily 3 days later due to worsening of the left [hemiparesis](#). Three days later, her INR was 9.96, and a repeat INR to rule out laboratory error was 11.3. [Warfarin](#) was discontinued, fresh frozen plasma was given, and [fluvoxamine](#) was discontinued. Six days later, [warfarin](#) was again started at 1 mg daily, and the INR increased over 4 days to 11.8. The elevated INR was attributed to the persisting effect of [fluvoxamine](#). She was eventually stabilized on [warfarin](#) 1 mg daily with INR values between 2 and 2.5 [116].

3.5.1.AZ| 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[114][115][113]. 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](#). In patients receiving [warfarin](#) and [fluvoxamine](#) concomitantly for 2 weeks, [warfarin](#) plasma concentrations increased by 98% and prothrombin times were prolonged. [Fluvoxamine](#) appears to inhibit several cytochrome P450 isoenzymes which may include 1A2 and 2C9 isozymes, which are responsible for [warfarin](#) metabolism [115][113].

3) Severity: major

4) Onset: delayed

5) Substantiation: probable

6) Clinical Management: When [fluvoxamine](#) 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 [fluvoxamine](#) therapy is initiated or discontinued. Periodically reassess the prothrombin time ratio and INR in patients receiving [fluvoxamine](#) and [anticoagulant therapy](#)[113].

7) Probable Mechanism: unknown

8) Literature Reports

a) According to a retrospective cohort study (n=234), there was an increased risk of clinically relevant bleeding (hospital admission due to bleeding) in patients receiving [warfarin](#) for [atrial fibrillation](#) during concomitant SSRI therapy or within 2 weeks following SSRI therapy termination. Patients with a mean age of 72 +/- 7 years receiving [warfarin](#) plus SSRI (n=117) were matched with randomly selected patients who received [warfarin](#) only (n=117). SSRI included [fluoxetine](#), [citalopram](#), [paroxetine](#), [sertraline](#), [fluvoxamine](#), or escitalopram. Nine patients experienced 11 bleeding episodes during 213.9 treatment years in the [warfarin](#) plus SSRI group, and 10 patients experienced 14 bleedings during 586.4 treatment years in the warfarin-only group. The corresponding total incidences of bleedings were 51.4 and 23.9 per 1000 treatment years, respectively. The hazard ratio for first bleedings during treatment with [warfarin](#) plus SSRI was 3.49 (95% CI; 1.37 to 8.91, p=0.009) compared with [warfarin](#) only. The SSRI implicated in patients experiencing bleeding at the time of concomitant administration were [sertraline](#) or [citalopram](#). The addition of an SSRI was not associated with a change in [warfarin](#) dose or INR (p=0.48 and p=0.31 respectively). The results of the study may be limited by earlier bleeding events, unknown patient adherence, and exclusion of [clopidogrel](#), dipyridamol, corticosteroids and anticoagulants other than [warfarin](#) in the model [114].

b) A population-based, case-controlled study of new coumarin users (acenocoumarol and phenprocoumon) with concomitant selective serotonin reuptake inhibitors (SSRIs) resulted in an increased risk of hospitalization due to nongastrointestinal bleeding. Using national pharmacy and hospitalization records, Netherlands researchers identified 1848 cases that were admitted for abnormal bleeding and compared them with 5818 control subjects also taking coumarins. Median duration of treatment in patients was 220 days (range, 1 to 4690 days). Patients on SSRIs showed greater risk for hospitalization for nongastrointestinal bleeding (adjusted odds ratio (OR) 1.7, 95% confidence interval (CI), 1.1 to 2.5), however, the rate of [gastrointestinal bleeding](#) (adjusted OR 0.8, 95% CI, 0.4 to 1.5) was not significantly different [115].

c) A hospitalized 80-year-old female was started on intravenous [heparin](#) and oral [warfarin](#) therapy due to an [embolic stroke](#) secondary to [atrial fibrillation](#) and [mitral stenosis](#). Her [warfarin](#) dose was maintained at 1 mg daily, with her INR between 2.5 and 3. [Fluvoxamine](#) 25 mg daily was started

for depression, and her [warfarin](#) dose was increased to 1.5 mg daily 3 days later due to worsening of the left [hemiparesis](#). Three days later, her INR was 9.96, and a repeat INR to rule out laboratory error was 11.3. [Warfarin](#) was discontinued, fresh frozen plasma was given, and [fluvoxamine](#) was discontinued. Six days later, [warfarin](#) was again started at 1 mg daily, and the INR increased over 4 days to 11.8. The elevated INR was attributed to the persisting effect of [fluvoxamine](#). She was eventually stabilized on [warfarin](#) 1 mg daily with INR values between 2 and 2.5 [116].

3.5.1.BA] 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](#) [272]. DHEA was also noted to cause mania in a patient with no previous personal or family history of [bipolar disorder](#) [273]. Elevated DHEA levels have been found in patients with mental disorders; DHEA suppression has led to improvement in psychotic symptoms [274]. DHEA possesses proserotonergic activity which may predispose patients to [manic episodes](#) [275]. DHEA is a precursor to androgenic steroids, which in high doses may precipitate mania [273]. 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](#) [271].

3.5.1.BB] 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 [114][115][113]. 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](#). In patients receiving

warfarin and **fluvoxamine** concomitantly for 2 weeks, **warfarin** plasma concentrations increased by 98% and prothrombin times were prolonged. **Fluvoxamine** appears to inhibit several cytochrome P450 isoenzymes which may include 1A2 and 2C9 isozymes, which are responsible for **warfarin** metabolism [115][113].

3) Severity: major

4) Onset: delayed

5) Substantiation: probable

6) Clinical Management: When **fluvoxamine** 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 **fluvoxamine** therapy is initiated or discontinued. Periodically reassess the prothrombin time ratio and INR in patients receiving **fluvoxamine** and **anticoagulant therapy**[113].

7) Probable Mechanism: unknown

8) Literature Reports

a) According to a retrospective cohort study (n=234), there was an increased risk of clinically relevant bleeding (hospital admission due to bleeding) in patients receiving **warfarin** for **atrial fibrillation** during concomitant SSRI therapy or within 2 weeks following SSRI therapy termination. Patients with a mean age of 72 +/- 7 years receiving **warfarin** plus SSRI (n=117) were matched with randomly selected patients who received **warfarin** only (n=117). SSRI included **fluoxetine**, **citalopram**, **paroxetine**, **sertraline**, **fluvoxamine**, or escitalopram. Nine patients experienced 11 bleeding episodes during 213.9 treatment years in the **warfarin** plus SSRI group, and 10 patients experienced 14 bleedings during 586.4 treatment years in the warfarin-only group. The corresponding total incidences of bleedings were 51.4 and 23.9 per 1000 treatment years, respectively. The hazard ratio for first bleedings during treatment with **warfarin** plus SSRI was 3.49 (95% CI; 1.37 to 8.91, p=0.009) compared with **warfarin** only. The SSRI implicated in patients experiencing bleeding at the time of concomitant administration were **sertraline** or **citalopram**. The addition of an SSRI was not associated with a change in **warfarin** dose or INR (p=0.48 and p=0.31 respectively). The results of the study may be limited by earlier bleeding events, unknown patient adherence, and exclusion of **clopidogrel**, dipyridamol, corticosteroids and anticoagulants other than **warfarin** in the model [114].

b) A population-based, case-controlled study of new coumarin users (acenocoumarol and phenprocoumon) with concomitant selective serotonin reuptake inhibitors (SSRIs) resulted in an increased risk of hospitalization due to nongastrointestinal bleeding. Using national pharmacy and hospitalization records, Netherlands researchers identified 1848 cases that were admitted for abnormal bleeding and compared them with 5818 control subjects also taking coumarins. Median duration of treatment in patients was 220 days (range, 1 to 4690 days). Patients on SSRIs showed greater risk for hospitalization for nongastrointestinal bleeding (adjusted odds ratio (OR) 1.7, 95% confidence interval (CI), 1.1 to 2.5), however, the rate of **gastrointestinal bleeding** (adjusted OR 0.8, 95% CI, 0.4 to 1.5) was not significantly different [115].

c) A hospitalized 80-year-old female was started on intravenous **heparin** and oral **warfarin** therapy due to an **embolic stroke** secondary to **atrial fibrillation** and **mitral stenosis**. Her **warfarin** dose was maintained at 1 mg daily, with her INR between 2.5 and 3. **Fluvoxamine** 25 mg daily was started for depression, and her **warfarin** dose was increased to 1.5 mg daily 3 days later due to worsening of the left **hemiparesis**. Three days later, her INR was 9.96, and a repeat INR to rule out laboratory error was 11.3. **Warfarin** was discontinued, fresh frozen plasma was given, and **fluvoxamine** was discontinued. Six days later, **warfarin** was again started at 1 mg daily, and the INR increased over

4 days to 11.8. The elevated INR was attributed to the persisting effect of [fluvoxamine](#). She was eventually stabilized on [warfarin](#) 1 mg daily with INR values between 2 and 2.5 [116].

3.5.1.BC] [Desipramine](#)

- 1) Interaction Effect: [desipramine](#) toxicity (dry mouth, urinary retention, sedation)
- 2) Summary: While an early report on [fluvoxamine](#) combined with [desipramine](#) or [imipramine](#) found increased TCA concentrations[110], later studies by the same investigators reported that [fluvoxamine](#) caused no significant alterations in [desipramine](#) pharmacokinetics [111][112].
- 3) Severity: minor
- 4) Onset: delayed
- 5) Substantiation: theoretical
- 6) Clinical Management: Monitor patients for signs of [desipramine](#) and [fluvoxamine](#) toxicity; lower doses of one or both agents may be required with concomitant therapy.
- 7) Probable Mechanism: decreased [desipramine](#) metabolism
- 8) Literature Reports

a) The addition of [fluvoxamine](#) to [imipramine](#) or [desipramine](#) in four patients was reported to result in greatly increased tricyclic antidepressant plasma levels [107]. Three of the four patients showed signs of tricyclic toxicity.

b) A controlled study in eight depressed patients found a slight, but insignificant, increase in [desipramine](#) concentrations, after 10 days, when [fluvoxamine](#) was added to [desipramine](#) therapy [108].

c) A [pharmacokinetic study](#) in 12 healthy volunteers reviewed concurrent use of [desipramine](#) and [fluvoxamine](#) [109]. No significant alterations in the pharmacokinetics of either drug were found.

3.5.1.BD] [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[114][115][113]. 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](#). In patients receiving [warfarin](#) and [fluvoxamine](#) concomitantly for 2 weeks, [warfarin](#) plasma concentrations increased by 98% and prothrombin times were prolonged. [Fluvoxamine](#) appears to inhibit several cytochrome P450 isoenzymes which may include 1A2 and 2C9 isozymes, which are responsible for [warfarin](#) metabolism [115][113].
- 3) Severity: major
- 4) Onset: delayed
- 5) Substantiation: probable
- 6) Clinical Management: When [fluvoxamine](#) 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 [fluvoxamine](#) therapy is initiated or discontinued. Periodically reassess the prothrombin time ratio and INR in patients receiving [fluvoxamine](#) and [anticoagulant therapy](#)[113].
- 7) Probable Mechanism: unknown
- 8) Literature Reports

a) According to a retrospective cohort study (n=234), there was an increased risk of clinically relevant bleeding (hospital admission due to bleeding) in patients receiving [warfarin](#) for [atrial fibrillation](#) during concomitant SSRI therapy or within 2 weeks following SSRI therapy termination. Patients with a mean age of 72 +/- 7 years receiving [warfarin](#) plus SSRI (n=117) were matched with randomly selected patients who received [warfarin](#) only (n=117). SSRI included [fluoxetine](#), [citalopram](#), [paroxetine](#), [sertraline](#), [fluvoxamine](#), or escitalopram. Nine patients experienced 11 bleeding episodes during 213.9 treatment years in the [warfarin](#) plus SSRI group, and 10 patients experienced 14 bleedings during 586.4 treatment years in the warfarin-only group. The corresponding total incidences of bleedings were 51.4 and 23.9 per 1000 treatment years, respectively. The hazard ratio for first bleedings during treatment with [warfarin](#) plus SSRI was 3.49 (95% CI; 1.37 to 8.91, p=0.009) compared with [warfarin](#) only. The SSRI implicated in patients experiencing bleeding at the time of concomitant administration were [sertraline](#) or [citalopram](#). The addition of an SSRI was not associated with a change in [warfarin](#) dose or INR (p=0.48 and p=0.31 respectively). The results of the study may be limited by earlier bleeding events, unknown patient adherence, and exclusion of [clopidogrel](#), dipyridamol, corticosteroids and anticoagulants other than [warfarin](#) in the model [114].

b) A population-based, case-controlled study of new coumarin users (acenocoumarol and phenprocoumon) with concomitant selective serotonin reuptake inhibitors (SSRIs) resulted in an increased risk of hospitalization due to nongastrointestinal bleeding. Using national pharmacy and hospitalization records, Netherlands researchers identified 1848 cases that were admitted for abnormal bleeding and compared them with 5818 control subjects also taking coumarins. Median duration of treatment in patients was 220 days (range, 1 to 4690 days). Patients on SSRIs showed greater risk for hospitalization for nongastrointestinal bleeding (adjusted odds ratio (OR) 1.7, 95% confidence interval (CI), 1.1 to 2.5), however, the rate of [gastrointestinal bleeding](#) (adjusted OR 0.8, 95% CI, 0.4 to 1.5) was not significantly different [115].

c) A hospitalized 80-year-old female was started on intravenous [heparin](#) and oral [warfarin](#) therapy due to an [embolic stroke](#) secondary to [atrial fibrillation](#) and [mitral stenosis](#). Her [warfarin](#) dose was maintained at 1 mg daily, with her INR between 2.5 and 3. [Fluvoxamine](#) 25 mg daily was started for depression, and her [warfarin](#) dose was increased to 1.5 mg daily 3 days later due to worsening of the left [hemiparesis](#). Three days later, her INR was 9.96, and a repeat INR to rule out laboratory error was 11.3. [Warfarin](#) was discontinued, fresh frozen plasma was given, and [fluvoxamine](#) was discontinued. Six days later, [warfarin](#) was again started at 1 mg daily, and the INR increased over 4 days to 11.8. The elevated INR was attributed to the persisting effect of [fluvoxamine](#). She was eventually stabilized on [warfarin](#) 1 mg daily with INR values between 2 and 2.5 [116].

3.5.1.BE] Desvenlafaxine

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

2) Summary: Desvenlafaxine is a serotonergic drug; concomitant use with another agent that affects the serotonergic neurotransmitter system may result in an increased risk of [serotonin syndrome](#) and should be approached with extreme caution. [Serotonin syndrome](#) may be life-threatening. 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 treatment initiation and dose increases of either drug. If [serotonin syndrome](#) develops, discontinue both agents and initiate supportive symptomatic therapy[231].

- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Use extreme caution with coadministration of desvenlafaxine 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. Immediate discontinuation of both agents and supportive symptomatic treatment is warranted if [serotonin syndrome](#) develops[231].
- 7) Probable Mechanism: additive serotonergic effect

3.5.1.BF] 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 [fluvoxamine](#), has the potential to cause [serotonin syndrome](#)[290]. [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 [291]. Dexfenfluramine should not be used in combination with [fluvoxamine](#) [292].
- 3) Severity: major
- 4) Onset: rapid
- 5) Substantiation: theoretical
- 6) Clinical Management: Concurrent use of dexfenfluramine and [fluvoxamine](#) 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 [fluvoxamine](#) or other serotonin specific reuptake inhibitors.
- 7) Probable Mechanism: additive serotonergic effects

3.5.1.BG] Dexibuprofen

- 1) Interaction Effect: an increased risk of bleeding
- 2) Summary: Caution is recommended with the concomitant use of NSAIDs and antidepressants, including SSRIs due to an increased risk of [intracranial hemorrhage](#)[367] and [gastrointestinal bleeding](#) [371][372][368][369]. Bleeding events have included [epistaxis](#), ecchymosis, [hematoma](#), [petechiae](#), and life-threatening hemorrhages [374][373][375][376]. When an SSRI and an NSAID are given concurrently, monitor the patient for signs of increased bleeding.
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: established
- 6) Clinical Management: Use caution if NSAIDs and SSRIs are coadministered. Concomitant use of NSAIDs and SSRIs may cause an increased risk of [intracranial hemorrhage](#)[367] and [gastrointestinal bleeding](#) [368][369]. When an SSRI and an NSAID are given concurrently, monitor the patient for signs of increased bleeding.
- 7) Probable Mechanism: depletion of [platelet](#) serotonin by SSRI; additive effects
- 8) Literature Reports
 - a) Concomitant use of NSAIDs and antidepressants, including tricyclic antidepressants, SSRIs, serotonin-norepinephrine reuptake inhibitors, and MAOIs, resulted in a 60% increased risk

of [intracranial hemorrhage](#) within 30 days of concomitant use compared with antidepressant use alone. There was no significant difference between the antidepressant drug classes and the increased risk; however, there was an increased risk associated with male patients compared with female patients [367].

b) 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. Combined use of an SSRI and NSAIDs or low-dose [aspirin](#) increased the risk to 12.2 and 5.2 times, 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 [370].

c) Two metaanalyses of incidents of upper GI bleed due to SSRIs, NSAIDs, and their combination found that SSRIs increased the risk by 1.73 [371] to 2.36 times [372], NSAIDs by 2.55 times [371], and the combination of SSRIs and NSAIDs by 4.02 [371] to 6.33 times [372].

d) The release of serotonin by [platelets](#) is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs and NSAIDs have been associated with an increased risk of bleeding [373].

3.5.1.BH] Dexketoprofen

1) Interaction Effect: an increased risk of bleeding

2) Summary: Caution is recommended with the concomitant use of NSAIDs and antidepressants, including SSRIs due to an increased risk of [intracranial hemorrhage](#)[367] and [gastrointestinal bleeding](#) [371][372][368][369]. Bleeding events have included [epistaxis](#), ecchymosis, [hematoma](#), [petechiae](#), and life-threatening hemorrhages [374][373][375][376]. When an SSRI and an NSAID are given concurrently, monitor the patient for signs of increased bleeding.

3) Severity: major

4) Onset: unspecified

5) Substantiation: established

6) Clinical Management: Use caution if NSAIDs and SSRIs are coadministered. Concomitant use of NSAIDs and SSRIs may cause an increased risk of [intracranial hemorrhage](#)[367] and [gastrointestinal bleeding](#) [368][369]. When an SSRI and an NSAID are given concurrently, monitor the patient for signs of increased bleeding.

7) Probable Mechanism: depletion of [platelet](#) serotonin by SSRI; additive effects

8) Literature Reports

a) Concomitant use of NSAIDs and antidepressants, including tricyclic antidepressants, SSRIs, serotonin-norepinephrine reuptake inhibitors, and MAOIs, resulted in a 60% increased risk of [intracranial hemorrhage](#) within 30 days of concomitant use compared with antidepressant use alone. There was no significant difference between the antidepressant drug classes and the increased risk; however, there was an increased risk associated with male patients compared with female patients [367].

b) 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. Combined use of an SSRI and NSAIDs or low-dose [aspirin](#) increased the risk to 12.2 and 5.2 times, 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 [370].

c) Two metaanalyses of incidents of upper GI bleed due to SSRIs, NSAIDs, and their combination found that SSRIs increased the risk by 1.73 [371] to 2.36 times [372], NSAIDs by 2.55 times [371], and the combination of SSRIs and NSAIDs by 4.02 [371] to 6.33 times [372].

d) The release of serotonin by [platelets](#) is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs and NSAIDs have been associated with an increased risk of bleeding [373].

3.5.1.BI] [Dextroamphetamine](#)

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

2) Summary: Coadministration of an [amphetamine](#) and a serotonergic agent that inhibits CYP2D6 may result in increased [amphetamine](#) exposure and additional risk for [serotonin syndrome](#). If concomitant use of an [amphetamine](#) and such an agent is clinically required, initiate with lower doses and monitor patients carefully, especially during treatment initiation and dosage adjustment. Discontinue both drugs if [serotonin syndrome](#) is suspected[377].

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Coadministration of an [amphetamine](#) and another serotonergic agent may result in [serotonin syndrome](#), because both drugs affect the serotonergic neurotransmitter system. Additionally, coadministration of an [amphetamine](#) with a CYP2D6 inhibitor may increase [amphetamine](#) exposure, because [amphetamines](#) and their derivatives are metabolized to some degree by CYP2D6. An increase in [amphetamine](#) exposure may further increase risk of [serotonin syndrome](#). If concomitant use of an [amphetamine](#) and a serotonergic agent that inhibits CYP2D6 is clinically required, initiate with lower doses and monitor patients carefully, especially during treatment initiation and dosage adjustment. Discontinue both drugs if [serotonin syndrome](#) is suspected[377].

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

3.5.1.BJ] [Dextromethorphan](#)

1) Interaction Effect: increased [dextromethorphan](#) plasma concentrations and increased risk of [serotonin syndrome](#)

2) Summary: [Fluvoxamine](#) is a weak CYP2D6 inhibitor[137] and [dextromethorphan](#) is a CYP2D6 substrate. While not specifically studied with [fluvoxamine](#), the concomitant use of [paroxetine](#) (another SSRI) with the combination of [dextromethorphan/quinidine](#) in one study resulted in increased AUC and Cmax of [paroxetine](#), [dextromethorphan](#), and [quinidine](#). As the concomitant use of [dextromethorphan](#) with [fluvoxamine](#) may increase the risk of [serotonin syndrome](#), initial dose reductions of [dextromethorphan](#) may be warranted [399] along with monitoring for signs/symptoms of [serotonin syndrome](#) (eg, altered mental status, [hypertension](#), restlessness, myoclonus, [hyperthermia](#), hyperreflexia, diaphoresis, shivering, and tremor).

3) Severity: major

4) Onset: delayed

5) Substantiation: theoretical

6) Clinical Management: Use caution when prescribing [dextromethorphan](#) to patients who are taking an SSRI (such as [fluvoxamine](#)), as concomitant use may result in an increased risk of [serotonin syndrome](#). Initial dose reductions of [dextromethorphan](#) may be warranted when administered with CYP2D6 inhibitors, such as [fluvoxamine](#)[399].

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

8) Literature Reports

a) In a group of 14 healthy subjects, the administration of [paroxetine](#) (20 mg once daily for 12 days) followed by a combination of [dextromethorphan](#) 30 mg/[quinidine](#) 30 mg (twice daily for 8 days) resulted in an increase in [paroxetine](#) AUC and C_{max} (1.7- and 1.5-fold, respectively) and a decrease in dextromethorphan AUC and C_{max} (34% and 33%, respectively). The [dextromethorphan/quinidine](#) exposure did not change significantly. In a second group of 13 healthy subjects, the administration of [dextromethorphan](#) 30 mg/[quinidine](#) 30 mg (twice daily for 8 days) followed by [paroxetine](#) (20 mg once daily for 12 days) resulted in an increase in [dextromethorphan](#) AUC and C_{max} (1.5- and 1.4-fold, respectively), a decrease in dextromethorphan AUC and C_{max} (14% and 18%, respectively) an increase in [quinidine](#) AUC and C_{max} (1.4- and 1.3-fold, respectively), and an increase in [paroxetine](#) AUC and C_{max} (2.3- and 2-fold, respectively) [399].

3.5.1.BK] [Diazepam](#)

1) Interaction Effect: [diazepam](#) and N-desmethyldiazepam accumulation

2) Summary: Coadministration of [fluvoxamine](#) 150 mg daily with a single oral dose of [diazepam](#) 10 mg resulted in a 65% decrease in clearance of [diazepam](#). The clearance of [diazepam's](#) primary active metabolite, N-desmethyldiazepam, is reduced to immeasurable levels. This effect may be more pronounced with increasing doses of [fluvoxamine](#)[293].

3) Severity: moderate

4) Onset: delayed

5) Substantiation: probable

6) Clinical Management: [Diazepam](#) and [fluvoxamine](#) should not be taken concurrently due to the possibility of significant [diazepam](#) accumulation. Consider switching to a benzodiazepine eliminated by glucuronidation (eg, [lorazepam](#), [oxazepam](#), [temazepam](#)) and monitor for signs of benzodiazepine intoxication (eg, sedation, dizziness, ataxia, weakness, decreased cognition or motor performance).

7) Probable Mechanism: reduced [diazepam](#) clearance

3.5.1.BL] [Diclofenac](#)

1) Interaction Effect: an increased risk of bleeding

2) Summary: Caution is recommended with the concomitant use of NSAIDs and antidepressants, including SSRIs due to an increased risk of [intracranial hemorrhage](#)[367] and [gastrointestinal bleeding](#) [371][372][368][369]. Bleeding events have included [epistaxis](#), ecchymosis, [hematoma](#), [petechiae](#), and life-threatening hemorrhages [374][373][375][376]. When an SSRI and an NSAID are given concurrently, monitor the patient for signs of increased bleeding.

3) Severity: major

4) Onset: unspecified

5) Substantiation: established

6) Clinical Management: Use caution if NSAIDs and SSRIs are coadministered. Concomitant use of NSAIDs and SSRIs may cause an increased risk of [intracranial hemorrhage](#)[367] and [gastrointestinal bleeding](#) [368][369]. When an SSRI and an NSAID are given concurrently, monitor the patient for signs of increased bleeding.

7) Probable Mechanism: depletion of [platelet](#) serotonin by SSRI; additive effects

8) Literature Reports

a) Concomitant use of NSAIDs and antidepressants, including tricyclic antidepressants, SSRIs, serotonin-norepinephrine reuptake inhibitors, and MAOIs, resulted in a 60% increased risk of **intracranial hemorrhage** within 30 days of concomitant use compared with antidepressant use alone. There was no significant difference between the antidepressant drug classes and the increased risk; however, there was an increased risk associated with male patients compared with female patients [367].

b) 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. Combined use of an SSRI and NSAIDs or low-dose **aspirin** increased the risk to 12.2 and 5.2 times, 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 [370].

c) Two metaanalyses of incidents of upper GI bleed due to SSRIs, NSAIDs, and their combination found that SSRIs increased the risk by 1.73 [371] to 2.36 times [372], NSAIDs by 2.55 times [371], and the combination of SSRIs and NSAIDs by 4.02 [371] to 6.33 times [372].

d) The release of serotonin by **platelets** is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs and NSAIDs have been associated with an increased risk of bleeding [373].

3.5.1.BM] 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[114][115][113]. 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**. In patients receiving **warfarin** and **fluvoxamine** concomitantly for 2 weeks, **warfarin** plasma concentrations increased by 98% and prothrombin times were prolonged. **Fluvoxamine** appears to inhibit several cytochrome P450 isoenzymes which may include 1A2 and 2C9 isozymes, which are responsible for **warfarin** metabolism [115][113].

3) Severity: major

4) Onset: delayed

5) Substantiation: probable

6) Clinical Management: When **fluvoxamine** 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 **fluvoxamine** therapy is initiated or discontinued. Periodically reassess the prothrombin time ratio and INR in patients receiving **fluvoxamine** and **anticoagulant therapy**[113].

7) Probable Mechanism: unknown

8) Literature Reports

a) According to a retrospective cohort study (n=234), there was an increased risk of clinically relevant bleeding (hospital admission due to bleeding) in patients receiving **warfarin** for **atrial**

fibrillation during concomitant SSRI therapy or within 2 weeks following SSRI therapy termination. Patients with a mean age of 72 +/- 7 years receiving **warfarin** plus SSRI (n=117) were matched with randomly selected patients who received **warfarin** only (n=117). SSRI included **fluoxetine**, **citalopram**, **paroxetine**, **sertraline**, **fluvoxamine**, or escitalopram. Nine patients experienced 11 bleeding episodes during 213.9 treatment years in the **warfarin** plus SSRI group, and 10 patients experienced 14 bleedings during 586.4 treatment years in the warfarin-only group. The corresponding total incidences of bleedings were 51.4 and 23.9 per 1000 treatment years, respectively. The hazard ratio for first bleedings during treatment with **warfarin** plus SSRI was 3.49 (95% CI; 1.37 to 8.91, p=0.009) compared with **warfarin** only. The SSRI implicated in patients experiencing bleeding at the time of concomitant administration were **sertraline** or **citalopram**. The addition of an SSRI was not associated with a change in **warfarin** dose or INR (p=0.48 and p=0.31 respectively). The results of the study may be limited by earlier bleeding events, unknown patient adherence, and exclusion of **clopidogrel**, dipyridamol, corticosteroids and anticoagulants other than **warfarin** in the model [114].

b) A population-based, case-controlled study of new coumarin users (acenocoumarol and phenprocoumon) with concomitant selective serotonin reuptake inhibitors (SSRIs) resulted in an increased risk of hospitalization due to nongastrointestinal bleeding. Using national pharmacy and hospitalization records, Netherlands researchers identified 1848 cases that were admitted for abnormal bleeding and compared them with 5818 control subjects also taking coumarins. Median duration of treatment in patients was 220 days (range, 1 to 4690 days). Patients on SSRIs showed greater risk for hospitalization for nongastrointestinal bleeding (adjusted odds ratio (OR) 1.7, 95% confidence interval (CI), 1.1 to 2.5), however, the rate of **gastrointestinal bleeding** (adjusted OR 0.8, 95% CI, 0.4 to 1.5) was not significantly different [115].

c) A hospitalized 80-year-old female was started on intravenous **heparin** and oral **warfarin** therapy due to an **embolic stroke** secondary to **atrial fibrillation** and **mitral stenosis**. Her **warfarin** dose was maintained at 1 mg daily, with her INR between 2.5 and 3. **Fluvoxamine** 25 mg daily was started for depression, and her **warfarin** dose was increased to 1.5 mg daily 3 days later due to worsening of the left **hemiparesis**. Three days later, her INR was 9.96, and a repeat INR to rule out laboratory error was 11.3. **Warfarin** was discontinued, fresh frozen plasma was given, and **fluvoxamine** was discontinued. Six days later, **warfarin** was again started at 1 mg daily, and the INR increased over 4 days to 11.8. The elevated INR was attributed to the persisting effect of **fluvoxamine**. She was eventually stabilized on **warfarin** 1 mg daily with INR values between 2 and 2.5 [116].

3.5.1.BN] **Diflunisal**

1) Interaction Effect: an increased risk of bleeding

2) Summary: Caution is recommended with the concomitant use of NSAIDs and antidepressants, including SSRIs due to an increased risk of **intracranial hemorrhage**[367] and **gastrointestinal bleeding** [371][372][368][369]. Bleeding events have included **epistaxis**, ecchymosis, **hematoma**, **petechiae**, and life-threatening hemorrhages [374][373][375][376]. When an SSRI and an NSAID are given concurrently, monitor the patient for signs of increased bleeding.

3) Severity: major

4) Onset: unspecified

5) Substantiation: established

6) Clinical Management: Use caution if NSAIDs and SSRIs are coadministered. Concomitant use of NSAIDs and SSRIs may cause an increased risk of **intracranial hemorrhage**[367] and **gastrointestinal bleeding** [368][369]. When an SSRI and an NSAID are given concurrently, monitor the patient for signs of increased bleeding.

7j) Probable Mechanism: depletion of [platelet](#) serotonin by SSRI; additive effects

8j) Literature Reports

a) Concomitant use of NSAIDs and antidepressants, including tricyclic antidepressants, SSRIs, serotonin-norepinephrine reuptake inhibitors, and MAOIs, resulted in a 60% increased risk of [intracranial hemorrhage](#) within 30 days of concomitant use compared with antidepressant use alone. There was no significant difference between the antidepressant drug classes and the increased risk; however, there was an increased risk associated with male patients compared with female patients [367].

b) 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. Combined use of an SSRI and NSAIDs or low-dose [aspirin](#) increased the risk to 12.2 and 5.2 times, 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 [370].

c) Two metaanalyses of incidents of upper GI bleed due to SSRIs, NSAIDs, and their combination found that SSRIs increased the risk by 1.73 [371] to 2.36 times [372], NSAIDs by 2.55 times [371], and the combination of SSRIs and NSAIDs by 4.02 [371] to 6.33 times [372].

d) The release of serotonin by [platelets](#) is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs and NSAIDs have been associated with an increased risk of bleeding [373].

3.5.1.BO| [Dihydroergotamine](#)

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

2j) Summary: Concomitant use of [fluvoxamine](#), a less potent 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 [fluvoxamine](#) and ergot derivatives[122][123].

3j) Severity: major

4j) Onset: unspecified

5j) Substantiation: theoretical

6j) Clinical Management: [Fluvoxamine](#) may increase the plasma concentrations of ergot derivatives. Use caution when [fluvoxamine](#) is coadministered with an ergot derivative, such as [dihydroergotamine](#), [ergotamine](#), or [methylergonovine](#), due to the potential for serious toxicity including [vasospasm](#) that can occur[122][123].

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

3.5.1.BP| [Diltiazem](#)

1j) Interaction Effect: bradycardia

2j) Summary: [Fluvoxamine](#) may inhibit the metabolism of [diltiazem](#), causing elevated [diltiazem](#) levels and bradycardia[217].

3j) Severity: minor

4j) Onset: rapid

- 5) Substantiation: theoretical
- 6) Clinical Management: Monitor patients for appropriate cardiovascular response to [calcium](#) channel blockade, with dose titration as required to achieve desired effect.
- 7) Probable Mechanism: decreased [diltiazem](#) metabolism

3.5.1.BQ| [Dipyridamole](#)

- 1) Interaction Effect: increased risk of bleeding
- 2) Summary: Exercise caution when coadministering a SSRI and an antiplatelet agent as this may increase the risk of bleeding events[139][138].[137]. Bleeding events reported have included [epistaxis](#), ecchymosis, [hematoma](#), [petechiae](#), and life-threatening hemorrhages. Monitor patient for signs of increased bleeding when [fluvoxamine](#) is administered with an antiplatelet agent concomitantly [137].
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: When [fluvoxamine](#) and an antiplatelet agent are given concurrently, monitor patient for signs of increased bleeding[137].
- 7) Probable Mechanism: unknown
- 8) Literature Reports

a) In a retrospective study of patients over 50 years of age with the diagnosis of acute [myocardial infarction](#) (N=27,058), SSRI use with any antiplatelet therapy significantly increased the risk of bleeding by 1.42-fold compared with [aspirin](#) use alone. Therapy with [aspirin](#), [clopidogrel](#), and an SSRI significantly increased risk by 2.35-fold compared with [aspirin](#) use alone and by 1.57-fold compared with [clopidogrel](#) and [aspirin](#) combination therapy [138].

b) In a systematic review and meta-analysis of 22 observational studies, SSRI use was associated with a significant 1.55 fold increase in risk of [upper gastrointestinal bleeding](#) (UGIB). Concomitant use of SSRIs and antiplatelet drugs was associated with a 2.48-fold increase in risk of UGIB (3 studies) [139].

3.5.1.BR| [Dipyrrone](#)

- 1) Interaction Effect: an increased risk of bleeding
- 2) Summary: Caution is recommended with the concomitant use of NSAIDs and antidepressants, including SSRIs due to an increased risk of [intracranial hemorrhage](#)[367] and [gastrointestinal bleeding](#) [371][372][368][369]. Bleeding events have included [epistaxis](#), ecchymosis, [hematoma](#), [petechiae](#), and life-threatening hemorrhages [374][373][375][376]. When an SSRI and an NSAID are given concurrently, monitor the patient for signs of increased bleeding.
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: established
- 6) Clinical Management: Use caution if NSAIDs and SSRIs are coadministered. Concomitant use of NSAIDs and SSRIs may cause an increased risk of [intracranial hemorrhage](#)[367] and [gastrointestinal bleeding](#) [368][369]. When an SSRI and an NSAID are given concurrently, monitor the patient for signs of increased bleeding.
- 7) Probable Mechanism: depletion of [platelet](#) serotonin by SSRI; additive effects
- 8) Literature Reports

a) Concomitant use of NSAIDs and antidepressants, including tricyclic antidepressants, SSRIs, serotonin-norepinephrine reuptake inhibitors, and MAOIs, resulted in a 60% increased risk

of [intracranial hemorrhage](#) within 30 days of concomitant use compared with antidepressant use alone. There was no significant difference between the antidepressant drug classes and the increased risk; however, there was an increased risk associated with male patients compared with female patients [367].

b) 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. Combined use of an SSRI and NSAIDs or low-dose [aspirin](#) increased the risk to 12.2 and 5.2 times, 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 [370].

c) Two metaanalyses of incidents of upper GI bleed due to SSRIs, NSAIDs, and their combination found that SSRIs increased the risk by 1.73 [371] to 2.36 times [372], NSAIDs by 2.55 times [371], and the combination of SSRIs and NSAIDs by 4.02 [371] to 6.33 times [372].

d) The release of serotonin by [platelets](#) is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs and NSAIDs have been associated with an increased risk of bleeding [373].

3.5.1.BS] [Dolasetron](#)

- 1) Interaction Effect: increased risk of [serotonin syndrome](#)
- 2) Summary: Concomitant use of [dolasetron](#) with a serotonergic agent may increase the risk of [serotonin syndrome](#). Monitor for the emergence of [serotonin syndrome](#). Discontinue treatment with [dolasetron](#) and institute supportive therapy if symptoms of [serotonin syndrome](#) occur[189][190].
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Concomitant use of [dolasetron](#) with a serotonergic agent may increase the risk of [serotonin syndrome](#). Monitor for the emergence of [serotonin syndrome](#). Discontinue treatment with [dolasetron](#) and institute supportive therapy if symptoms of [serotonin syndrome](#) occur[189][190].
- 7) Probable Mechanism: unknown

3.5.1.BT] [Domperidone](#)

- 1) Interaction Effect: increased domperidone exposure and an increased risk of QT prolongation
- 2) Summary: Coadministration of [fluvoxamine](#), a potential CYP3A4 inhibitor[40], with domperidone may result in increased plasma concentrations of domperidone and may have an effect on QT interval prolongation. Concomitant use of domperidone and [fluvoxamine](#) 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 [339].
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical

6) Clinical Management: Use caution with the concomitant administration of domperidone and [fluvoxamine](#) 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[339].

7) Probable Mechanism: inhibition of CYP3A4-mediated domperidone metabolism

3.5.1.BU] [Donepezil](#)

1) Interaction Effect: increased [donepezil](#) exposure and increased risk of seizure

2) Summary: Concomitant use of [donepezil](#) (a CYP2D6 substrate) with a CYP2D6 inhibitor may increase exposure of [donepezil](#). Additionally both drugs have been associated with lowering the seizure threshold[281]. If coadministered, monitor for donepezil-associated adverse events, including seizures.

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Concomitant use of [donepezil](#) (a CYP2D6 substrate) with a CYP2D6 inhibitor may increase exposure of [donepezil](#). Additionally both drugs have been associated with lowering the seizure threshold[281]. If coadministered, monitor for donepezil-associated adverse events, including seizures.

7) Probable Mechanism: inhibition of CYP2D6-mediated metabolism of [donepezil](#); additive seizure threshold lowering effects

3.5.1.BV] [Doxorubicin](#)

1) Interaction Effect: increased [DOXOrubicin](#) exposure

2) Summary: Avoid concurrent use of [DOXOrubicin](#), a CYP2D6 substrate, with CYP2D6 inhibitors, as increased [DOXOrubicin](#) plasma concentrations may occur[208]. Although no formal drug interaction studies have been done with [DOXOrubicin hydrochloride liposome](#) injection, it may interact with drugs known to interact with the conventional formulation of [DOXOrubicin](#) [209].

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Avoid concurrent use of [DOXOrubicin](#) with CYP2D6 inhibitors, as increased [DOXOrubicin](#) plasma concentrations may result[208].

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

3.5.1.BW] [Doxorubicin Hydrochloride Liposome](#)

1) Interaction Effect: increased [DOXOrubicin](#) exposure

2) Summary: Avoid concurrent use of [DOXOrubicin](#), a CYP2D6 substrate, with CYP2D6 inhibitors, as increased [DOXOrubicin](#) plasma concentrations may occur[208]. Although no formal drug interaction studies have been done with [DOXOrubicin hydrochloride liposome](#) injection, it may interact with drugs known to interact with the conventional formulation of [DOXOrubicin](#) [209].

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Avoid concurrent use of [DOXOrubicin](#) with CYP2D6 inhibitors, as increased [DOXOrubicin](#) plasma concentrations may result[208].

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

3.5.1.BX] Droperidol

- 1) Interaction Effect: an increased risk of [cardiotoxicity](#) (QT prolongation, [torsades de pointes](#), [cardiac arrest](#))
- 2) Summary: Any drug known to have the potential to prolong the QT interval should not be used together with [droperidol](#). Possible pharmacodynamic interactions can occur between [droperidol](#) and potentially arrhythmogenic agents, such as certain antidepressants that prolong the QT interval. If concomitant use cannot be avoided, treatment should be undertaken with extreme caution and [ECG monitoring](#) (prior to treatment and 2 to 3 hours after completing treatment) should be implemented[211].
- 3) Severity: major
- 4) Onset: rapid
- 5) Substantiation: theoretical
- 6) Clinical Management: Concomitant use of [droperidol](#) and other QT prolonging drugs, such as certain antidepressants, is not recommended. If concomitant use cannot be avoided, [droperidol](#) should be administered with extreme caution and [ECG monitoring](#) (prior to treatment and 2 to 3 hours after treatment is complete) is recommended[211].
- 7) Probable Mechanism: additive cardiac effects

3.5.1.BY] Droxidol

- 1) Interaction Effect: an increased risk of bleeding
- 2) Summary: Caution is recommended with the concomitant use of NSAIDs and antidepressants, including SSRIs due to an increased risk of [intracranial hemorrhage](#)[367] and [gastrointestinal bleeding](#) [371][372][368][369]. Bleeding events have included [epistaxis](#), ecchymosis, [hematoma](#), [petechiae](#), and life-threatening hemorrhages [374][373][375][376]. When an SSRI and an NSAID are given concurrently, monitor the patient for signs of increased bleeding.
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: established
- 6) Clinical Management: Use caution if NSAIDs and SSRIs are coadministered. Concomitant use of NSAIDs and SSRIs may cause an increased risk of [intracranial hemorrhage](#)[367] and [gastrointestinal bleeding](#) [368][369]. When an SSRI and an NSAID are given concurrently, monitor the patient for signs of increased bleeding.
- 7) Probable Mechanism: depletion of [platelet](#) serotonin by SSRI; additive effects
- 8) Literature Reports

a) Concomitant use of NSAIDs and antidepressants, including tricyclic antidepressants, SSRIs, serotonin-norepinephrine reuptake inhibitors, and MAOIs, resulted in a 60% increased risk of [intracranial hemorrhage](#) within 30 days of concomitant use compared with antidepressant use alone. There was no significant difference between the antidepressant drug classes and the increased risk; however, there was an increased risk associated with male patients compared with female patients [367].

b) 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. Combined use of an SSRI and NSAIDs or low-dose [aspirin](#) increased the risk to 12.2 and 5.2 times, 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 [370].

c) Two metaanalyses of incidents of upper GI bleed due to SSRIs, NSAIDs, and their combination found that SSRIs increased the risk by 1.73 [371] to 2.36 times [372], NSAIDs by 2.55 times [371], and the combination of SSRIs and NSAIDs by 4.02 [371] to 6.33 times [372].

d) The release of serotonin by [platelets](#) is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs and NSAIDs have been associated with an increased risk of bleeding [373].

3.5.1.BZ] [Duloxetine](#)

1) Interaction Effect: increased [duloxetine](#) bioavailability and an increased risk of [serotonin syndrome](#)

2) Summary: [Duloxetine](#) is a selective serotonin and [norepinephrine](#) reuptake inhibitor (SSNRI) that is primarily metabolized by the CYP1A2 and CYP2D6 isozymes. The concomitant use of [duloxetine](#) with [fluvoxamine](#), a SSRI, is not recommended due to the potential for [serotonin syndrome](#). In addition, coadministration of [fluvoxamine](#) 100 mg (a CYP1A2 inhibitor) with [duloxetine](#) 40 mg twice a day in 14 CYP2D6 poor metabolizer subjects resulted in a 6-fold increase in [duloxetine](#) AUC and Cmax. Also, when 14 male patients were given [duloxetine](#) 60 mg together with [fluvoxamine](#) 100 mg, [duloxetine](#) AUC, Cmax, and half-life increased by 6-fold, about 2.5-fold, and 3-fold, respectively[343].

3) Severity: major

4) Onset: unspecified

5) Substantiation: established

6) Clinical Management: The concomitant use of [duloxetine](#) and [fluvoxamine](#) is not recommended due to the potential for development of [serotonin syndrome](#). Additionally, concomitant use has resulted in significantly increased [duloxetine](#) exposure and serum levels[343].

7) Probable Mechanism: inhibition of CYP1A2-mediated [duloxetine](#) metabolism; additive serotonergic effects

3.5.1.CA] [Edoxaban](#)

1) Interaction Effect: increased risk of bleeding

2) Summary: Concomitant use of edoxaban and SSRIs may increase the risk of bleeding. If coadministration is necessary, promptly evaluate any signs or symptoms of blood loss[205].

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Concomitant use of edoxaban and SSRIs may increase the risk of bleeding. If coadministration is necessary, promptly evaluate any signs or symptoms of blood loss[205].

7) Probable Mechanism: unknown

3.5.1.CB] [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[404].

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[404].

7) Probable Mechanism: additive serotonergic effects

3.5.1.CC] Eliglustat

1) Interaction Effect: increased eliglustat exposure and subsequent prolongation of the QT interval

2) Summary: Avoid coadministration of eliglustat with weak CYP3A4 inhibitors in poor CYP2D6 metabolizers with [Gaucher disease type 1](#), as resulting increases in eliglustat exposure can progress to serious [cardiac arrhythmias](#), including QT-interval prolongation. Although not specifically studied in poor metabolizers, eliglustat coadministration with a moderate CYP3A inhibitor was predicted to increase eliglustat C_{max} by 2.5- to 2.8-fold and AUC by 2.9- to 3.2-fold among extensive and intermediate CYP2D6 metabolizers. Do not administer eliglustat with strong or moderate CYP3A4 inhibitors plus strong or moderate CYP2D6 inhibitors, as concurrent use is contraindicated for all patients[185].

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Coadministration of eliglustat with weak CYP3A4 inhibitors in poor CYP2D6 metabolizers with [Gaucher disease type 1](#) is not recommended, as resulting increases in eliglustat exposure can progress to serious [cardiac arrhythmias](#), including QT-interval prolongation. Do not administer eliglustat with strong or moderate CYP3A4 inhibitors plus strong or moderate CYP2D6 inhibitors, as concurrent use is contraindicated for all patients[185].

7) Probable Mechanism: inhibition of CYP3A4-mediated eliglustat metabolism

8) Literature Reports

a) Though not specifically studied in poor metabolizers with [Gaucher disease type 1](#), eliglustat use with the moderate CYP3A4 inhibitor, [fluconazole](#), was predicted to cause 2.8- and 3.2-fold increases in eliglustat C_{max} and AUC, respectively, in extensive metabolizers and 2.5- and 2.9-fold increases in intermediate metabolizers [185]

b) Though not specifically studied among poor CYP2D6 metabolizers with [Gaucher disease type 1](#), simulations with extensive CYP2D6 metabolizers suggested that eliglustat C_{max} and AUC would increase 16.7- and 24.2-fold, respectively, with concomitant use of [paroxetine](#) (a strong CYP2D6 inhibitor), plus [ketoconazole](#) (a strong CYP3A inhibitor). Among intermediate CYP2D6 metabolizers, the predicted eliglustat C_{max} and AUC was 7.5- and 9.8-fold higher, respectively, with concurrent use of [paroxetine](#) plus [ketoconazole](#). Treatment with moderate CYP2D6 and CYP3A4 inhibitors would increase eliglustat C_{max} and AUC an estimated 10.2- and 13.6-fold, respectively, with concomitant use of [terbinafine](#) (a moderate CYP2D6 inhibitor) plus [fluconazole](#) (a moderate CYP3A4 inhibitor) among extensive CYP2D6 metabolizers. Eliglustat C_{max} and AUC were predicted to increased by 4.2- and 5-fold, respectively, among intermediate CYP2D6 metabolizers treated with [terbinafine](#) plus [fluconazole](#) [185].

3.5.1.CD] Eltrombopag

- 1) Interaction Effect: increased eltrombopag plasma concentrations
- 2) Summary: Concomitant use of eltrombopag and [fluvoxamine](#), a strong CYP1A2 inhibitor, may result in elevated eltrombopag plasma concentrations due to inhibition of CYP1A2-mediated eltrombopag metabolism. The patient should be monitored for excessive eltrombopag exposure when eltrombopag and [fluvoxamine](#) are coadministered[280].
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Concomitant use of eltrombopag and [fluvoxamine](#), a strong CYP1A2 inhibitor, may result in elevated eltrombopag plasma concentrations. Monitor the patient for excessive eltrombopag exposure when eltrombopag and [fluvoxamine](#) are coadministered[280].
- 7) Probable Mechanism: inhibition of CYP1A2-mediated eltrombopag metabolism by [fluvoxamine](#)

3.5.1.CE] [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[114][115][113]. 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](#). In patients receiving [warfarin](#) and [fluvoxamine](#) concomitantly for 2 weeks, [warfarin](#) plasma concentrations increased by 98% and prothrombin times were prolonged. [Fluvoxamine](#) appears to inhibit several cytochrome P450 isoenzymes which may include 1A2 and 2C9 isozymes, which are responsible for [warfarin](#) metabolism [115][113].
- 3) Severity: major
- 4) Onset: delayed
- 5) Substantiation: probable
- 6) Clinical Management: When [fluvoxamine](#) 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 [fluvoxamine](#) therapy is initiated or discontinued. Periodically reassess the prothrombin time ratio and INR in patients receiving [fluvoxamine](#) and [anticoagulant therapy](#)[113].
- 7) Probable Mechanism: unknown
- 8) Literature Reports

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

events, unknown patient adherence, and exclusion of [clopidogrel](#), dipyridamol, corticosteroids and anticoagulants other than [warfarin](#) in the model [114].

b) A population-based, case-controlled study of new coumarin users (acenocoumarol and phenprocoumon) with concomitant selective serotonin reuptake inhibitors (SSRIs) resulted in an increased risk of hospitalization due to nongastrointestinal bleeding. Using national pharmacy and hospitalization records, Netherlands researchers identified 1848 cases that were admitted for abnormal bleeding and compared them with 5818 control subjects also taking coumarins. Median duration of treatment in patients was 220 days (range, 1 to 4690 days). Patients on SSRIs showed greater risk for hospitalization for nongastrointestinal bleeding (adjusted odds ratio (OR) 1.7, 95% confidence interval (CI), 1.1 to 2.5), however, the rate of [gastrointestinal bleeding](#) (adjusted OR 0.8, 95% CI, 0.4 to 1.5) was not significantly different [115].

c) A hospitalized 80-year-old female was started on intravenous [heparin](#) and oral [warfarin](#) therapy due to an [embolic stroke](#) secondary to [atrial fibrillation](#) and [mitral stenosis](#). Her [warfarin](#) dose was maintained at 1 mg daily, with her INR between 2.5 and 3. [Fluvoxamine](#) 25 mg daily was started for depression, and her [warfarin](#) dose was increased to 1.5 mg daily 3 days later due to worsening of the left [hemiparesis](#). Three days later, her INR was 9.96, and a repeat INR to rule out laboratory error was 11.3. [Warfarin](#) was discontinued, fresh frozen plasma was given, and [fluvoxamine](#) was discontinued. Six days later, [warfarin](#) was again started at 1 mg daily, and the INR increased over 4 days to 11.8. The elevated INR was attributed to the persisting effect of [fluvoxamine](#). She was eventually stabilized on [warfarin](#) 1 mg daily with INR values between 2 and 2.5 [116].

3.5.1.CF] [Epoprostenol](#)

1) Interaction Effect: increased risk of bleeding

2) Summary: Exercise caution when coadministering a SSRI and an antiplatelet agent as this may increase the risk of bleeding events[139][138].[137]. Bleeding events reported have included [epistaxis](#), ecchymosis, [hematoma](#), [petechiae](#), and life-threatening hemorrhages. Monitor patient for signs of increased bleeding when [fluvoxamine](#) is administered with an antiplatelet agent concomitantly [137].

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: When [fluvoxamine](#) and an antiplatelet agent are given concurrently, monitor patient for signs of increased bleeding[137].

7) Probable Mechanism: unknown

8) Literature Reports

a) In a retrospective study of patients over 50 years of age with the diagnosis of acute [myocardial infarction](#) (N=27,058), SSRI use with any antiplatelet therapy significantly increased the risk of bleeding by 1.42-fold compared with [aspirin](#) use alone. Therapy with [aspirin](#), [clopidogrel](#), and an SSRI significantly increased risk by 2.35-fold compared with [aspirin](#) use alone and by 1.57-fold compared with [clopidogrel](#) and [aspirin](#) combination therapy [138].

b) In a systematic review and meta-analysis of 22 observational studies, SSRI use was associated with a significant 1.55 fold increase in risk of [upper gastrointestinal bleeding](#) (UGIB). Concomitant use of SSRIs and antiplatelet drugs was associated with a 2.48-fold increase in risk of UGIB (3 studies) [139].

3.5.1.CG] [Eptifibatide](#)

- 1) Interaction Effect: increased risk of bleeding
- 2) Summary: Exercise caution when coadministering a SSRI and an antiplatelet agent as this may increase the risk of bleeding events[139][138].[137]. Bleeding events reported have included [epistaxis](#), ecchymosis, [hematoma](#), [petechiae](#), and life-threatening hemorrhages. Monitor patient for signs of increased bleeding when [fluvoxamine](#) is administered with an antiplatelet agent concomitantly [137].
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: When [fluvoxamine](#) and an antiplatelet agent are given concurrently, monitor patient for signs of increased bleeding[137].
- 7) Probable Mechanism: unknown
- 8) Literature Reports

a) In a retrospective study of patients over 50 years of age with the diagnosis of acute [myocardial infarction](#) (N=27,058), SSRI use with any antiplatelet therapy significantly increased the risk of bleeding by 1.42-fold compared with [aspirin](#) use alone. Therapy with [aspirin](#), [clopidogrel](#), and an SSRI significantly increased risk by 2.35-fold compared with [aspirin](#) use alone and by 1.57-fold compared with [clopidogrel](#) and [aspirin](#) combination therapy [138].

b) In a systematic review and meta-analysis of 22 observational studies, SSRI use was associated with a significant 1.55 fold increase in risk of [upper gastrointestinal bleeding](#) (UGIB). Concomitant use of SSRIs and antiplatelet drugs was associated with a 2.48-fold increase in risk of UGIB (3 studies) [139].

3.5.1.CH] [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 [fluvoxamine](#), a less potent 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 [fluvoxamine](#) and ergot derivatives[122][123].
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: [Fluvoxamine](#) may increase the plasma concentrations of ergot derivatives. Use caution when [fluvoxamine](#) is coadministered with an ergot derivative, such as [dihydroergotamine](#), [ergotamine](#), or [methylethergonovine](#), due to the potential for serious toxicity including [vasospasm](#) that can occur[122][123].
- 7) Probable Mechanism: inhibition of CYP3A4-mediated ergot metabolism by [fluvoxamine](#)

3.5.1.CI] [Ergonovine](#)

- 1) Interaction Effect: increased plasma concentrations of ergot derivatives and increased risk of [ergotism](#) (nausea, vomiting, vasospastic ischemia)
- 2) Summary: Concomitant use of [fluvoxamine](#), a less potent 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 [fluvoxamine](#) and ergot derivatives[122][123].
- 3) Severity: major
- 4) Onset: unspecified

- 5) Substantiation: theoretical
- 6) Clinical Management: [Fluvoxamine](#) may increase the plasma concentrations of ergot derivatives. Use caution when [fluvoxamine](#) is coadministered with an ergot derivative, such as [dihydroergotamine](#), [ergotamine](#), or [methylergonovine](#), due to the potential for serious toxicity including [vasospasm](#) that can occur[122][123].
- 7) Probable Mechanism: inhibition of CYP3A4-mediated ergot metabolism by [fluvoxamine](#)

3.5.1.CJ] [Ergotamine](#)

- 1) Interaction Effect: increased plasma concentrations of ergot derivatives and increased risk of [ergotism](#) (nausea, vomiting, vasospastic ischemia)
- 2) Summary: Concomitant use of [fluvoxamine](#), a less potent 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 [fluvoxamine](#) and ergot derivatives[122][123].
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: [Fluvoxamine](#) may increase the plasma concentrations of ergot derivatives. Use caution when [fluvoxamine](#) is coadministered with an ergot derivative, such as [dihydroergotamine](#), [ergotamine](#), or [methylergonovine](#), due to the potential for serious toxicity including [vasospasm](#) that can occur[122][123].
- 7) Probable Mechanism: inhibition of CYP3A4-mediated ergot metabolism by [fluvoxamine](#)

3.5.1.CK] [Escitalopram](#)

- 1) Interaction Effect: increased risk of [serotonin syndrome](#)
- 2) Summary: [Serotonin syndrome](#) may result from the concomitant use of escitalopram and another SSRI. If concomitant use is necessary, monitor patients for symptoms of [serotonin syndrome](#), including neuromuscular abnormalities, autonomic instability, gastrointestinal symptoms, and mental status changes, especially during treatment initiation and dose increases. [Serotonin syndrome](#) can be life-threatening. If [serotonin syndrome](#) develops, discontinue escitalopram and any concomitant serotonergic agent and initiate supportive care[256].
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Coadministration of escitalopram and other SSRIs is not recommended, because it may result in a life-threatening condition called [serotonin syndrome](#). If concomitant use is necessary, discuss the risks of [serotonin syndrome](#) with the patient and monitor closely for symptoms of [serotonin syndrome](#) (mental status changes, autonomic instability, neuromuscular symptoms, seizures, and gastrointestinal symptoms), especially during treatment initiation and dose increases. If [serotonin syndrome](#) develops, discontinue escitalopram and any concomitant serotonergic agent and initiate supportive care[256].
- 7) Probable Mechanism: additive serotonergic effect

3.5.1.CL] [Estazolam](#)

- 1) Interaction Effect: increased [estazolam](#) plasma concentrations and risk of [estazolam](#) toxicity
- 2) Summary: [Fluvoxamine](#) is a inhibitor of CYP3A and [estazolam](#) metabolism is catalyzed by CYP3A, therefore [fluvoxamine](#) is expected to increase plasma [estazolam](#) concentration resulting in an increased risk of [estazolam](#) toxicity and associated adverse effects[233].

- 3) Severity: moderate
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Monitor for signs of benzodiazepine intoxication (eg, sedation, dizziness, ataxia, weakness, decreased cognition or motor performance). If symptoms are present, reduce [estazolam](#) dose or consider switching to a benzodiazepine eliminated by glucuronidation (eg, [lorazepam](#), [oxazepam](#), [temazepam](#)).
- 7) Probable Mechanism: [fluvoxamine](#) inhibition of P450-3A isoform-mediated [estazolam](#) metabolism

3.5.1.CM] [Etodolac](#)

- 1) Interaction Effect: an increased risk of bleeding
- 2) Summary: Caution is recommended with the concomitant use of NSAIDs and antidepressants, including SSRIs due to an increased risk of [intracranial hemorrhage](#)[367] and [gastrointestinal bleeding](#) [371][372][368][369]. Bleeding events have included [epistaxis](#), ecchymosis, [hematoma](#), [petechiae](#), and life-threatening hemorrhages [374][373][375][376]. When an SSRI and an NSAID are given concurrently, monitor the patient for signs of increased bleeding.
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: established
- 6) Clinical Management: Use caution if NSAIDs and SSRIs are coadministered. Concomitant use of NSAIDs and SSRIs may cause an increased risk of [intracranial hemorrhage](#)[367] and [gastrointestinal bleeding](#) [368][369]. When an SSRI and an NSAID are given concurrently, monitor the patient for signs of increased bleeding.
- 7) Probable Mechanism: depletion of [platelet](#) serotonin by SSRI; additive effects
- 8) Literature Reports

a) Concomitant use of NSAIDs and antidepressants, including tricyclic antidepressants, SSRIs, serotonin-norepinephrine reuptake inhibitors, and MAOIs, resulted in a 60% increased risk of [intracranial hemorrhage](#) within 30 days of concomitant use compared with antidepressant use alone. There was no significant difference between the antidepressant drug classes and the increased risk; however, there was an increased risk associated with male patients compared with female patients [367].

b) 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. Combined use of an SSRI and NSAIDs or low-dose [aspirin](#) increased the risk to 12.2 and 5.2 times, 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 [370].

c) Two metaanalyses of incidents of upper GI bleed due to SSRIs, NSAIDs, and their combination found that SSRIs increased the risk by 1.73 [371] to 2.36 times [372], NSAIDs by 2.55 times [371], and the combination of SSRIs and NSAIDs by 4.02 [371] to 6.33 times [372].

d) The release of serotonin by [platelets](#) is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs and NSAIDs have been associated with an increased risk of bleeding [373].

3.5.1.CN] Etofenamate

- 1) Interaction Effect: an increased risk of bleeding
- 2) Summary: Caution is recommended with the concomitant use of NSAIDs and antidepressants, including SSRIs due to an increased risk of [intracranial hemorrhage](#)[367] and [gastrointestinal bleeding](#) [371][372][368][369]. Bleeding events have included [epistaxis](#), ecchymosis, [hematoma](#), [petechiae](#), and life-threatening hemorrhages [374][373][375][376]. When an SSRI and an NSAID are given concurrently, monitor the patient for signs of increased bleeding.
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: established
- 6) Clinical Management: Use caution if NSAIDs and SSRIs are coadministered. Concomitant use of NSAIDs and SSRIs may cause an increased risk of [intracranial hemorrhage](#)[367] and [gastrointestinal bleeding](#) [368][369]. When an SSRI and an NSAID are given concurrently, monitor the patient for signs of increased bleeding.
- 7) Probable Mechanism: depletion of [platelet](#) serotonin by SSRI; additive effects
- 8) Literature Reports

a) Concomitant use of NSAIDs and antidepressants, including tricyclic antidepressants, SSRIs, serotonin-norepinephrine reuptake inhibitors, and MAOIs, resulted in a 60% increased risk of [intracranial hemorrhage](#) within 30 days of concomitant use compared with antidepressant use alone. There was no significant difference between the antidepressant drug classes and the increased risk; however, there was an increased risk associated with male patients compared with female patients [367].

b) 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. Combined use of an SSRI and NSAIDs or low-dose [aspirin](#) increased the risk to 12.2 and 5.2 times, 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 [370].

c) Two metaanalyses of incidents of upper GI bleed due to SSRIs, NSAIDs, and their combination found that SSRIs increased the risk by 1.73 [371] to 2.36 times [372], NSAIDs by 2.55 times [371], and the combination of SSRIs and NSAIDs by 4.02 [371] to 6.33 times [372].

d) The release of serotonin by [platelets](#) is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs and NSAIDs have been associated with an increased risk of bleeding [373].

3.5.1.CO] Etoricoxib

- 1) Interaction Effect: an increased risk of bleeding
- 2) Summary: Caution is recommended with the concomitant use of NSAIDs and antidepressants, including SSRIs due to an increased risk of [intracranial hemorrhage](#)[367] and [gastrointestinal bleeding](#) [371][372][368][369]. Bleeding events have included [epistaxis](#), ecchymosis, [hematoma](#), [petechiae](#), and life-threatening hemorrhages [374][373][375][376]. When an SSRI and an NSAID are given concurrently, monitor the patient for signs of increased bleeding.

- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: established
- 6) Clinical Management: Use caution if NSAIDs and SSRIs are coadministered. Concomitant use of NSAIDs and SSRIs may cause an increased risk of [intracranial hemorrhage](#)[367] and [gastrointestinal bleeding](#) [368][369]. When an SSRI and an NSAID are given concurrently, monitor the patient for signs of increased bleeding.
- 7) Probable Mechanism: depletion of [platelet](#) serotonin by SSRI; additive effects
- 8) Literature Reports

a) Concomitant use of NSAIDs and antidepressants, including tricyclic antidepressants, SSRIs, serotonin-norepinephrine reuptake inhibitors, and MAOIs, resulted in a 60% increased risk of [intracranial hemorrhage](#) within 30 days of concomitant use compared with antidepressant use alone. There was no significant difference between the antidepressant drug classes and the increased risk; however, there was an increased risk associated with male patients compared with female patients [367].

b) 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. Combined use of an SSRI and NSAIDs or low-dose [aspirin](#) increased the risk to 12.2 and 5.2 times, 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 [370].

c) Two metaanalyses of incidents of upper GI bleed due to SSRIs, NSAIDs, and their combination found that SSRIs increased the risk by 1.73 [371] to 2.36 times [372], NSAIDs by 2.55 times [371], and the combination of SSRIs and NSAIDs by 4.02 [371] to 6.33 times [372].

d) The release of serotonin by [platelets](#) is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs and NSAIDs have been associated with an increased risk of bleeding [373].

3.5.1.CP] Felbinac

- 1) Interaction Effect: an increased risk of bleeding
- 2) Summary: Caution is recommended with the concomitant use of NSAIDs and antidepressants, including SSRIs due to an increased risk of [intracranial hemorrhage](#)[367] and [gastrointestinal bleeding](#) [371][372][368][369]. Bleeding events have included [epistaxis](#), ecchymosis, [hematoma](#), [petechiae](#), and life-threatening hemorrhages [374][373][375][376]. When an SSRI and an NSAID are given concurrently, monitor the patient for signs of increased bleeding.
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: established
- 6) Clinical Management: Use caution if NSAIDs and SSRIs are coadministered. Concomitant use of NSAIDs and SSRIs may cause an increased risk of [intracranial hemorrhage](#)[367] and [gastrointestinal bleeding](#) [368][369]. When an SSRI and an NSAID are given concurrently, monitor the patient for signs of increased bleeding.
- 7) Probable Mechanism: depletion of [platelet](#) serotonin by SSRI; additive effects
- 8) Literature Reports

a)) Concomitant use of NSAIDs and antidepressants, including tricyclic antidepressants, SSRIs, serotonin-norepinephrine reuptake inhibitors, and MAOIs, resulted in a 60% increased risk of [intracranial hemorrhage](#) within 30 days of concomitant use compared with antidepressant use alone. There was no significant difference between the antidepressant drug classes and the increased risk; however, there was an increased risk associated with male patients compared with female patients [367].

b)) 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. Combined use of an SSRI and NSAIDs or low-dose [aspirin](#) increased the risk to 12.2 and 5.2 times, 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 [370].

c)) Two metaanalyses of incidents of upper GI bleed due to SSRIs, NSAIDs, and their combination found that SSRIs increased the risk by 1.73 [371] to 2.36 times [372], NSAIDs by 2.55 times [371], and the combination of SSRIs and NSAIDs by 4.02 [371] to 6.33 times [372].

d)) The release of serotonin by [platelets](#) is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs and NSAIDs have been associated with an increased risk of bleeding [373].

3.5.1.CQ| [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 [fluvoxamine](#), has the potential to cause [serotonin syndrome](#)[340]. [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 [341]. Until more data are available, [fenfluramine](#) should not be used in combination with [fluvoxamine](#).

3)) Severity: major

4)) Onset: rapid

5)) Substantiation: theoretical

6)) Clinical Management: Concurrent use of [fenfluramine](#) and [fluvoxamine](#) 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 [fluvoxamine](#) or other serotonin specific reuptake inhibitors.

7)) Probable Mechanism: additive serotonergic effects

3.5.1.CR| [Fenoprofen](#)

1)) Interaction Effect: an increased risk of bleeding

2)) Summary: Caution is recommended with the concomitant use of NSAIDs and antidepressants, including SSRIs due to an increased risk of [intracranial hemorrhage](#)[367] and [gastrointestinal bleeding](#) [371][372][368][369]. Bleeding events have included [epistaxis](#), ecchymosis, [hematoma](#), [petechiae](#), and life-

threatening hemorrhages [374][373][375][376]. When an SSRI and an NSAID are given concurrently, monitor the patient for signs of increased bleeding.

3) Severity: major

4) Onset: unspecified

5) Substantiation: established

6) Clinical Management: Use caution if NSAIDs and SSRIs are coadministered. Concomitant use of NSAIDs and SSRIs may cause an increased risk of [intracranial hemorrhage](#)[367] and [gastrointestinal bleeding](#) [368][369]. When an SSRI and an NSAID are given concurrently, monitor the patient for signs of increased bleeding.

7) Probable Mechanism: depletion of [platelet](#) serotonin by SSRI; additive effects

8) Literature Reports

a) Concomitant use of NSAIDs and antidepressants, including tricyclic antidepressants, SSRIs, serotonin-norepinephrine reuptake inhibitors, and MAOIs, resulted in a 60% increased risk of [intracranial hemorrhage](#) within 30 days of concomitant use compared with antidepressant use alone. There was no significant difference between the antidepressant drug classes and the increased risk; however, there was an increased risk associated with male patients compared with female patients [367].

b) 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. Combined use of an SSRI and NSAIDs or low-dose [aspirin](#) increased the risk to 12.2 and 5.2 times, 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 [370].

c) Two metaanalyses of incidents of upper GI bleed due to SSRIs, NSAIDs, and their combination found that SSRIs increased the risk by 1.73 [371] to 2.36 times [372], NSAIDs by 2.55 times [371], and the combination of SSRIs and NSAIDs by 4.02 [371] to 6.33 times [372].

d) The release of serotonin by [platelets](#) is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs and NSAIDs have been associated with an increased risk of bleeding [373].

3.5.1.CS| [Fentanyl](#)

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

2) Summary: [Fentanyl](#) is proserotonergic and has been associated with [serotonin syndrome](#) when coadministered with serotonergic drugs[191], including SSRIs [382][381][383]. [Serotonin syndrome](#) may also result from concomitant use of [fentanyl](#) with serotonin-norepinephrine reuptake inhibitors, tricyclic antidepressants, or other synthetic piperidine opioids. If possible, consider replacing serotonergic opioids with non-serotonergic opioids [191]. Monitor patients for symptoms of [serotonin syndrome](#), including neuromuscular abnormalities, autonomic hyperactivity, and mental status changes. [Serotonin syndrome](#) can be life-threatening. If [serotonin syndrome](#) develops, discontinue the offending agents and provide supportive care and other therapy as necessary [120].

3) Severity: major

4) Onset: delayed

5) Substantiation: theoretical

6j) Clinical Management: [Fentanyl](#) is a proserotonergic, synthetic piperidine opioid and has been associated with [serotonin syndrome](#) when coadministered with other serotonergic drugs. Therefore, use caution with coadministration of [fentanyl](#) and a serotonergic drug, such as an SSRI, serotonin-norepinephrine reuptake inhibitor, tricyclic antidepressant, or another synthetic piperidine opioid, as this may result in additive serotonergic effects and may increase the risk of [serotonin syndrome](#). If possible, consider replacing serotonergic opioids (eg, [fentanyl](#)) with non-serotonergic opioids (eg, [morphine](#)) [191]. Monitor patients for symptoms of [serotonin syndrome](#), including neuromuscular abnormalities (eg, hyperreflexia, tremor, muscle rigidity, clonus, peripheral hypertonicity, shivering), autonomic hyperactivity (eg, [tachycardia](#), mydriasis, diaphoresis, the presence of bowel sounds, diarrhea), and mental status changes (eg, agitation, [delirium](#)). [Serotonin syndrome](#) can be life-threatening. If [serotonin syndrome](#) develops, discontinue the offending agents and provide supportive care and other therapy as necessary [120].

7j) Probable Mechanism: additive serotonergic effect

8j) Literature Reports

a) [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 [ciproheptadine](#). After 3 days, the patient's temperature and CPK level normalized and she later extubated with no further complications [381].

b) [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 [cycloheptadine](#) with resolution of symptoms after 3 days [382].

c) A case of postoperative [serotonin syndrome](#) following the administration of [fentanyl](#) for general [anesthesia](#) and post operative analgesia was reported in a 60-year-old woman also receiving [paroxetine](#). Outpatient medications included only [paroxetine](#) and thyroxine for a history of depression and [hypothyroidism](#). The patient was admitted for an extensive resection of a recurrent left chest wall [myxofibrosarcoma](#) and given [propofol](#) and 200 micrograms (mcg) of [fentanyl](#) for the [induction of anesthesia](#). The patient also received an additional 800 mcg of [fentanyl](#) (intermittent 50 mcg boluses) intraoperatively and a subsequent [fentanyl](#) infusion (100 to 200 mcg/hr) for postoperative sedation and analgesia (2545 mcg of [fentanyl](#) received over 36 hours). The [fentanyl](#) infusion was continued 36 hours postoperatively, at which time intermittent agitation, bilateral hypertonia and hyperreflexia, and bilateral inducible ankle clonus were observed on neurological examination. Symptoms were more severe in the lower limbs and on the right side of the body. A [CT scan](#) of the brain was unremarkable and all other examination findings, including a [thyroid function test](#), were within normal limits with the exception of elevated blood pressure (180/90 mmHg), which spontaneously resolved 24 hours after the procedure. [Fentanyl](#) was discontinued, and 24 hours later, there was marked improvement in neurological symptoms and complete recovery by postoperative day 4. The patient was ultimately discharged home with no further complications [383].

3.5.1.CT] Fepradinol

1) Interaction Effect: an increased risk of bleeding

2) Summary: Caution is recommended with the concomitant use of NSAIDs and antidepressants, including SSRIs due to an increased risk of [intracranial hemorrhage](#)[367] and [gastrointestinal bleeding](#) [371][372][368][369]. Bleeding events have included [epistaxis](#), ecchymosis, [hematoma](#), [petechiae](#), and life-threatening hemorrhages [374][373][375][376]. When an SSRI and an NSAID are given concurrently, monitor the patient for signs of increased bleeding.

3) Severity: major

4) Onset: unspecified

5) Substantiation: established

6) Clinical Management: Use caution if NSAIDs and SSRIs are coadministered. Concomitant use of NSAIDs and SSRIs may cause an increased risk of [intracranial hemorrhage](#)[367] and [gastrointestinal bleeding](#) [368][369]. When an SSRI and an NSAID are given concurrently, monitor the patient for signs of increased bleeding.

7) Probable Mechanism: depletion of [platelet](#) serotonin by SSRI; additive effects

8) Literature Reports

a) Concomitant use of NSAIDs and antidepressants, including tricyclic antidepressants, SSRIs, serotonin-norepinephrine reuptake inhibitors, and MAOIs, resulted in a 60% increased risk of [intracranial hemorrhage](#) within 30 days of concomitant use compared with antidepressant use alone. There was no significant difference between the antidepressant drug classes and the increased risk; however, there was an increased risk associated with male patients compared with female patients [367].

b) 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. Combined use of an

SSRI and NSAIDs or low-dose [aspirin](#) increased the risk to 12.2 and 5.2 times, 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 [370].

c) Two metaanalyses of incidents of upper GI bleed due to SSRIs, NSAIDs, and their combination found that SSRIs increased the risk by 1.73 [371] to 2.36 times [372], NSAIDs by 2.55 times [371], and the combination of SSRIs and NSAIDs by 4.02 [371] to 6.33 times [372].

d) The release of serotonin by [platelets](#) is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs and NSAIDs have been associated with an increased risk of bleeding [373].

3.5.1.CU] Feprazone

1) Interaction Effect: an increased risk of bleeding

2) Summary: Caution is recommended with the concomitant use of NSAIDs and antidepressants, including SSRIs due to an increased risk of [intracranial hemorrhage](#)[367] and [gastrointestinal bleeding](#) [371][372][368][369]. Bleeding events have included [epistaxis](#), ecchymosis, [hematoma](#), [petechiae](#), and life-threatening hemorrhages [374][373][375][376]. When an SSRI and an NSAID are given concurrently, monitor the patient for signs of increased bleeding.

3) Severity: major

4) Onset: unspecified

5) Substantiation: established

6) Clinical Management: Use caution if NSAIDs and SSRIs are coadministered. Concomitant use of NSAIDs and SSRIs may cause an increased risk of [intracranial hemorrhage](#)[367] and [gastrointestinal bleeding](#) [368][369]. When an SSRI and an NSAID are given concurrently, monitor the patient for signs of increased bleeding.

7) Probable Mechanism: depletion of [platelet](#) serotonin by SSRI; additive effects

8) Literature Reports

a) Concomitant use of NSAIDs and antidepressants, including tricyclic antidepressants, SSRIs, serotonin-norepinephrine reuptake inhibitors, and MAOIs, resulted in a 60% increased risk of [intracranial hemorrhage](#) within 30 days of concomitant use compared with antidepressant use alone. There was no significant difference between the antidepressant drug classes and the increased risk; however, there was an increased risk associated with male patients compared with female patients [367].

b) 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. Combined use of an SSRI and NSAIDs or low-dose [aspirin](#) increased the risk to 12.2 and 5.2 times, 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 [370].

c) Two metaanalyses of incidents of upper GI bleed due to SSRIs, NSAIDs, and their combination found that SSRIs increased the risk by 1.73 [371] to 2.36 times [372], NSAIDs by 2.55 times [371], and the combination of SSRIs and NSAIDs by 4.02 [371] to 6.33 times [372].

d)) The release of serotonin by [platelets](#) is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs and NSAIDs have been associated with an increased risk of bleeding [373].

3.5.1.CV] Floctafenine

1)) Interaction Effect: an increased risk of bleeding

2)) Summary: Caution is recommended with the concomitant use of NSAIDs and antidepressants, including SSRIs due to an increased risk of [intracranial hemorrhage](#)[367] and [gastrointestinal bleeding](#) [371][372][368][369]. Bleeding events have included [epistaxis](#), ecchymosis, [hematoma](#), [petechiae](#), and life-threatening hemorrhages [374][373][375][376]. When an SSRI and an NSAID are given concurrently, monitor the patient for signs of increased bleeding.

3)) Severity: major

4)) Onset: unspecified

5)) Substantiation: established

6)) Clinical Management: Use caution if NSAIDs and SSRIs are coadministered. Concomitant use of NSAIDs and SSRIs may cause an increased risk of [intracranial hemorrhage](#)[367] and [gastrointestinal bleeding](#) [368][369]. When an SSRI and an NSAID are given concurrently, monitor the patient for signs of increased bleeding.

7)) Probable Mechanism: depletion of [platelet](#) serotonin by SSRI; additive effects

8)) Literature Reports

a)) Concomitant use of NSAIDs and antidepressants, including tricyclic antidepressants, SSRIs, serotonin-norepinephrine reuptake inhibitors, and MAOIs, resulted in a 60% increased risk of [intracranial hemorrhage](#) within 30 days of concomitant use compared with antidepressant use alone. There was no significant difference between the antidepressant drug classes and the increased risk; however, there was an increased risk associated with male patients compared with female patients [367].

b)) 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. Combined use of an SSRI and NSAIDs or low-dose [aspirin](#) increased the risk to 12.2 and 5.2 times, 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 [370].

c)) Two metaanalyses of incidents of upper GI bleed due to SSRIs, NSAIDs, and their combination found that SSRIs increased the risk by 1.73 [371] to 2.36 times [372], NSAIDs by 2.55 times [371], and the combination of SSRIs and NSAIDs by 4.02 [371] to 6.33 times [372].

d)) The release of serotonin by [platelets](#) is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs and NSAIDs have been associated with an increased risk of bleeding [373].

3.5.1.CW] Flufenamic Acid

1)) Interaction Effect: an increased risk of bleeding

2)) Summary: Caution is recommended with the concomitant use of NSAIDs and antidepressants, including SSRIs due to an increased risk of [intracranial hemorrhage](#)[367] and [gastrointestinal bleeding](#)

[371][372][368][369]. Bleeding events have included [epistaxis](#), ecchymosis, [hematoma](#), [petechiae](#), and life-threatening hemorrhages [374][373][375][376]. When an SSRI and an NSAID are given concurrently, monitor the patient for signs of increased bleeding.

3) Severity: major

4) Onset: unspecified

5) Substantiation: established

6) Clinical Management: Use caution if NSAIDs and SSRIs are coadministered. Concomitant use of NSAIDs and SSRIs may cause an increased risk of [intracranial hemorrhage](#)[367] and [gastrointestinal bleeding](#) [368][369]. When an SSRI and an NSAID are given concurrently, monitor the patient for signs of increased bleeding.

7) Probable Mechanism: depletion of [platelet](#) serotonin by SSRI; additive effects

8) Literature Reports

a) Concomitant use of NSAIDs and antidepressants, including tricyclic antidepressants, SSRIs, serotonin-norepinephrine reuptake inhibitors, and MAOIs, resulted in a 60% increased risk of [intracranial hemorrhage](#) within 30 days of concomitant use compared with antidepressant use alone. There was no significant difference between the antidepressant drug classes and the increased risk; however, there was an increased risk associated with male patients compared with female patients [367].

b) 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. Combined use of an SSRI and NSAIDs or low-dose [aspirin](#) increased the risk to 12.2 and 5.2 times, 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 [370].

c) Two metaanalyses of incidents of upper GI bleed due to SSRIs, NSAIDs, and their combination found that SSRIs increased the risk by 1.73 [371] to 2.36 times [372], NSAIDs by 2.55 times [371], and the combination of SSRIs and NSAIDs by 4.02 [371] to 6.33 times [372].

d) The release of serotonin by [platelets](#) is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs and NSAIDs have been associated with an increased risk of bleeding [373].

3.5.1.CX] [Fluoxetine](#)

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

2) Summary: Concurrent use of [fluoxetine](#) (an SSRI and potent CYP2D6 inhibitor) with [fluvoxamine](#) (an SSRI and CYP2D6 substrate) may increase [fluvoxamine](#) exposure, result in additive serotonergic effects, and increase the risk of [serotonin syndrome](#). If concomitant use of [fluoxetine](#) and [fluvoxamine](#) is required, monitor for signs and symptoms of [serotonin syndrome](#)[197][20]. 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 [120]. If [serotonin syndrome](#) develops, discontinue [fluoxetine](#) and [fluvoxamine](#) and provide supportive care as necessary [197][20][120]

3) Severity: major

- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: The concomitant use of [fluoxetine](#), a potent CYP2D6 inhibitor, with [fluvoxamine](#), a CYP2D6 substrate, should be undertaken with caution as this may increase [fluvoxamine](#) exposure. Coadministration of these 2 SSRIs may also result in additive serotonergic effects and may increase the risk of [serotonin syndrome](#). If concomitant use is necessary, discuss the risks of [serotonin syndrome](#) with the patient and monitor closely for symptoms of [serotonin syndrome](#) (mental status changes, autonomic instability, neuromuscular symptoms, seizures, and gastrointestinal symptoms), especially during treatment initiation and dose increases. If [serotonin syndrome](#) develops, discontinue [fluoxetine](#) and [fluvoxamine](#) and initiate supportive care[197][20].
- 7) Probable Mechanism: inhibition of CYP2D6-mediated metabolism of [fluvoxamine](#) by [fluoxetine](#); additive serotonergic effect

3.5.1.CY| [Flurbiprofen](#)

- 1) Interaction Effect: an increased risk of bleeding
- 2) Summary: Caution is recommended with the concomitant use of NSAIDs and antidepressants, including SSRIs due to an increased risk of [intracranial hemorrhage](#)[367] and [gastrointestinal bleeding](#) [371][372][368][369]. Bleeding events have included [epistaxis](#), ecchymosis, [hematoma](#), [petechiae](#), and life-threatening hemorrhages [374][373][375][376]. When an SSRI and an NSAID are given concurrently, monitor the patient for signs of increased bleeding.
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: established
- 6) Clinical Management: Use caution if NSAIDs and SSRIs are coadministered. Concomitant use of NSAIDs and SSRIs may cause an increased risk of [intracranial hemorrhage](#)[367] and [gastrointestinal bleeding](#) [368][369]. When an SSRI and an NSAID are given concurrently, monitor the patient for signs of increased bleeding.
- 7) Probable Mechanism: depletion of [platelet](#) serotonin by SSRI; additive effects
- 8) Literature Reports

a) Concomitant use of NSAIDs and antidepressants, including tricyclic antidepressants, SSRIs, serotonin-norepinephrine reuptake inhibitors, and MAOIs, resulted in a 60% increased risk of [intracranial hemorrhage](#) within 30 days of concomitant use compared with antidepressant use alone. There was no significant difference between the antidepressant drug classes and the increased risk; however, there was an increased risk associated with male patients compared with female patients [367].

b) 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. Combined use of an SSRI and NSAIDs or low-dose [aspirin](#) increased the risk to 12.2 and 5.2 times, 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 [370].

c) Two metaanalyses of incidents of upper GI bleed due to SSRIs, NSAIDs, and their combination found that SSRIs increased the risk by 1.73 [371] to 2.36 times [372], NSAIDs by 2.55 times [371], and the combination of SSRIs and NSAIDs by 4.02 [371] to 6.33 times [372].

d)) The release of serotonin by [platelets](#) is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs and NSAIDs have been associated with an increased risk of bleeding [373].

3.5.1.CZ| [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[114][115][113]. 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](#). In patients receiving [warfarin](#) and [fluvoxamine](#) concomitantly for 2 weeks, [warfarin](#) plasma concentrations increased by 98% and prothrombin times were prolonged. [Fluvoxamine](#) appears to inhibit several cytochrome P450 isoenzymes which may include 1A2 and 2C9 isozymes, which are responsible for [warfarin](#) metabolism [115][113].

3)) Severity: major

4)) Onset: delayed

5)) Substantiation: probable

6)) Clinical Management: When [fluvoxamine](#) 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 [fluvoxamine](#) therapy is initiated or discontinued. Periodically reassess the prothrombin time ratio and INR in patients receiving [fluvoxamine](#) and [anticoagulant therapy](#)[113].

7)) Probable Mechanism: unknown

8)) Literature Reports

a)) According to a retrospective cohort study (n=234), there was an increased risk of clinically relevant bleeding (hospital admission due to bleeding) in patients receiving [warfarin](#) for [atrial fibrillation](#) during concomitant SSRI therapy or within 2 weeks following SSRI therapy termination. Patients with a mean age of 72 +/- 7 years receiving [warfarin](#) plus SSRI (n=117) were matched with randomly selected patients who received [warfarin](#) only (n=117). SSRI included [fluoxetine](#), [citalopram](#), [paroxetine](#), [sertraline](#), [fluvoxamine](#), or escitalopram. Nine patients experienced 11 bleeding episodes during 213.9 treatment years in the [warfarin](#) plus SSRI group, and 10 patients experienced 14 bleedings during 586.4 treatment years in the warfarin-only group. The corresponding total incidences of bleedings were 51.4 and 23.9 per 1000 treatment years, respectively. The hazard ratio for first bleedings during treatment with [warfarin](#) plus SSRI was 3.49 (95% CI; 1.37 to 8.91, p=0.009) compared with [warfarin](#) only. The SSRI implicated in patients experiencing bleeding at the time of concomitant administration were [sertraline](#) or [citalopram](#). The addition of an SSRI was not associated with a change in [warfarin](#) dose or INR (p=0.48 and p=0.31 respectively). The results of the study may be limited by earlier bleeding events, unknown patient adherence, and exclusion of [clopidogrel](#), dipyridamol, corticosteroids and anticoagulants other than [warfarin](#) in the model [114].

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

greater risk for hospitalization for nongastrointestinal bleeding (adjusted odds ratio (OR) 1.7, 95% confidence interval (CI), 1.1 to 2.5), however, the rate of [gastrointestinal bleeding](#) (adjusted OR 0.8, 95% CI, 0.4 to 1.5) was not significantly different [115].

c) A hospitalized 80-year-old female was started on intravenous [heparin](#) and oral [warfarin](#) therapy due to an [embolic stroke](#) secondary to [atrial fibrillation](#) and [mitral stenosis](#). Her [warfarin](#) dose was maintained at 1 mg daily, with her INR between 2.5 and 3. [Fluvoxamine](#) 25 mg daily was started for depression, and her [warfarin](#) dose was increased to 1.5 mg daily 3 days later due to worsening of the left [hemiparesis](#). Three days later, her INR was 9.96, and a repeat INR to rule out laboratory error was 11.3. [Warfarin](#) was discontinued, fresh frozen plasma was given, and [fluvoxamine](#) was discontinued. Six days later, [warfarin](#) was again started at 1 mg daily, and the INR increased over 4 days to 11.8. The elevated INR was attributed to the persisting effect of [fluvoxamine](#). She was eventually stabilized on [warfarin](#) 1 mg daily with INR values between 2 and 2.5 [116].

3.5.1.DA| [Fosphenytoin](#)

- 1) Interaction Effect: an increased risk of [phenytoin](#) toxicity (ataxia, hyperreflexia, [nystagmus](#), tremors)
- 2) Summary: [Fluvoxamine](#) inhibits several of the isoenzymes of the CYP2C9, CYP1A2, and CYP3A4 (oxidative metabolism). Since [phenytoin](#) is eliminated at least partially via the CYP2C9 pathway, it is possible that coadministration with [fluvoxamine](#) may cause elevations in [phenytoin](#) plasma levels[201].
- 3) Severity: moderate
- 4) Onset: delayed
- 5) Substantiation: probable
- 6) Clinical Management: Consideration should be given to monitoring of [phenytoin](#) serum levels when [fluvoxamine](#) is added or withdrawn from therapy and dosage adjustments made accordingly. Patients should be counseled to be aware of the potential side effects of [phenytoin](#) toxicity such as drowsiness, ataxia, and [nystagmus](#), and to notify their physician if such side effects occur.
- 7) Probable Mechanism: decreased oxidative metabolism
- 8) Literature Reports

a) During an in vitro study, the inhibitory effects of [fluvoxamine](#) on CYP2C9 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). [Fluvoxamine](#), a strong inhibitor of HPPH, impaired the formation of HPPH, which can lead to an increase in steady-state [phenytoin](#) levels [199].

b) [Phenytoin](#) intoxication occurred in a patient after administration of [fluvoxamine](#). Serum [phenytoin](#) concentration dramatically increased from 16.6 to 49.1 mcg/mL during treatment with [fluvoxamine](#). [Fluvoxamine](#) may inhibit the metabolism of [phenytoin](#), mediated by CYP2C9 and CYP2C19 enzymes [200].

3.5.1.DB| [Frovatriptan](#)

- 1) Interaction Effect: an increased risk of [serotonin syndrome](#)
- 2) Summary: There have been case reports of weakness, hyperreflexia, and incoordination following concomitant use of [sumatriptan](#), a 5-hydroxytryptamine-1 (5HT-1) agonist, and a serotonin specific reuptake inhibitor (SSRI)[401]. Because [frovatriptan](#) is a 5HT 1B/1D agonist, a similar interaction between SSRIs and [frovatriptan](#) may occur [402]. 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](#) [118].

3) Severity: major

4) Onset: delayed

5) Substantiation: probable

6) Clinical Management: Coadministration of a triptan, such as [frovatriptan](#), and an SSRI may result in a life-threatening condition called [serotonin syndrome](#). Be aware that triptans may be commonly used intermittently and that either the triptan or the SSRI may be prescribed by a different physician. If these agents are used together, discuss the risks of [serotonin syndrome](#) with the patient and monitor closely for symptoms of [serotonin syndrome](#) (restlessness, [hyperthermia](#), hyperreflexia, incoordination).

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

3.5.1.DC| [Furazolidone](#)

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

2) Summary: Concomitant use of [fluvoxamine](#) and an MAOI is contraindicated. Concurrent administration or overlapping therapy with [fluvoxamine](#) and an MAOI may result in [serotonin syndrome](#), a hyperserotonergic state characterized by symptoms such as agitation and hallucinations, myoclonus, changes in mental status, hyperreflexia, diaphoresis, rigidity, and tremor. Serious, even fatal, reactions have been reported with concomitant use of SSRIs and MAOIs. A minimum of 14 days should elapse after discontinuing an MAOI intended to treat psychiatric disorders before initiating therapy with [fluvoxamine](#), and a minimum of 14 days should elapse after discontinuing [fluvoxamine](#) before initiating therapy with an MAOI intended to treat psychiatric disorders[20].

3) Severity: contraindicated

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Concurrent use of [fluvoxamine](#) and an MAOI is contraindicated. Wait at least 14 days after discontinuing an MAOI intended to treat psychiatric disorders before initiating [fluvoxamine](#). Wait at least 14 days after discontinuing [fluvoxamine](#) before initiating therapy with an MAOI intended to treat psychiatric disorders[20].

7) Probable Mechanism: additive serotonergic effect

3.5.1.DD| [Galantamine](#)

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

2) Summary: Based upon in vitro studies, the major enzymes involved in [galantamine](#) metabolism are CYP3A4 and CYP2D6. [Fluvoxamine](#) 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 [fluvoxamine](#) (N=14), demonstrated a 25-33% decrease in [galantamine](#) clearance. The resulting plasma concentration increase of [galantamine](#) may warrant caution when it is coadministered with [fluvoxamine](#). Monitor for [galantamine](#) toxicity including anorexia, nausea, vomiting, dizziness, [arrhythmias](#) or [gastrointestinal bleeding](#)[97].

3) Severity: moderate

4) Onset: unspecified

5) Substantiation: probable

6) Clinical Management: Increased [galantamine](#) plasma concentrations may result from [fluvoxamine](#) inhibition of [galantamine](#) CYP2D6-mediated metabolism. Monitor for [galantamine](#) toxicity including anorexia, nausea, vomiting, dizziness, [arrhythmias](#), or [gastrointestinal bleeding](#)[97].

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

3.5.1.DE] Ginkgo

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

2J) 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[259]. 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 [260][261], and has demonstrated serotonergic activity in animals [262] 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 [263]. Ginkgo biloba extract inhibited MAO-A/MAO-B in the rat brain in vitro [260][261] and MAO-B in human [platelets](#) in vitro [261]. No significant MAO inhibition was found in mice following oral consumption [264].

3J) Severity: moderate

4J) Onset: delayed

5J) Substantiation: probable

6J) Clinical Management: Monitor patients closely for symptoms of [serotonin syndrome](#) if ginkgo is combined with selective serotonin reuptake inhibitors (SSRIs).

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

8J) Literature Reports

aJ) 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 [258].

3.5.1.DF] Glimepiride

1J) Interaction Effect: an increase in plasma concentrations of [glimepiride](#)

2J) Summary: Caution is advised when [fluvoxamine](#) is coadministered with [glimepiride](#). An increase in plasma concentrations of [glimepiride](#) has been documented in healthy patients when used concomitantly with [fluvoxamine](#) without a significant effect on blood glucose concentrations[405].

3J) Severity: minor

4J) Onset: rapid

5J) Substantiation: established

6J) Clinical Management: Use [glimepiride](#) and [fluvoxamine](#) concomitantly with caution or use therapeutic alternative. Monitor the patient for [hypoglycemia](#) if used concurrently.

7J) Probable Mechanism: inhibition of the metabolism of [glimepiride](#) through the cytochrome P450 2C9 enzyme

8J) Literature Reports

a)) Plasma concentrations of [glimepiride](#) were moderately increased when used concomitantly with [fluvoxamine](#). A double-blind, randomized, crossover study with three phases including a 4-week washout period between the phases was conducted in twelve healthy volunteers. The aim of the study is to investigate the effects of [fluvoxamine](#) on the pharmacokinetics and pharmacodynamics of [glimepiride](#). Subjects received [fluvoxamine](#) 100 mg or placebo orally once daily for 4 days. On day 4, a single oral dose of 0.5 mg of [glimepiride](#) was administered after the patients fasted overnight. Meals were served 15 minutes after, 3 hours after, and 7 hours after [glimepiride](#) administration. For the [fluvoxamine](#) phase, the peak concentration (C_{max}) was 143% (p less than 0.05) of the respective placebo value, and the half-life was increased from 2 to 2.3 hours (p less than 0.01). The increase in the area under the concentration-time curve (AUC) was not significant, and differences in blood glucose levels were not statistically significant [405].

3.5.1.DG] [Granisetron](#)

- 1)) Interaction Effect: increased risk of [serotonin syndrome](#)
- 2)) Summary: Concomitant use of [granisetron](#) with a serotonergic agent may increase the risk of [serotonin syndrome](#). Instruct patients of the increased risk of [serotonin syndrome](#) with concurrent use of these drugs. Monitor for the emergence of [serotonin syndrome](#) and discontinue treatment with [granisetron](#) and institute supportive therapy if symptoms of [serotonin syndrome](#) occur[187].
- 3)) Severity: major
- 4)) Onset: unspecified
- 5)) Substantiation: theoretical
- 6)) Clinical Management: Concomitant use of [granisetron](#) with a serotonergic agent may increase the risk of [serotonin syndrome](#). Instruct patients of the increased risk of [serotonin syndrome](#) with concurrent use of these drugs. Monitor for the emergence of [serotonin syndrome](#) and discontinue treatment with [granisetron](#) and institute supportive therapy if symptoms of [serotonin syndrome](#) occur[187].
- 7)) Probable Mechanism: unknown

3.5.1.DH] [Guarana](#)

- 1)) Interaction Effect: symptoms of excessive [caffeine](#) (insomnia, headache, restlessness, nervousness, palpitations, and [arrhythmias](#))
- 2)) Summary: The primary pharmacologically-active ingredient of guarana is [caffeine](#). [Fluvoxamine](#) inhibits CYP1A2 and CYP2D6 which are responsible for [caffeine](#) metabolism. Decreased [caffeine](#) clearance and increased half-life have been demonstrated in humans. Signs and symptoms of [caffeine](#) excess may result if the compounds are taken together. Patients should avoid guarana use during therapy with [fluvoxamine](#) in order to avoid complications[151].
- 3)) Severity: moderate
- 4)) Onset: rapid
- 5)) Substantiation: theoretical
- 6)) Clinical Management: Patients should be advised of the [caffeine](#) content of guarana, and of symptoms of excess if taken with [fluvoxamine](#) (insomnia, headache, restlessness, nervousness, palpitations, and [arrhythmias](#)) as well as symptoms of [caffeine](#) withdrawal which may accompany abrupt discontinuation of guarana (headache, fatigue, depression, anxiety, and insomnia). Patients should avoid guarana use during therapy with [fluvoxamine](#) in order to avoid complications.
- 7)) Probable Mechanism: [fluvoxamine](#) may inhibit the metabolism of the [caffeine](#) content of guarana
- 8)) Literature Reports

a)) In an open, randomized, cross-over study of 8 volunteers, [fluvoxamine](#) significantly decreased [caffeine](#) total clearance and increased [caffeine](#) half-life. [Fluvoxamine](#) was administered as 50

milligrams (mg) for 4 days, then 100 mg for 8 days while subjects abstained from all [caffeine](#) intake. [Caffeine](#) 200 mg was then administered orally. Total clearance of [caffeine](#) decreased from 107 milliliters/minute (ml/min) to 21 ml/min, and half-life increased from 5 hours to 31 hours. Patients taking [fluvoxamine](#) should restrict [caffeine](#) intake [143].

b) In vitro, [fluvoxamine](#) was found to be a very potent inhibitor of the formation of N-demethylated [caffeine](#) metabolites with K_i values of 0.08 micromoles (mcmol) to 0.28 mcmol. The formation of 1,7-dimethylxanthine was abolished by 10 mcmol of [fluvoxamine](#), implying the N3-demethylation of [caffeine](#) is almost entirely catalyzed by CYP1A2 [144].

c) At least 14 metabolites are formed from [caffeine](#) whose main route of elimination is N3-demethylation to paraxanthine (1,7-methylxanthine) which accounts for greater than 80% of [caffeine](#) elimination [145].

d) CYP1A2 is the major enzyme metabolizing [caffeine](#) to 1,7-dimethylxanthine [146][147][148]. CYP1A2 is also a major enzyme in the formation of 3,7-dimethylxanthine and 1,3-dimethylxanthine from [caffeine](#) [149][146][150].

3.5.1.DI] [Haloperidol](#)

- 1) Interaction Effect: an increased risk of [haloperidol](#) toxicity
- 2) Summary: [Haloperidol](#) serum concentrations were increased by the coadministration of [fluvoxamine](#) in a small double blind, randomized, placebo controlled, crossover study[240].
- 3) Severity: moderate
- 4) Onset: delayed
- 5) Substantiation: probable
- 6) Clinical Management: Caution should be used when [fluvoxamine](#) is administered with [haloperidol](#). Monitor serum concentrations of [haloperidol](#) and adjust the dose accordingly. Also monitor the patient for signs and symptoms of worsening clinical and [cognitive assessments](#).
- 7) Probable Mechanism: inhibition of cytochrome P450-mediated metabolism of [haloperidol](#)
- 8) Literature Reports

a) Four inpatient males with [chronic schizophrenia](#) were stabilized on [haloperidol](#) and [benztropine](#) orally. In randomized order, the patients were then placed on [fluvoxamine](#) for six weeks or identically appearing placebo. Results showed that the addition of [fluvoxamine](#) to [haloperidol](#) therapy significantly elevated serum concentrations of [haloperidol](#). In addition, [haloperidol](#) concentrations did not plateau during the six-week period of [fluvoxamine](#) treatment, indicating that the [haloperidol](#) concentrations may have continued to increase at a constant dose of [fluvoxamine](#). The coadministration of [haloperidol](#) and [fluvoxamine](#) also worsened all measures of clinical and cognitive function assessments, including delayed recall memory and attentional function. It is possible that [haloperidol](#) may require the cytochrome P450 1A2 system for metabolism, and [fluvoxamine](#) is known to be a potent inhibitor of this enzyme pathway [239].

3.5.1.DJ] [Heparin](#)

- 1) Interaction Effect: an increased risk of bleeding
- 2) Summary: The release of serotonin by [platelets](#) is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs and anticoagulants has been associated with an increased risk of bleeding[114][115][113]. 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](#). In patients receiving

warfarin and **fluvoxamine** concomitantly for 2 weeks, **warfarin** plasma concentrations increased by 98% and prothrombin times were prolonged. **Fluvoxamine** appears to inhibit several cytochrome P450 isoenzymes which may include 1A2 and 2C9 isozymes, which are responsible for **warfarin** metabolism [115][113].

3) Severity: major

4) Onset: delayed

5) Substantiation: probable

6) Clinical Management: When **fluvoxamine** 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 **fluvoxamine** therapy is initiated or discontinued. Periodically reassess the prothrombin time ratio and INR in patients receiving **fluvoxamine** and **anticoagulant therapy**[113].

7) Probable Mechanism: unknown

8) Literature Reports

a) According to a retrospective cohort study (n=234), there was an increased risk of clinically relevant bleeding (hospital admission due to bleeding) in patients receiving **warfarin** for **atrial fibrillation** during concomitant SSRI therapy or within 2 weeks following SSRI therapy termination. Patients with a mean age of 72 +/- 7 years receiving **warfarin** plus SSRI (n=117) were matched with randomly selected patients who received **warfarin** only (n=117). SSRI included **fluoxetine**, **citalopram**, **paroxetine**, **sertraline**, **fluvoxamine**, or escitalopram. Nine patients experienced 11 bleeding episodes during 213.9 treatment years in the **warfarin** plus SSRI group, and 10 patients experienced 14 bleedings during 586.4 treatment years in the warfarin-only group. The corresponding total incidences of bleedings were 51.4 and 23.9 per 1000 treatment years, respectively. The hazard ratio for first bleedings during treatment with **warfarin** plus SSRI was 3.49 (95% CI; 1.37 to 8.91, p=0.009) compared with **warfarin** only. The SSRI implicated in patients experiencing bleeding at the time of concomitant administration were **sertraline** or **citalopram**. The addition of an SSRI was not associated with a change in **warfarin** dose or INR (p=0.48 and p=0.31 respectively). The results of the study may be limited by earlier bleeding events, unknown patient adherence, and exclusion of **clopidogrel**, dipyridamol, corticosteroids and anticoagulants other than **warfarin** in the model [114].

b) A population-based, case-controlled study of new coumarin users (acenocoumarol and phenprocoumon) with concomitant selective serotonin reuptake inhibitors (SSRIs) resulted in an increased risk of hospitalization due to nongastrointestinal bleeding. Using national pharmacy and hospitalization records, Netherlands researchers identified 1848 cases that were admitted for abnormal bleeding and compared them with 5818 control subjects also taking coumarins. Median duration of treatment in patients was 220 days (range, 1 to 4690 days). Patients on SSRIs showed greater risk for hospitalization for nongastrointestinal bleeding (adjusted odds ratio (OR) 1.7, 95% confidence interval (CI), 1.1 to 2.5), however, the rate of **gastrointestinal bleeding** (adjusted OR 0.8, 95% CI, 0.4 to 1.5) was not significantly different [115].

c) A hospitalized 80-year-old female was started on intravenous **heparin** and oral **warfarin** therapy due to an **embolic stroke** secondary to **atrial fibrillation** and **mitral stenosis**. Her **warfarin** dose was maintained at 1 mg daily, with her INR between 2.5 and 3. **Fluvoxamine** 25 mg daily was started for depression, and her **warfarin** dose was increased to 1.5 mg daily 3 days later due to worsening of the left **hemiparesis**. Three days later, her INR was 9.96, and a repeat INR to rule out laboratory error was 11.3. **Warfarin** was discontinued, fresh frozen plasma was given, and **fluvoxamine** was discontinued. Six days later, **warfarin** was again started at 1 mg daily, and the INR increased over

4 days to 11.8. The elevated INR was attributed to the persisting effect of [fluvoxamine](#). She was eventually stabilized on [warfarin](#) 1 mg daily with INR values between 2 and 2.5 [116].

3.5.1.DK| Hydroxytryptophan

- 1) Interaction Effect: an increased risk of [serotonin syndrome](#) ([hypertension](#), [hyperthermia](#), myoclonus, mental status changes)
- 2) Summary: Potentially life-threatening [serotonin syndrome](#) has been reported with SSRIs when used concomitantly with other serotonergic drugs, such as hydroxytryptophan or tryptophan. If coadministration is clinically warranted, monitor for the development of [serotonin syndrome](#), especially during treatment initiation and dose increases[166].
- 3) Severity: major
- 4) Onset: rapid
- 5) Substantiation: theoretical
- 6) Clinical Management: Potentially life-threatening [serotonin syndrome](#) has been reported with SSRIs when used concomitantly with other serotonergic drugs, such as hydroxytryptophan or tryptophan. If coadministration is clinically warranted, monitor for the development of [serotonin syndrome](#), especially during treatment initiation and dose increases[166].
- 7) Probable Mechanism: additive serotonergic effect
- 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 [167].

3.5.1.DL| Ibuprofen

- 1) Interaction Effect: an increased risk of bleeding
- 2) Summary: Caution is recommended with the concomitant use of NSAIDs and antidepressants, including SSRIs due to an increased risk of [intracranial hemorrhage](#)[367] and [gastrointestinal bleeding](#) [371][372][368][369]. Bleeding events have included [epistaxis](#), ecchymosis, [hematoma](#), [petechiae](#), and life-threatening hemorrhages [374][373][375][376]. When an SSRI and an NSAID are given concurrently, monitor the patient for signs of increased bleeding.
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: established
- 6) Clinical Management: Use caution if NSAIDs and SSRIs are coadministered. Concomitant use of NSAIDs and SSRIs may cause an increased risk of [intracranial hemorrhage](#)[367] and [gastrointestinal bleeding](#) [368][369]. When an SSRI and an NSAID are given concurrently, monitor the patient for signs of increased bleeding.
- 7) Probable Mechanism: depletion of [platelet](#) serotonin by SSRI; additive effects
- 8) Literature Reports

a) Concomitant use of NSAIDs and antidepressants, including tricyclic antidepressants, SSRIs, serotonin-norepinephrine reuptake inhibitors, and MAOIs, resulted in a 60% increased risk of [intracranial hemorrhage](#) within 30 days of concomitant use compared with antidepressant use alone. There was no significant difference between the antidepressant drug classes and the increased risk; however, there was an increased risk associated with male patients compared with female patients [367].

b) 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. Combined use of an SSRI and NSAIDs or low-dose [aspirin](#) increased the risk to 12.2 and 5.2 times, 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 [370].

c) Two metaanalyses of incidents of upper GI bleed due to SSRIs, NSAIDs, and their combination found that SSRIs increased the risk by 1.73 [371] to 2.36 times [372], NSAIDs by 2.55 times [371], and the combination of SSRIs and NSAIDs by 4.02 [371] to 6.33 times [372].

d) The release of serotonin by [platelets](#) is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs and NSAIDs have been associated with an increased risk of bleeding [373].

3.5.1.DM] [Ibuprofen](#) Lysine

1) Interaction Effect: an increased risk of bleeding

2) Summary: Caution is recommended with the concomitant use of NSAIDs and antidepressants, including SSRIs due to an increased risk of [intracranial hemorrhage](#)[367] and [gastrointestinal bleeding](#) [371][372][368][369]. Bleeding events have included [epistaxis](#), ecchymosis, [hematoma](#), [petechiae](#), and life-threatening hemorrhages [374][373][375][376]. When an SSRI and an NSAID are given concurrently, monitor the patient for signs of increased bleeding.

3) Severity: major

4) Onset: unspecified

5) Substantiation: established

6) Clinical Management: Use caution if NSAIDs and SSRIs are coadministered. Concomitant use of NSAIDs and SSRIs may cause an increased risk of [intracranial hemorrhage](#)[367] and [gastrointestinal bleeding](#) [368][369]. When an SSRI and an NSAID are given concurrently, monitor the patient for signs of increased bleeding.

7) Probable Mechanism: depletion of [platelet](#) serotonin by SSRI; additive effects

8) Literature Reports

a) Concomitant use of NSAIDs and antidepressants, including tricyclic antidepressants, SSRIs, serotonin-norepinephrine reuptake inhibitors, and MAOIs, resulted in a 60% increased risk of [intracranial hemorrhage](#) within 30 days of concomitant use compared with antidepressant use alone. There was no significant difference between the antidepressant drug classes and the increased risk; however, there was an increased risk associated with male patients compared with female patients [367].

b) 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. Combined use of an SSRI and NSAIDs or low-dose [aspirin](#) increased the risk to 12.2 and 5.2 times, 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 [370].

c) Two metaanalyses of incidents of upper GI bleed due to SSRIs, NSAIDs, and their combination found that SSRIs increased the risk by 1.73 [371] to 2.36 times [372], NSAIDs by 2.55 times [371], and the combination of SSRIs and NSAIDs by 4.02 [371] to 6.33 times [372].

d) The release of serotonin by [platelets](#) is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs and NSAIDs have been associated with an increased risk of bleeding [373].

3.5.1.DN| [Iloprost](#)

1) Interaction Effect: increased risk of bleeding

2) Summary: Exercise caution when coadministering a SSRI and an antiplatelet agent as this may increase the risk of bleeding events[139][138].[137]. Bleeding events reported have included [epistaxis](#), ecchymosis, [hematoma](#), [petechiae](#), and life-threatening hemorrhages. Monitor patient for signs of increased bleeding when [fluvoxamine](#) is administered with an antiplatelet agent concomitantly [137].

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: When [fluvoxamine](#) and an antiplatelet agent are given concurrently, monitor patient for signs of increased bleeding[137].

7) Probable Mechanism: unknown

8) Literature Reports

a) In a retrospective study of patients over 50 years of age with the diagnosis of acute [myocardial infarction](#) (N=27,058), SSRI use with any antiplatelet therapy significantly increased the risk of bleeding by 1.42-fold compared with [aspirin](#) use alone. Therapy with [aspirin](#), [clopidogrel](#), and an SSRI significantly increased risk by 2.35-fold compared with [aspirin](#) use alone and by 1.57-fold compared with [clopidogrel](#) and [aspirin](#) combination therapy [138].

b) In a systematic review and meta-analysis of 22 observational studies, SSRI use was associated with a significant 1.55 fold increase in risk of [upper gastrointestinal bleeding](#) (UGIB). Concomitant use of SSRIs and antiplatelet drugs was associated with a 2.48-fold increase in risk of UGIB (3 studies) [139].

3.5.1.DO| [Imipramine](#)

1) Interaction Effect: [imipramine](#) toxicity (dry mouth, urinary retention, sedation)

2) Summary: Addition of [fluvoxamine](#) to [imipramine](#) or [desipramine](#) therapy can result in significantly increased tricyclic antidepressant plasma levels and signs of tricyclic toxicity[102][103][104]. [Fluvoxamine](#) significantly increases [imipramine](#) half-life and reduces clearance [104]. The addition of [fluvoxamine](#) to [imipramine](#) or [desipramine](#) therapy may result in greatly increased tricyclic antidepressant plasma levels and tricyclic toxicity [102][103]. A bidirectional effect is suggested, in which [fluvoxamine](#) increases [imipramine](#) concentrations (by interfering with N-demethylation), and [imipramine](#) increases [fluvoxamine](#) levels [105].

3) Severity: moderate

4) Onset: delayed

5) Substantiation: probable

6) Clinical Management: Monitor patients for signs of [imipramine](#) and [fluvoxamine](#) toxicity; lower doses of one or both agents may be required with concomitant therapy.

7) Probable Mechanism: decreased [imipramine](#) metabolism

8) Literature Reports

a) The pharmacokinetics of combined [imipramine](#) and [fluvoxamine](#) were studied in healthy volunteers [98]. After a 7-day course of [fluvoxamine](#), [imipramine](#) half-life was significantly increased (from 23 to 41 hours) and clearance decreased (from 1.02 to 0.28 L/h/kg).

b) The addition of [fluvoxamine](#) to [imipramine](#) or [desipramine](#) in four patients was reported to result in greatly increased tricyclic antidepressant plasma levels [99]. Three of four patients showed signs of tricyclic toxicity. The effect of [fluvoxamine](#) 100 mg daily for 10 days on plasma concentrations of [imipramine](#) was studied in seven depressed patients on maintenance therapy [100]. [Imipramine](#) plasma levels were three to four times higher during [fluvoxamine](#) coadministration. One patient complained of anticholinergic effects, along with tremor and confusion. The mechanism of this drug interaction was inhibition of demethylation of [imipramine](#). A [pharmacokinetic study](#) in healthy volunteers demonstrated a significantly increased [imipramine](#) half-life and reduced clearance [98].

c) Metabolism of tricyclic antidepressants coadministered with [fluvoxamine](#) was studied in eight depressed patients (two patients received [imipramine](#)) [101]. [Fluvoxamine](#) was found to interfere with N-demethylation of [imipramine](#). The combination of [fluvoxamine](#) and [imipramine](#) led to increased plasma levels of [imipramine](#) and decreased concentrations of the N-demethylated [imipramine](#) metabolite desimipramine. In addition, TCA-fluvoxamine coadministration apparently raised plasma levels of [fluvoxamine](#).

3.5.1.DP| Indomethacin

1) Interaction Effect: an increased risk of bleeding

2) Summary: Caution is recommended with the concomitant use of NSAIDs and antidepressants, including SSRIs due to an increased risk of [intracranial hemorrhage](#)[367] and [gastrointestinal bleeding](#) [371][372][368][369]. Bleeding events have included [epistaxis](#), ecchymosis, [hematoma](#), [petechiae](#), and life-threatening hemorrhages [374][373][375][376]. When an SSRI and an NSAID are given concurrently, monitor the patient for signs of increased bleeding.

3) Severity: major

4) Onset: unspecified

5) Substantiation: established

6) Clinical Management: Use caution if NSAIDs and SSRIs are coadministered. Concomitant use of NSAIDs and SSRIs may cause an increased risk of [intracranial hemorrhage](#)[367] and [gastrointestinal bleeding](#) [368][369]. When an SSRI and an NSAID are given concurrently, monitor the patient for signs of increased bleeding.

7) Probable Mechanism: depletion of [platelet](#) serotonin by SSRI; additive effects

8) Literature Reports

a) Concomitant use of NSAIDs and antidepressants, including tricyclic antidepressants, SSRIs, serotonin-norepinephrine reuptake inhibitors, and MAOIs, resulted in a 60% increased risk of [intracranial hemorrhage](#) within 30 days of concomitant use compared with antidepressant use alone. There was no significant difference between the antidepressant drug classes and the increased risk; however, there was an increased risk associated with male patients compared with female patients [367].

b) 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. Combined use of an SSRI and NSAIDs or low-dose [aspirin](#) increased the risk to 12.2 and 5.2 times, 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 [370].

c) Two metaanalyses of incidents of upper GI bleed due to SSRIs, NSAIDs, and their combination found that SSRIs increased the risk by 1.73 [371] to 2.36 times [372], NSAIDs by 2.55 times [371], and the combination of SSRIs and NSAIDs by 4.02 [371] to 6.33 times [372].

d) The release of serotonin by [platelets](#) is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs and NSAIDs have been associated with an increased risk of bleeding [373].

3.5.1.DQ| [Iobenguane I 123](#)

1) Interaction Effect: potential for false negative imaging results

2) Summary: Iobenguane is similar in structure to the neurotransmitter [norepinephrine](#) and is taken up by the [norepinephrine](#) transporter in adrenergic nerve terminals. It is stored in the presynaptic storage vesicles. Iobenguane will accumulate in adrenergically innervated tissues and labeling iobenguane with the isotope [iodine 123](#) will provide images of specific organs and tissues. Antidepressants that inhibit [norepinephrine](#) transporter function, such as SSRIs, tricyclic antidepressants, and MAOIs, may interfere with the clinical efficacy of [iobenguane I 123](#). Increasing the dose of [iobenguane I 123](#) will not overcome any potential [norepinephrine](#) uptake inhibition by these drugs. If [iobenguane I 123](#) imaging is necessary, discontinue this drug for at least 5 biological half-lives when clinically feasible[238].

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Concomitant use of [iobenguane I 123](#) and this drug has the potential to inhibit [norepinephrine](#) transporter function and cause false negative imaging results. Increasing the dose of [iobenguane I 123](#) will not overcome any potential [norepinephrine](#) uptake inhibition by these drugs. If [iobenguane I 123](#) imaging is necessary, discontinue this drug for at least 5 biological half-lives when clinically feasible[238].

7) Probable Mechanism: inhibition of [norepinephrine](#) transporter function by antidepressants

3.5.1.DR| [Iproniazid](#)

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

2) Summary: Concomitant use of [fluvoxamine](#) and an MAOI is contraindicated. Concurrent administration or overlapping therapy with [fluvoxamine](#) and an MAOI may result in [serotonin syndrome](#), a hyperserotonergic state characterized by symptoms such as agitation and hallucinations, myoclonus, changes in mental status, hyperreflexia, diaphoresis, rigidity, and tremor. Serious, even fatal, reactions have been reported with concomitant use of SSRIs and MAOIs. A minimum of 14 days should elapse after discontinuing an MAOI intended to treat psychiatric disorders before initiating therapy with [fluvoxamine](#), and a minimum of 14 days should elapse after discontinuing [fluvoxamine](#) before initiating therapy with an MAOI intended to treat psychiatric disorders[20].

3) Severity: contraindicated

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Concurrent use of [fluvoxamine](#) and an MAOI is contraindicated. Wait at least 14 days after discontinuing an MAOI intended to treat psychiatric disorders before initiating [fluvoxamine](#). Wait at least 14 days after discontinuing [fluvoxamine](#) before initiating therapy with an MAOI intended to treat psychiatric disorders[20].

7) Probable Mechanism: additive serotonergic effect

3.5.1.DS] [Isocarboxazid](#)

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

2) Summary: Concomitant use of [fluvoxamine](#) and an MAOI is contraindicated. Concurrent administration or overlapping therapy with [fluvoxamine](#) and an MAOI may result in [serotonin syndrome](#), a hyperserotonergic state characterized by symptoms such as agitation and hallucinations, myoclonus, changes in mental status, hyperreflexia, diaphoresis, rigidity, and tremor. Serious, even fatal, reactions have been reported with concomitant use of SSRIs and MAOIs. A minimum of 14 days should elapse after discontinuing an MAOI intended to treat psychiatric disorders before initiating therapy with [fluvoxamine](#), and a minimum of 14 days should elapse after discontinuing [fluvoxamine](#) before initiating therapy with an MAOI intended to treat psychiatric disorders[20].

3) Severity: contraindicated

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Concurrent use of [fluvoxamine](#) and an MAOI is contraindicated. Wait at least 14 days after discontinuing an MAOI intended to treat psychiatric disorders before initiating [fluvoxamine](#). Wait at least 14 days after discontinuing [fluvoxamine](#) before initiating therapy with an MAOI intended to treat psychiatric disorders[20].

7) Probable Mechanism: additive serotonergic effect

3.5.1.DT] [Ketoprofen](#)

1) Interaction Effect: an increased risk of bleeding

2) Summary: Caution is recommended with the concomitant use of NSAIDs and antidepressants, including SSRIs due to an increased risk of [intracranial hemorrhage](#)[367] and [gastrointestinal bleeding](#) [371][372][368][369]. Bleeding events have included [epistaxis](#), ecchymosis, [hematoma](#), [petechiae](#), and life-threatening hemorrhages [374][373][375][376]. When an SSRI and an NSAID are given concurrently, monitor the patient for signs of increased bleeding.

3) Severity: major

4) Onset: unspecified

5) Substantiation: established

6) Clinical Management: Use caution if NSAIDs and SSRIs are coadministered. Concomitant use of NSAIDs and SSRIs may cause an increased risk of [intracranial hemorrhage](#)[367] and [gastrointestinal bleeding](#) [368][369]. When an SSRI and an NSAID are given concurrently, monitor the patient for signs of increased bleeding.

7) Probable Mechanism: depletion of [platelet](#) serotonin by SSRI; additive effects

8) Literature Reports

a) Concomitant use of NSAIDs and antidepressants, including tricyclic antidepressants, SSRIs, serotonin-norepinephrine reuptake inhibitors, and MAOIs, resulted in a 60% increased risk of [intracranial hemorrhage](#) within 30 days of concomitant use compared with antidepressant use alone. There was no significant difference between the antidepressant drug classes and the increased risk; however, there was an increased risk associated with male patients compared with female patients [367].

b)) 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. Combined use of an SSRI and NSAIDs or low-dose [aspirin](#) increased the risk to 12.2 and 5.2 times, 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 [370].

c)) Two metaanalyses of incidents of upper GI bleed due to SSRIs, NSAIDs, and their combination found that SSRIs increased the risk by 1.73 [371] to 2.36 times [372], NSAIDs by 2.55 times [371], and the combination of SSRIs and NSAIDs by 4.02 [371] to 6.33 times [372].

d)) The release of serotonin by [platelets](#) is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs and NSAIDs have been associated with an increased risk of bleeding [373].

3.5.1.DU] Ketorolac

1)) Interaction Effect: an increased risk of bleeding

2)) Summary: Caution is recommended with the concomitant use of NSAIDs and antidepressants, including SSRIs due to an increased risk of [intracranial hemorrhage](#)[367] and [gastrointestinal bleeding](#) [371][372][368][369]. Bleeding events have included [epistaxis](#), ecchymosis, [hematoma](#), [petechiae](#), and life-threatening hemorrhages [374][373][375][376]. When an SSRI and an NSAID are given concurrently, monitor the patient for signs of increased bleeding.

3)) Severity: major

4)) Onset: unspecified

5)) Substantiation: established

6)) Clinical Management: Use caution if NSAIDs and SSRIs are coadministered. Concomitant use of NSAIDs and SSRIs may cause an increased risk of [intracranial hemorrhage](#)[367] and [gastrointestinal bleeding](#) [368][369]. When an SSRI and an NSAID are given concurrently, monitor the patient for signs of increased bleeding.

7)) Probable Mechanism: depletion of [platelet](#) serotonin by SSRI; additive effects

8)) Literature Reports

a)) Concomitant use of NSAIDs and antidepressants, including tricyclic antidepressants, SSRIs, serotonin-norepinephrine reuptake inhibitors, and MAOIs, resulted in a 60% increased risk of [intracranial hemorrhage](#) within 30 days of concomitant use compared with antidepressant use alone. There was no significant difference between the antidepressant drug classes and the increased risk; however, there was an increased risk associated with male patients compared with female patients [367].

b)) 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. Combined use of an SSRI and NSAIDs or low-dose [aspirin](#) increased the risk to 12.2 and 5.2 times, 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 [370].

- c) Two metaanalyses of incidents of upper GI bleed due to SSRIs, NSAIDs, and their combination found that SSRIs increased the risk by 1.73 [371] to 2.36 times [372], NSAIDs by 2.55 times [371], and the combination of SSRIs and NSAIDs by 4.02 [371] to 6.33 times [372].
- d) The release of serotonin by [platelets](#) is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs and NSAIDs have been associated with an increased risk of bleeding [373].

3.5.1.DV] 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 [fluvoxamine](#) that prolong the QT interval[385].
- 3) Severity: contraindicated
- 4) Onset: delayed
- 5) Substantiation: theoretical
- 6) Clinical Management: Levomethadyl is contraindicated in patients being treated with [fluvoxamine](#) as it may precipitate QT prolongation and interact with levomethadyl.
- 7) Probable Mechanism: unknown

3.5.1.DW] Levomilnacipran

- 1) Interaction Effect: increased risk of [serotonin syndrome](#) ([hypertension](#), [hyperthermia](#), myoclonus, mental status changes)
- 2) Summary: Levomilnacipran is a serotonergic drug; concomitant use with another agent that affects the serotonergic neurotransmitter system may result in an increased risk of potentially life-threatening [serotonin syndrome](#) and should be approached with extreme caution. 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[400].
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Use extreme caution with coadministration of levomilnacipran and another serotonergic drug, 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[400].
- 7) Probable Mechanism: additive serotonergic effects

3.5.1.DX] Levothyroxine

- 1) Interaction Effect: increased [levothyroxine](#) requirements
- 2) Summary: Use caution with coadministration of [levothyroxine](#) and an SSRI. In patients stabilized on [levothyroxine](#), administration of [sertraline](#), for example, may require an increase in [levothyroxine](#) dose[380].
- 3) Severity: moderate
- 4) Onset: unspecified

- 5J) Substantiation: theoretical
- 6J) Clinical Management: Use caution with coadministration of [levothyroxine](#) and an SSRI. In patients stabilized on [levothyroxine](#), administration of [sertraline](#), for example, may require an increase in [levothyroxine](#) dose[380].
- 7J) Probable Mechanism: unknown

3.5.1.DY] [Linezolid](#)

- 1J) Interaction Effect: an increased risk of [serotonin syndrome](#) ([hypertension](#), [tachycardia](#), [hyperthermia](#), myoclonus, mental status changes)
- 2J) Summary: Concurrent use of [fluvoxamine](#) and an MAOI, such as [linezolid](#), is contraindicated. If urgent treatment with [linezolid](#) is necessary in a patient receiving [fluvoxamine](#), alternatives are not available, and risk/benefit has been evaluated, promptly discontinue [fluvoxamine](#) and then [linezolid](#) may be administered. Monitor for [serotonin syndrome](#) for 2 weeks or until 24 hours after the last dose of [linezolid](#), whichever comes first. [Fluvoxamine](#) can be resumed 24 hours after the last dose of [linezolid](#)[153].
- 3J) Severity: contraindicated
- 4J) Onset: unspecified
- 5J) Substantiation: theoretical
- 6J) Clinical Management: Concurrent use of [fluvoxamine](#) and an MAOI, such as [linezolid](#), is contraindicated. If urgent treatment with [linezolid](#) is necessary in a patient receiving [fluvoxamine](#), alternatives are not available, and risk/benefit has been evaluated, promptly discontinue [fluvoxamine](#) and then [linezolid](#) may be administered. Monitor for [serotonin syndrome](#) for 2 weeks or until 24 hours after the last dose of [linezolid](#), whichever comes first. [Fluvoxamine](#) can be resumed 24 hours after the last dose of [linezolid](#)[153].
- 7J) Probable Mechanism: additive serotonergic effects

3.5.1.DZ] [Lisdexamfetamine](#)

- 1J) Interaction Effect: increased [amphetamine](#) exposure and increased risk of [serotonin syndrome](#)
- 2J) Summary: Coadministration of an [amphetamine](#) and a serotonergic agent that inhibits CYP2D6 may result in increased [amphetamine](#) exposure and additional risk for [serotonin syndrome](#). If concomitant use of an [amphetamine](#) and such an agent is clinically required, initiate with lower doses and monitor patients carefully, especially during treatment initiation and dosage adjustment. Discontinue both drugs if [serotonin syndrome](#) is suspected[377].
- 3J) Severity: major
- 4J) Onset: unspecified
- 5J) Substantiation: theoretical
- 6J) Clinical Management: Coadministration of an [amphetamine](#) and another serotonergic agent may result in [serotonin syndrome](#), because both drugs affect the serotonergic neurotransmitter system. Additionally, coadministration of an [amphetamine](#) with a CYP2D6 inhibitor may increase [amphetamine](#) exposure, because [amphetamines](#) and their derivatives are metabolized to some degree by CYP2D6. An increase in [amphetamine](#) exposure may further increase risk of [serotonin syndrome](#). If concomitant use of an [amphetamine](#) and a serotonergic agent that inhibits CYP2D6 is clinically required, initiate with lower doses and monitor patients carefully, especially during treatment initiation and dosage adjustment. Discontinue both drugs if [serotonin syndrome](#) is suspected[377].
- 7J) Probable Mechanism: inhibition of CYP2D6-mediated metabolism of [amphetamine](#); additive serotonergic effects

3.5.1.EA] [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[352]. 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](#) [353][354]. Two studies have failed to identify a pharmacokinetic interaction between [lithium](#) and [citalopram](#) [355][356]. 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 [357]. Concurrent use of [fluvoxamine](#) and [lithium](#) has led to case reports of increased [lithium](#) levels and [neurotoxicity](#), [serotonin syndrome](#), somnolence, and mania [352][358][359] [360]. No pharmacokinetic interference was apparent during a multiple-dose study of coadministered [lithium](#) and [paroxetine](#) [361]. 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) [358][352].
- 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](#) [344]. [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](#) [345].

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** [346].

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** [347].

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 [348].

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 [349].

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 [350].

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 [351].

3.5.1.EB] Lomitapide

1) Interaction Effect: increased exposure of lomitapide

2) Summary: The concomitant use of lomitapide (a CYP3A4 substrate) and a weak CYP3A4 inhibitor may cause increased exposure to lomitapide. When the weak CYP3A4 inhibitor, [atorvastatin](#) was coadministered with lomitapide, the systemic exposure of lomitapide increased by approximately 2-fold. If concurrent use is required, the maximum lomitapide dosage is 30 mg daily. When initiating a weak CYP3A4 inhibitor in patients already taking lomitapide 10 mg/day or more, decrease the lomitapide dose by 50%. Then carefully titrate based on response and tolerability to a maximum of 30 mg/day[133].

3) Severity: moderate

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: The concomitant use of lomitapide (a CYP3A4 substrate) with a weak CYP3A4 inhibitor may cause increased exposure to lomitapide. If concurrent use is required, the maximum lomitapide dosage is 30 mg daily. When initiating a weak CYP3A4 inhibitor in patients already taking lomitapide 10 mg/day or more, decrease the lomitapide dose by 50%. Then carefully titrate based on response and tolerability to a maximum of 30 mg/day[133]

7) Probable Mechanism: inhibition of CYP3A4-mediated lomitapide metabolism

8) Literature Reports

a) The concomitant administration of the weak CYP3A4 inhibitor [atorvastatin](#) 80 mg daily with a single 20-mg dose of lomitapide increased the AUC of lomitapide 2-fold and Cmax 2.1-fold compared with lomitapide administered alone [133].

3.5.1.EC] Lorcaserin

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

2) 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[186].

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) 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[186].

7) Probable Mechanism: additive serotonergic effects

3.5.1.ED] Lornoxicam

1) Interaction Effect: an increased risk of bleeding

2) Summary: Caution is recommended with the concomitant use of NSAIDs and antidepressants, including SSRIs due to an increased risk of [intracranial hemorrhage](#)[367] and [gastrointestinal bleeding](#)

[371][372][368][369]. Bleeding events have included [epistaxis](#), ecchymosis, [hematoma](#), [petechiae](#), and life-threatening hemorrhages [374][373][375][376]. When an SSRI and an NSAID are given concurrently, monitor the patient for signs of increased bleeding.

3) Severity: major

4) Onset: unspecified

5) Substantiation: established

6) Clinical Management: Use caution if NSAIDs and SSRIs are coadministered. Concomitant use of NSAIDs and SSRIs may cause an increased risk of [intracranial hemorrhage](#)[367] and [gastrointestinal bleeding](#) [368][369]. When an SSRI and an NSAID are given concurrently, monitor the patient for signs of increased bleeding.

7) Probable Mechanism: depletion of [platelet](#) serotonin by SSRI; additive effects

8) Literature Reports

a) Concomitant use of NSAIDs and antidepressants, including tricyclic antidepressants, SSRIs, serotonin-norepinephrine reuptake inhibitors, and MAOIs, resulted in a 60% increased risk of [intracranial hemorrhage](#) within 30 days of concomitant use compared with antidepressant use alone. There was no significant difference between the antidepressant drug classes and the increased risk; however, there was an increased risk associated with male patients compared with female patients [367].

b) 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. Combined use of an SSRI and NSAIDs or low-dose [aspirin](#) increased the risk to 12.2 and 5.2 times, 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 [370].

c) Two metaanalyses of incidents of upper GI bleed due to SSRIs, NSAIDs, and their combination found that SSRIs increased the risk by 1.73 [371] to 2.36 times [372], NSAIDs by 2.55 times [371], and the combination of SSRIs and NSAIDs by 4.02 [371] to 6.33 times [372].

d) The release of serotonin by [platelets](#) is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs and NSAIDs have been associated with an increased risk of bleeding [373].

3.5.1.EE] [Lovastatin](#)

1) Interaction Effect: increased plasma concentrations of selected statins and increased risk for [myopathy](#) and [rhabdomyolysis](#)

2) Summary: Coadministration of [fluvoxamine](#) with selected statins may result in increased plasma levels of the statin drug and an increased risk for [myopathy](#). Monitor the patient and consider lowering the dosage of the statin drug[188].

3) Severity: moderate

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Coadministration of [fluvoxamine](#) with selected statins may result in increased plasma levels of the statin drug and an increased risk for [myopathy](#). Monitor the patient for unexplained muscle pain, tenderness, and weakness, and consider lowering the dosage of the statin drug[188].

7) Probable Mechanism: inhibition of CYP3A4-mediated statin metabolism

3.5.1.EF] Loxoprofen

- 1) Interaction Effect: an increased risk of bleeding
- 2) Summary: Caution is recommended with the concomitant use of NSAIDs and antidepressants, including SSRIs due to an increased risk of [intracranial hemorrhage](#)[367] and [gastrointestinal bleeding](#) [371][372][368][369]. Bleeding events have included [epistaxis](#), ecchymosis, [hematoma](#), [petechiae](#), and life-threatening hemorrhages [374][373][375][376]. When an SSRI and an NSAID are given concurrently, monitor the patient for signs of increased bleeding.
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: established
- 6) Clinical Management: Use caution if NSAIDs and SSRIs are coadministered. Concomitant use of NSAIDs and SSRIs may cause an increased risk of [intracranial hemorrhage](#)[367] and [gastrointestinal bleeding](#) [368][369]. When an SSRI and an NSAID are given concurrently, monitor the patient for signs of increased bleeding.
- 7) Probable Mechanism: depletion of [platelet](#) serotonin by SSRI; additive effects
- 8) Literature Reports

a) Concomitant use of NSAIDs and antidepressants, including tricyclic antidepressants, SSRIs, serotonin-norepinephrine reuptake inhibitors, and MAOIs, resulted in a 60% increased risk of [intracranial hemorrhage](#) within 30 days of concomitant use compared with antidepressant use alone. There was no significant difference between the antidepressant drug classes and the increased risk; however, there was an increased risk associated with male patients compared with female patients [367].

b) 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. Combined use of an SSRI and NSAIDs or low-dose [aspirin](#) increased the risk to 12.2 and 5.2 times, 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 [370].

c) Two metaanalyses of incidents of upper GI bleed due to SSRIs, NSAIDs, and their combination found that SSRIs increased the risk by 1.73 [371] to 2.36 times [372], NSAIDs by 2.55 times [371], and the combination of SSRIs and NSAIDs by 4.02 [371] to 6.33 times [372].

d) The release of serotonin by [platelets](#) is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs and NSAIDs have been associated with an increased risk of bleeding [373].

3.5.1.EG] Lumiracoxib

- 1) Interaction Effect: an increased risk of bleeding
- 2) Summary: Caution is recommended with the concomitant use of NSAIDs and antidepressants, including SSRIs due to an increased risk of [intracranial hemorrhage](#)[367] and [gastrointestinal bleeding](#) [371][372][368][369]. Bleeding events have included [epistaxis](#), ecchymosis, [hematoma](#), [petechiae](#), and life-threatening hemorrhages [374][373][375][376]. When an SSRI and an NSAID are given concurrently, monitor the patient for signs of increased bleeding.

- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: established
- 6) Clinical Management: Use caution if NSAIDs and SSRIs are coadministered. Concomitant use of NSAIDs and SSRIs may cause an increased risk of [intracranial hemorrhage](#)[367] and [gastrointestinal bleeding](#) [368][369]. When an SSRI and an NSAID are given concurrently, monitor the patient for signs of increased bleeding.
- 7) Probable Mechanism: depletion of [platelet](#) serotonin by SSRI; additive effects
- 8) Literature Reports

a) Concomitant use of NSAIDs and antidepressants, including tricyclic antidepressants, SSRIs, serotonin-norepinephrine reuptake inhibitors, and MAOIs, resulted in a 60% increased risk of [intracranial hemorrhage](#) within 30 days of concomitant use compared with antidepressant use alone. There was no significant difference between the antidepressant drug classes and the increased risk; however, there was an increased risk associated with male patients compared with female patients [367].

b) 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. Combined use of an SSRI and NSAIDs or low-dose [aspirin](#) increased the risk to 12.2 and 5.2 times, 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 [370].

c) Two metaanalyses of incidents of upper GI bleed due to SSRIs, NSAIDs, and their combination found that SSRIs increased the risk by 1.73 [371] to 2.36 times [372], NSAIDs by 2.55 times [371], and the combination of SSRIs and NSAIDs by 4.02 [371] to 6.33 times [372].

d) The release of serotonin by [platelets](#) is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs and NSAIDs have been associated with an increased risk of bleeding [373].

3.5.1.EH] [Maprotiline](#)

- 1) Interaction Effect: [maprotiline](#) toxicity (dry mouth, urinary retention, sedation)
- 2) Summary: An interaction of [fluvoxamine](#) with tricyclic antidepressants (TCAs) was reported[327]. Plasma concentrations of TCAs were increased when combined with [fluvoxamine](#). This effect was less prominent with [maprotiline](#) compared with [imipramine](#), [clomipramine](#), or [amitriptyline](#). In addition, TCAs appeared to increase [fluvoxamine](#) levels.
- 3) Severity: minor
- 4) Onset: delayed
- 5) Substantiation: probable
- 6) Clinical Management: Monitor patients for excess tricyclic antidepressant side effects such as dry mouth and lethargy. [Maprotiline](#) doses may need to be reduced in some clinical situations.
- 7) Probable Mechanism: decreased [maprotiline](#) metabolism
- 8) Literature Reports

a) Metabolism of tricyclic antidepressants coadministered with [fluvoxamine](#) was studied in eight depressed patients (one patient received [maprotiline](#)) [326]. [Fluvoxamine](#) was found to

interfere with N-demethylation of [maprotiline](#). The combination of [fluvoxamine](#) and [maprotiline](#) led to increased plasma levels of [maprotiline](#) and decreased concentrations of [maprotiline's](#) N-demethylated metabolite, desmethylmaprotiline. Also, plasma levels of [fluvoxamine](#) were increased.

3.5.1.EI] Mate

1) Interaction Effect: increased [caffeine](#) levels (insomnia, headache, restlessness, nervousness, palpitations, and [arrhythmias](#))

2) Summary: The primary pharmacologically-active ingredient of mate is [caffeine](#). [Fluvoxamine](#) inhibits CYP1A2 and CYP2D6 which are responsible for [caffeine](#) metabolism. Decreased [caffeine](#) clearance and increased half-life have been demonstrated in humans[132]. Signs and symptoms of [caffeine](#) excess may result if the compounds are taken together. Patients should avoid mate use during therapy with [fluvoxamine](#) in order to avoid possible complications.

3) Severity: moderate

4) Onset: rapid

5) Substantiation: theoretical

6) Clinical Management: Patients should be advised of the [caffeine](#) content of mate, and of symptoms of excess if taken with [fluvoxamine](#) (insomnia, headache, restlessness, nervousness, palpitations, and [arrhythmias](#)), as well as symptoms of [caffeine](#) withdrawal which may accompany abrupt discontinuation of mate (e.g., headache, fatigue, depression, anxiety, and insomnia). Patients should avoid mate use during therapy with [fluvoxamine](#) in order to avoid possible complications.

7) Probable Mechanism: inhibition of [caffeine](#) metabolism

8) Literature Reports

a) In an open, randomized, cross-over study of 8 volunteers, [fluvoxamine](#) significantly decreased [caffeine](#) total clearance and increased [caffeine](#) half-life. [Fluvoxamine](#) was administered as 50 milligrams (mg) for 4 days, then 100 mg for 8 days while subjects abstained from all [caffeine](#) intake. [Caffeine](#) 200 mg was then administered orally. Total clearance of [caffeine](#) decreased from 107 milliliters/minute (mL/min) to 21 mL/min, and half-life increased from 5 hours to 31 hours. Patients taking [fluvoxamine](#) should restrict [caffeine](#) intake [124].

b) In vitro, [fluvoxamine](#) was found to be a very potent inhibitor of the formation of N-demethylated [caffeine](#) metabolites with K_i values of 0.08 micromoles (mcmol) to 0.28 mcmol. The formation of 1,7-dimethylxanthine was abolished by 10 mcmol of [fluvoxamine](#), implying the N3-demethylation of [caffeine](#) is almost entirely catalyzed by CYP1A2 [125].

c) At least 14 metabolites are formed from [caffeine](#) whose main route of elimination is N3-demethylation to paraxanthine (1,7-methylxanthine) which accounts for greater than 80% of [caffeine](#) elimination [126]. CYP1A2 is the major enzyme metabolizing [caffeine](#) to 1,7-dimethylxanthine [127][128][129]. CYP1A2 is also a major enzyme in the formation of 3,7-dimethylxanthine and 1,3-dimethylxanthine from [caffeine](#) [130][127][131].

3.5.1.EJ] Meclofenamate

1) Interaction Effect: an increased risk of bleeding

2) Summary: Caution is recommended with the concomitant use of NSAIDs and antidepressants, including SSRIs due to an increased risk of [intracranial hemorrhage](#)[367] and [gastrointestinal bleeding](#) [371][372][368][369]. Bleeding events have included [epistaxis](#), ecchymosis, [hematoma](#), [petechiae](#), and life-threatening hemorrhages [374][373][375][376]. When an SSRI and an NSAID are given concurrently, monitor the patient for signs of increased bleeding.

- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: established
- 6) Clinical Management: Use caution if NSAIDs and SSRIs are coadministered. Concomitant use of NSAIDs and SSRIs may cause an increased risk of [intracranial hemorrhage](#)[367] and [gastrointestinal bleeding](#) [368][369]. When an SSRI and an NSAID are given concurrently, monitor the patient for signs of increased bleeding.
- 7) Probable Mechanism: depletion of [platelet](#) serotonin by SSRI; additive effects
- 8) Literature Reports

a) Concomitant use of NSAIDs and antidepressants, including tricyclic antidepressants, SSRIs, serotonin-norepinephrine reuptake inhibitors, and MAOIs, resulted in a 60% increased risk of [intracranial hemorrhage](#) within 30 days of concomitant use compared with antidepressant use alone. There was no significant difference between the antidepressant drug classes and the increased risk; however, there was an increased risk associated with male patients compared with female patients [367].

b) 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. Combined use of an SSRI and NSAIDs or low-dose [aspirin](#) increased the risk to 12.2 and 5.2 times, 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 [370].

c) Two metaanalyses of incidents of upper GI bleed due to SSRIs, NSAIDs, and their combination found that SSRIs increased the risk by 1.73 [371] to 2.36 times [372], NSAIDs by 2.55 times [371], and the combination of SSRIs and NSAIDs by 4.02 [371] to 6.33 times [372].

d) The release of serotonin by [platelets](#) is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs and NSAIDs have been associated with an increased risk of bleeding [373].

3.5.1.EK] [Mefenamic Acid](#)

- 1) Interaction Effect: an increased risk of bleeding
- 2) Summary: Caution is recommended with the concomitant use of NSAIDs and antidepressants, including SSRIs due to an increased risk of [intracranial hemorrhage](#)[367] and [gastrointestinal bleeding](#) [371][372][368][369]. Bleeding events have included [epistaxis](#), ecchymosis, [hematoma](#), [petechiae](#), and life-threatening hemorrhages [374][373][375][376]. When an SSRI and an NSAID are given concurrently, monitor the patient for signs of increased bleeding.
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: established
- 6) Clinical Management: Use caution if NSAIDs and SSRIs are coadministered. Concomitant use of NSAIDs and SSRIs may cause an increased risk of [intracranial hemorrhage](#)[367] and [gastrointestinal bleeding](#) [368][369]. When an SSRI and an NSAID are given concurrently, monitor the patient for signs of increased bleeding.
- 7) Probable Mechanism: depletion of [platelet](#) serotonin by SSRI; additive effects
- 8) Literature Reports

a) Concomitant use of NSAIDs and antidepressants, including tricyclic antidepressants, SSRIs, serotonin-norepinephrine reuptake inhibitors, and MAOIs, resulted in a 60% increased risk of [intracranial hemorrhage](#) within 30 days of concomitant use compared with antidepressant use alone. There was no significant difference between the antidepressant drug classes and the increased risk; however, there was an increased risk associated with male patients compared with female patients [367].

b) 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. Combined use of an SSRI and NSAIDs or low-dose [aspirin](#) increased the risk to 12.2 and 5.2 times, 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 [370].

c) Two metaanalyses of incidents of upper GI bleed due to SSRIs, NSAIDs, and their combination found that SSRIs increased the risk by 1.73 [371] to 2.36 times [372], NSAIDs by 2.55 times [371], and the combination of SSRIs and NSAIDs by 4.02 [371] to 6.33 times [372].

d) The release of serotonin by [platelets](#) is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs and NSAIDs have been associated with an increased risk of bleeding [373].

3.5.1.EL] [Melatonin](#)

1) Interaction Effect: increased central nervous system depression

2) Summary: [Fluvoxamine](#) significantly increased [melatonin](#) levels and increased drowsiness when given with [melatonin](#) in a study of 5 healthy volunteers[395]. Endogenous [melatonin](#) levels increased following [fluvoxamine](#) administration in 7 healthy subjects [396]. [Fluvoxamine](#) may inhibit [melatonin](#) elimination [395], or metabolism via cytochrome P450 1A2 or 2C19 [396]. Patients taking [fluvoxamine](#) with or without [melatonin](#) supplementation should be monitored for changes in sleep and central nervous system depression.

3) Severity: minor

4) Onset: rapid

5) Substantiation: probable

6) Clinical Management: Monitor patients taking [fluvoxamine](#) with [melatonin](#) supplementation for changes in sleep patterns and signs of excessive central nervous system depression. Downward titration of [melatonin](#) dosages may be required during concomitant administration with [fluvoxamine](#).

7) Probable Mechanism: inhibition of cytochrome P450 enzymes, possibly CYP1A2 and CYP2C19, responsible for [melatonin](#) metabolism

8) Literature Reports

a) The bioavailability of oral [melatonin](#) was significantly increased after coadministration of [fluvoxamine](#). Five volunteers (one CYP2D6 poor metabolizer) were included in a study that was designed to evaluate the effects of [fluvoxamine](#) on the pharmacokinetics of [melatonin](#). A single dose of [melatonin](#) 5 mg was administered to all subjects. One week later a single oral dose of [fluvoxamine](#) 50 mg was administered to all subjects. Blood samples were evaluated at certain time points after administration of each agent. An increase in [melatonin](#) serum concentrations occurred in all subjects with a 23-fold increase in area under the concentration-time curve (AUC) (6.2 to

141.3 mcg h/L) and a twelve-fold increase in maximum serum concentration (C_{max}) (2.18 to 25.1 ng/ml) of [melatonin](#). The effects of [fluvoxamine](#) on [melatonin](#) pharmacokinetics were effectively greater in the poor CYP2D6 metabolizer. The author suggests that this is most likely due to inhibition of the elimination of [melatonin](#) rather than an increased production of [melatonin](#) [394].

3.5.1.EM] [Meloxicam](#)

- 1) Interaction Effect: an increased risk of bleeding
- 2) Summary: Caution is recommended with the concomitant use of NSAIDs and antidepressants, including SSRIs due to an increased risk of [intracranial hemorrhage](#)[367] and [gastrointestinal bleeding](#) [371][372][368][369]. Bleeding events have included [epistaxis](#), ecchymosis, [hematoma](#), [petechiae](#), and life-threatening hemorrhages [374][373][375][376]. When an SSRI and an NSAID are given concurrently, monitor the patient for signs of increased bleeding.
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: established
- 6) Clinical Management: Use caution if NSAIDs and SSRIs are coadministered. Concomitant use of NSAIDs and SSRIs may cause an increased risk of [intracranial hemorrhage](#)[367] and [gastrointestinal bleeding](#) [368][369]. When an SSRI and an NSAID are given concurrently, monitor the patient for signs of increased bleeding.
- 7) Probable Mechanism: depletion of [platelet](#) serotonin by SSRI; additive effects
- 8) Literature Reports

a) Concomitant use of NSAIDs and antidepressants, including tricyclic antidepressants, SSRIs, serotonin-norepinephrine reuptake inhibitors, and MAOIs, resulted in a 60% increased risk of [intracranial hemorrhage](#) within 30 days of concomitant use compared with antidepressant use alone. There was no significant difference between the antidepressant drug classes and the increased risk; however, there was an increased risk associated with male patients compared with female patients [367].

b) 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. Combined use of an SSRI and NSAIDs or low-dose [aspirin](#) increased the risk to 12.2 and 5.2 times, 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 [370].

c) Two metaanalyses of incidents of upper GI bleed due to SSRIs, NSAIDs, and their combination found that SSRIs increased the risk by 1.73 [371] to 2.36 times [372], NSAIDs by 2.55 times [371], and the combination of SSRIs and NSAIDs by 4.02 [371] to 6.33 times [372].

d) The release of serotonin by [platelets](#) is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs and NSAIDs have been associated with an increased risk of bleeding [373].

3.5.1.EN] [Meperidine](#)

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

2) Summary: **Meperidine** is considered a proserotonergic opioid and has been associated with **serotonin syndrome** when used concomitantly with other serotonergic agents[191]. Increased serotonin levels which may produce additive serotonergic effects can occur if serotonergic agents are taken concurrently with **meperidine**. 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 [120]. Use caution if **meperidine** and a serotonergic agent are coadministered and monitor patients for signs and symptoms of **serotonin syndrome**.

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Use caution with concomitant administration of **meperidine** and this drug as this interaction may result in additive serotonergic effects and increase the risk of **serotonin syndrome**. If coadministration is required, appropriate monitoring may be warranted.

7) Probable Mechanism: additive serotonergic effects

3.5.1.EO] **Methadone**

1) Interaction Effect: increased plasma **methadone** levels

2) Summary: When **fluvoxamine** is added to patients receiving **maintenance methadone** therapy, significantly increased **methadone** plasma level:dose ratios are seen. Symptoms of opioid toxicity were observed in one patient. In another patient, **opioid withdrawal** symptoms were observed following discontinuation of **fluvoxamine**[171].

3) Severity: moderate

4) Onset: delayed

5) Substantiation: probable

6) Clinical Management: Monitor closely if adding or withdrawing **fluvoxamine** in patients on chronic **methadone**.

7) Probable Mechanism: inhibition by **fluvoxamine** of cytochrome P450 3A4-mediated **methadone** metabolism

8) Literature Reports

a) A 28-year-old female who was admitted to a hospital for the management of an acute exacerbation of **asthma** had a stabilized medication regimen which included **methadone** 70 mg daily, **diazepam** 2 mg twice daily, **albuterol**, **ipratropium**, **ranitidine**, and **spironolactone**. Three weeks before admission, she had started **fluvoxamine** 100 mg daily. The patient's **asthma** was not considered to be in a significant exacerbation upon further testing, although hypoxemia and hypercapnia indicating **hypoventilation** was present. **Methadone** was decreased to 50 mg daily and **diazepam** was discontinued. Analysis of a blood sample taken at admission showed that the serum **methadone** concentration was 262 ng/mL. Twelve days later, oxygenation had improved and the **methadone** concentration was measured at 202 ng/mL. The reduction in serum **methadone** concentration and clinical improvement observed after **methadone** was decreased suggest that **fluvoxamine** may have inhibited the cytochrome P450 3A4-mediated metabolism of **methadone**, although **diazepam** may have compounded this interaction [170].

3.5.1.EP] **Methamphetamine**

1) Interaction Effect: increased **amphetamine** exposure and increased risk of **serotonin syndrome**

2J) Summary: Coadministration of an [amphetamine](#) and a serotonergic agent that inhibits CYP2D6 may result in increased [amphetamine](#) exposure and additional risk for [serotonin syndrome](#). If concomitant use of an [amphetamine](#) and such an agent is clinically required, initiate with lower doses and monitor patients carefully, especially during treatment initiation and dosage adjustment. Discontinue both drugs if [serotonin syndrome](#) is suspected[377].

3J) Severity: major

4J) Onset: unspecified

5J) Substantiation: theoretical

6J) Clinical Management: Coadministration of an [amphetamine](#) and another serotonergic agent may result in [serotonin syndrome](#), because both drugs affect the serotonergic neurotransmitter system. Additionally, coadministration of an [amphetamine](#) with a CYP2D6 inhibitor may increase [amphetamine](#) exposure, because [amphetamines](#) and their derivatives are metabolized to some degree by CYP2D6. An increase in [amphetamine](#) exposure may further increase risk of [serotonin syndrome](#). If concomitant use of an [amphetamine](#) and a serotonergic agent that inhibits CYP2D6 is clinically required, initiate with lower doses and monitor patients carefully, especially during treatment initiation and dosage adjustment. Discontinue both drugs if [serotonin syndrome](#) is suspected[377].

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

3.5.1.EQJ Methylene Blue

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

2J) Summary: Concurrent use of [fluvoxamine](#) and IV methylene blue, an MAOI, is contraindicated due to reports of [serotonin syndrome](#) with concurrent use of an SSRI and methylene blue 1 to 8 mg/kg administered IV[153]. No cases have been identified in patients receiving methylene blue up to 5 mg for lymphatic mapping in [breast cancer](#) [184]. While the risk of concurrent [fluvoxamine](#) with other forms of methylene blue is unclear, interactions are possible with methylene blue administered orally, by injection, or in IV doses lower than 1 mg/kg. If urgent treatment with IV methylene blue is necessary in a patient receiving [fluvoxamine](#), alternatives are not available, and risk/benefit has been evaluated, promptly discontinue [fluvoxamine](#) and then administer IV methylene blue [153]. Use the lowest possible dose of methylene blue [183]. Monitor for 2 weeks or until 24 hours after the last dose of IV methylene blue, whichever comes first. [Fluvoxamine](#) can be resumed 24 hours after the last methylene blue dose [153].

3J) Severity: contraindicated

4J) Onset: unspecified

5J) Substantiation: theoretical

6J) Clinical Management: Concurrent use of [fluvoxamine](#) and IV methylene blue (an MAOI) is contraindicated. If urgent treatment with IV methylene blue is necessary in a patient receiving [fluvoxamine](#), alternatives are not available, and risk/benefit has been evaluated, promptly discontinue [fluvoxamine](#) and then administer IV methylene blue[153]. Use the lowest possible dose of methylene blue [183]. Monitor for [serotonin syndrome](#) for 2 weeks or until 24 hours after the last dose of IV methylene blue, whichever comes first. [Fluvoxamine](#) can be resumed 24 hours after the last dose of methylene blue. While the risk of concurrent [fluvoxamine](#) with other forms of methylene blue is unclear, interactions are possible with methylene blue administered orally, by injection, or in IV doses lower than 1 mg/kg [153].

7J) Probable Mechanism: additive serotonergic effect

8J) Literature Reports

aJ) Patients treated with SSRIs who are undergoing lymphatic mapping for [breast cancer](#) are not expected to experience an interaction with concomitant use of methylene blue. Doses of methylene blue used in lymphatic mapping are many times lower (5 mg total) compared with doses used

when [serotonin syndrome](#) occurred with concomitant use of an SSRI and methylene blue (eg, 1 to 8 mg/kg). No case reports of [serotonin syndrome](#) have been reported in patients taking SSRIs who received methylene blue in lymphatic mapping; however, health care providers should still be aware of the potential for an interaction between methylene blue and SSRIs in this setting [184].

3.5.1.ER] [Methylergonovine](#)

- 1) Interaction Effect: increased plasma concentrations of ergot derivatives and increased risk of [ergotism](#) (nausea, vomiting, vasospastic ischemia)
- 2) Summary: Concomitant use of [fluvoxamine](#), a less potent 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 [fluvoxamine](#) and ergot derivatives[122][123].
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: [Fluvoxamine](#) may increase the plasma concentrations of ergot derivatives. Use caution when [fluvoxamine](#) is coadministered with an ergot derivative, such as [dihydroergotamine](#), [ergotamine](#), or [methylergonovine](#), due to the potential for serious toxicity including [vasospasm](#) that can occur[122][123].
- 7) Probable Mechanism: inhibition of CYP3A4-mediated ergot metabolism by [fluvoxamine](#)

3.5.1.ES] [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[276].
- 3) Severity: moderate
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Use caution when prescribing [methylphenidate](#) to patients who take a 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[276].
- 7) Probable Mechanism: inhibition of selective serotonin reuptake inhibitor metabolism by [methylphenidate](#)

3.5.1.ET] [Metoclopramide](#)

- 1) Interaction Effect: an increased risk of extrapyramidal reactions or [neuroleptic malignant syndrome](#)
- 2) Summary: Concomitant use of [fluvoxamine](#) with [metoclopramide](#) may increase the risk of extrapyramidal symptoms, such as [tardive dyskinesia](#) or [neuroleptic malignant syndrome](#), and is contraindicated[386]. 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 [387].
- 3) Severity: contraindicated

- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Concomitant use of [fluvoxamine](#) with [metoclopramide](#) is contraindicated[386]. 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 [387].
- 7) Probable Mechanism: unknown

3.5.1.EU] [Mexiletine](#)

- 1) Interaction Effect: decreased [mexiletine](#) metabolism
- 2) Summary: In a single-dose study, concurrent administration of [fluvoxamine](#) and [mexiletine](#) reduced the clearance of [mexiletine](#) by 37%, significantly increasing the mean serum peak concentration and area under the concentration-time curve[215][216].
- 3) Severity: moderate
- 4) Onset: rapid
- 5) Substantiation: probable
- 6) Clinical Management: Monitor patients for signs and symptoms of [mexiletine](#) toxicity (nausea, dizziness, [cardiac arrhythmias](#)). Monitor liver function, [complete blood count](#), and [electrocardiogram](#) if [mexiletine](#) toxicity is suspected, and reduce [mexiletine](#) dose as required.
- 7) Probable Mechanism: fluvoxamine-induced inhibition of CYP1A2-mediated [mexiletine](#) metabolism
- 8) Literature Reports

a) Co-administration of [fluvoxamine](#) with [mexiletine](#) significantly reduced the metabolism and clearance of [mexiletine](#). In a randomized, cross-over study, healthy Japanese men (n=6) received either a single oral dose of [mexiletine](#) 200 milligrams (mg) or a 7-day regimen of oral [fluvoxamine](#) 50 mg twice daily followed by [fluvoxamine](#) plus a single dose of [mexiletine](#) 200 mg on day 8. Serial blood samples were measured over the 24 hours following each [mexiletine](#) dose. Thereafter, each subject crossed over to the opposing study arm following a 7-day wash-out period. Compared with control values, concurrent administration of [fluvoxamine](#) with [mexiletine](#) provoked a significant increase in the mean maximum serum concentration (0.536 versus 0.623 micrograms/milliliter (mcg/mL), p=0.0074) and area under the concentration-time curve (5.71 versus 7.46 mcg x hour/mL, p=0.0028). Co-administration significantly decreased mean oral clearance by 37% (0.551 versus 0.341 L/hour/kilogram, p=0.015). The study authors proposed fluvoxamine-induced inhibition of CYP1A2 metabolism as the mechanism of action [214].

3.5.1.EV] [Midazolam](#)

- 1) Interaction Effect: elevated serum [midazolam](#) concentrations
- 2) Summary: [Fluvoxamine](#) coadministration (100 mg daily) with [alprazolam](#) 1 mg four times daily resulted in a 2-fold increase in [alprazolam](#) steady-state plasma concentrations, AUC, Cmax, and half-life. Elevated plasma levels of [alprazolam](#) were associated with impaired psychomotor performance and memory. This suggests that [fluvoxamine](#) is a potent inhibitor of cytochrome P450 3A4 enzymes, which are responsible for [alprazolam](#) metabolism. Because [midazolam](#) also relies on CYP3A4 for metabolism, a similar interaction with [fluvoxamine](#) seems likely[365].
- 3) Severity: moderate
- 4) Onset: delayed
- 5) Substantiation: probable

6) Clinical Management: When [midazolam](#) and [fluvoxamine](#) are coadministered, monitor patients for benzodiazepine toxicity (sedation, lethargy, slurred speech). [Midazolam](#) doses may need to be reduced, or consider switching to a benzodiazepine eliminated by glucuronidation (eg, [lorazepam](#), [oxazepam](#), [temazepam](#)).

7) Probable Mechanism: inhibition of [midazolam](#) metabolism due to cytochrome P450 3A4 enzyme inhibition

3.5.1.EW] 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[277].

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[277].

7) Probable Mechanism: additive serotonergic effect

3.5.1.EX] Mirtazapine

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

2) Summary: Concomitant use of [mirtazapine](#) with other serotonergic agents may increase the risk of [serotonin syndrome](#) due to additive serotonergic effects. Monitor for symptoms of [serotonin syndrome](#), especially during treatment initiation and dose increases, and if the patient shows symptoms, treatment with [mirtazapine](#) and any concomitant serotonergic agent should be discontinued[268]. 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 after discontinuation of the offending agents, provide supportive care and other therapy as necessary [120].

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: If concomitant use with other serotonergic drugs is clinically warranted, monitor for the emergence of [serotonin syndrome](#), particularly during treatment initiation and dose increases. Discontinue use of both agents if a patient shows symptoms of [serotonin syndrome](#)[268].

7) Probable Mechanism: additive serotonin effects

8) Literature Reports

a) Within a few hours of starting [mirtazapine](#) and shortly after stopping [fluoxetine](#), a 75-year-old woman experienced symptoms consistent with [serotonin syndrome](#). Current medication for depression included [fluoxetine](#), [chlorpromazine](#), and [lorazepam](#). Due to lack of response, [fluoxetine](#) was discontinued and soon afterward [mirtazapine](#) 30 mg/day was started. 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 [269].

b)) A 26-year-old woman with [anorexia nervosa](#) receiving [fluvoxamine](#) for 4 months developed symptoms of [serotonin syndrome](#) after [mirtazapine](#) was initiated. The symptoms of twitching, tremors, agitation, restlessness, and "feeling like she could crawl out of her skin" developed over a period of 4 days after starting [mirtazapine](#) 30 mg/day. Symptoms rapidly progressed to twitching, tremors, and restlessness. She was hospitalized with further symptoms of diaphoresis, flushing, fasciculations, and nausea and treated with [cyproheptadine](#), [acetaminophen](#), and IV fluids. She remained afebrile throughout the event. Symptoms completely resolved within 24 hours [270].

3.5.1.EY] Moclobemide

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

2)) Summary: Concomitant use of [fluvoxamine](#) and an MAOI is contraindicated. Concurrent administration or overlapping therapy with [fluvoxamine](#) and an MAOI may result in [serotonin syndrome](#), a hyperserotonergic state characterized by symptoms such as agitation and hallucinations, myoclonus, changes in mental status, hyperreflexia, diaphoresis, rigidity, and tremor. Serious, even fatal, reactions have been reported with concomitant use of SSRIs and MAOIs. A minimum of 14 days should elapse after discontinuing an MAOI intended to treat psychiatric disorders before initiating therapy with [fluvoxamine](#), and a minimum of 14 days should elapse after discontinuing [fluvoxamine](#) before initiating therapy with an MAOI intended to treat psychiatric disorders[20].

3)) Severity: contraindicated

4)) Onset: unspecified

5)) Substantiation: theoretical

6)) Clinical Management: Concurrent use of [fluvoxamine](#) and an MAOI is contraindicated. Wait at least 14 days after discontinuing an MAOI intended to treat psychiatric disorders before initiating [fluvoxamine](#). Wait at least 14 days after discontinuing [fluvoxamine](#) before initiating therapy with an MAOI intended to treat psychiatric disorders[20].

7)) Probable Mechanism: additive serotonergic effect

3.5.1.EZ] Morniflumate

1)) Interaction Effect: an increased risk of bleeding

2)) Summary: Caution is recommended with the concomitant use of NSAIDs and antidepressants, including SSRIs due to an increased risk of [intracranial hemorrhage](#)[367] and [gastrointestinal bleeding](#) [371][372][368][369]. Bleeding events have included [epistaxis](#), ecchymosis, [hematoma](#), [petechiae](#), and life-threatening hemorrhages [374][373][375][376]. When an SSRI and an NSAID are given concurrently, monitor the patient for signs of increased bleeding.

3)) Severity: major

4)) Onset: unspecified

5)) Substantiation: established

6)) Clinical Management: Use caution if NSAIDs and SSRIs are coadministered. Concomitant use of NSAIDs and SSRIs may cause an increased risk of [intracranial hemorrhage](#)[367] and [gastrointestinal](#)

bleeding [368][369]. When an SSRI and an NSAID are given concurrently, monitor the patient for signs of increased bleeding.

7) Probable Mechanism: depletion of platelet serotonin by SSRI; additive effects

8) Literature Reports

a) Concomitant use of NSAIDs and antidepressants, including tricyclic antidepressants, SSRIs, serotonin-norepinephrine reuptake inhibitors, and MAOIs, resulted in a 60% increased risk of intracranial hemorrhage within 30 days of concomitant use compared with antidepressant use alone. There was no significant difference between the antidepressant drug classes and the increased risk; however, there was an increased risk associated with male patients compared with female patients [367].

b) 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. Combined use of an SSRI and NSAIDs or low-dose aspirin increased the risk to 12.2 and 5.2 times, 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 [370].

c) Two metaanalyses of incidents of upper GI bleed due to SSRIs, NSAIDs, and their combination found that SSRIs increased the risk by 1.73 [371] to 2.36 times [372], NSAIDs by 2.55 times [371], and the combination of SSRIs and NSAIDs by 4.02 [371] to 6.33 times [372].

d) The release of serotonin by platelets is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs and NSAIDs have been associated with an increased risk of bleeding [373].

3.5.1.FA] Nabumetone

1) Interaction Effect: an increased risk of bleeding

2) Summary: Caution is recommended with the concomitant use of NSAIDs and antidepressants, including SSRIs due to an increased risk of intracranial hemorrhage[367] and gastrointestinal bleeding [371][372][368][369]. Bleeding events have included epistaxis, ecchymosis, hematoma, petechiae, and life-threatening hemorrhages [374][373][375][376]. When an SSRI and an NSAID are given concurrently, monitor the patient for signs of increased bleeding.

3) Severity: major

4) Onset: unspecified

5) Substantiation: established

6) Clinical Management: Use caution if NSAIDs and SSRIs are coadministered. Concomitant use of NSAIDs and SSRIs may cause an increased risk of intracranial hemorrhage[367] and gastrointestinal bleeding [368][369]. When an SSRI and an NSAID are given concurrently, monitor the patient for signs of increased bleeding.

7) Probable Mechanism: depletion of platelet serotonin by SSRI; additive effects

8) Literature Reports

a) Concomitant use of NSAIDs and antidepressants, including tricyclic antidepressants, SSRIs, serotonin-norepinephrine reuptake inhibitors, and MAOIs, resulted in a 60% increased risk of intracranial hemorrhage within 30 days of concomitant use compared with antidepressant use alone. There was no significant difference between the antidepressant drug classes and the

increased risk; however, there was an increased risk associated with male patients compared with female patients [367].

b) 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. Combined use of an SSRI and NSAIDs or low-dose [aspirin](#) increased the risk to 12.2 and 5.2 times, 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 [370].

c) Two metaanalyses of incidents of upper GI bleed due to SSRIs, NSAIDs, and their combination found that SSRIs increased the risk by 1.73 [371] to 2.36 times [372], NSAIDs by 2.55 times [371], and the combination of SSRIs and NSAIDs by 4.02 [371] to 6.33 times [372].

d) The release of serotonin by [platelets](#) is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs and NSAIDs have been associated with an increased risk of bleeding [373].

3.5.1.FB| 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[114][115][113]. 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](#). In patients receiving [warfarin](#) and [fluvoxamine](#) concomitantly for 2 weeks, [warfarin](#) plasma concentrations increased by 98% and prothrombin times were prolonged. [Fluvoxamine](#) appears to inhibit several cytochrome P450 isoenzymes which may include 1A2 and 2C9 isozymes, which are responsible for [warfarin](#) metabolism [115][113].

3) Severity: major

4) Onset: delayed

5) Substantiation: probable

6) Clinical Management: When [fluvoxamine](#) 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 [fluvoxamine](#) therapy is initiated or discontinued. Periodically reassess the prothrombin time ratio and INR in patients receiving [fluvoxamine](#) and [anticoagulant therapy](#)[113].

7) Probable Mechanism: unknown

8) Literature Reports

a) According to a retrospective cohort study (n=234), there was an increased risk of clinically relevant bleeding (hospital admission due to bleeding) in patients receiving [warfarin](#) for [atrial fibrillation](#) during concomitant SSRI therapy or within 2 weeks following SSRI therapy termination. Patients with a mean age of 72 +/- 7 years receiving [warfarin](#) plus SSRI (n=117) were matched with randomly selected patients who received [warfarin](#) only (n=117). SSRI included [fluoxetine](#), [citalopram](#), [paroxetine](#), [sertraline](#), [fluvoxamine](#), or [escitalopram](#). Nine patients experienced 11 bleeding episodes during 213.9 treatment years in the [warfarin](#) plus SSRI group, and 10 patients experienced 14 bleedings during 586.4 treatment years in the warfarin-only

group. The corresponding total incidences of bleedings were 51.4 and 23.9 per 1000 treatment years, respectively. The hazard ratio for first bleedings during treatment with [warfarin](#) plus SSRI was 3.49 (95% CI; 1.37 to 8.91, $p=0.009$) compared with [warfarin](#) only. The SSRI implicated in patients experiencing bleeding at the time of concomitant administration were [sertraline](#) or [citalopram](#). The addition of an SSRI was not associated with a change in [warfarin](#) dose or INR ($p=0.48$ and $p=0.31$ respectively). The results of the study may be limited by earlier bleeding events, unknown patient adherence, and exclusion of [clopidogrel](#), dipyridamol, corticosteroids and anticoagulants other than [warfarin](#) in the model [114].

b) A population-based, case-controlled study of new coumarin users (acenocoumarol and phenprocoumon) with concomitant selective serotonin reuptake inhibitors (SSRIs) resulted in an increased risk of hospitalization due to nongastrointestinal bleeding. Using national pharmacy and hospitalization records, Netherlands researchers identified 1848 cases that were admitted for abnormal bleeding and compared them with 5818 control subjects also taking coumarins. Median duration of treatment in patients was 220 days (range, 1 to 4690 days). Patients on SSRIs showed greater risk for hospitalization for nongastrointestinal bleeding (adjusted odds ratio (OR) 1.7, 95% confidence interval (CI), 1.1 to 2.5), however, the rate of [gastrointestinal bleeding](#) (adjusted OR 0.8, 95% CI, 0.4 to 1.5) was not significantly different [115].

c) A hospitalized 80-year-old female was started on intravenous [heparin](#) and oral [warfarin](#) therapy due to an [embolic stroke](#) secondary to [atrial fibrillation](#) and [mitral stenosis](#). Her [warfarin](#) dose was maintained at 1 mg daily, with her INR between 2.5 and 3. [Fluvoxamine](#) 25 mg daily was started for depression, and her [warfarin](#) dose was increased to 1.5 mg daily 3 days later due to worsening of the left [hemiparesis](#). Three days later, her INR was 9.96, and a repeat INR to rule out laboratory error was 11.3. [Warfarin](#) was discontinued, fresh frozen plasma was given, and [fluvoxamine](#) was discontinued. Six days later, [warfarin](#) was again started at 1 mg daily, and the INR increased over 4 days to 11.8. The elevated INR was attributed to the persisting effect of [fluvoxamine](#). She was eventually stabilized on [warfarin](#) 1 mg daily with INR values between 2 and 2.5 [116].

3.5.1.FC] [Naproxen](#)

1) Interaction Effect: an increased risk of bleeding

2) Summary: Caution is recommended with the concomitant use of NSAIDs and antidepressants, including SSRIs due to an increased risk of [intracranial hemorrhage](#)[367] and [gastrointestinal bleeding](#) [371][372][368][369]. Bleeding events have included [epistaxis](#), ecchymosis, [hematoma](#), [petechiae](#), and life-threatening hemorrhages [374][373][375][376]. When an SSRI and an NSAID are given concurrently, monitor the patient for signs of increased bleeding.

3) Severity: major

4) Onset: unspecified

5) Substantiation: established

6) Clinical Management: Use caution if NSAIDs and SSRIs are coadministered. Concomitant use of NSAIDs and SSRIs may cause an increased risk of [intracranial hemorrhage](#)[367] and [gastrointestinal bleeding](#) [368][369]. When an SSRI and an NSAID are given concurrently, monitor the patient for signs of increased bleeding.

7) Probable Mechanism: depletion of [platelet](#) serotonin by SSRI; additive effects

8) Literature Reports

a) Concomitant use of NSAIDs and antidepressants, including tricyclic antidepressants, SSRIs, serotonin-norepinephrine reuptake inhibitors, and MAOIs, resulted in a 60% increased risk of [intracranial hemorrhage](#) within 30 days of concomitant use compared with antidepressant use alone. There was no significant difference between the antidepressant drug classes and the

increased risk; however, there was an increased risk associated with male patients compared with female patients [367].

b) 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. Combined use of an SSRI and NSAIDs or low-dose [aspirin](#) increased the risk to 12.2 and 5.2 times, 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 [370].

c) Two metaanalyses of incidents of upper GI bleed due to SSRIs, NSAIDs, and their combination found that SSRIs increased the risk by 1.73 [371] to 2.36 times [372], NSAIDs by 2.55 times [371], and the combination of SSRIs and NSAIDs by 4.02 [371] to 6.33 times [372].

d) The release of serotonin by [platelets](#) is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs and NSAIDs have been associated with an increased risk of bleeding [373].

3.5.1.FD] [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[218]. 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](#) [118].

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.FE] [Nepafenac](#)

1) Interaction Effect: an increased risk of bleeding

2) Summary: Caution is recommended with the concomitant use of NSAIDs and antidepressants, including SSRIs due to an increased risk of [intracranial hemorrhage](#)[367] and [gastrointestinal bleeding](#) [371][372][368][369]. Bleeding events have included [epistaxis](#), ecchymosis, [hematoma](#), [petechiae](#), and life-threatening hemorrhages [374][373][375][376]. When an SSRI and an NSAID are given concurrently, monitor the patient for signs of increased bleeding.

3) Severity: major

- 4) Onset: unspecified
- 5) Substantiation: established
- 6) Clinical Management: Use caution if NSAIDs and SSRIs are coadministered. Concomitant use of NSAIDs and SSRIs may cause an increased risk of [intracranial hemorrhage](#)[367] and [gastrointestinal bleeding](#) [368][369]. When an SSRI and an NSAID are given concurrently, monitor the patient for signs of increased bleeding.
- 7) Probable Mechanism: depletion of [platelet](#) serotonin by SSRI; additive effects
- 8) Literature Reports

a) Concomitant use of NSAIDs and antidepressants, including tricyclic antidepressants, SSRIs, serotonin-norepinephrine reuptake inhibitors, and MAOIs, resulted in a 60% increased risk of [intracranial hemorrhage](#) within 30 days of concomitant use compared with antidepressant use alone. There was no significant difference between the antidepressant drug classes and the increased risk; however, there was an increased risk associated with male patients compared with female patients [367].

b) 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. Combined use of an SSRI and NSAIDs or low-dose [aspirin](#) increased the risk to 12.2 and 5.2 times, 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 [370].

c) Two metaanalyses of incidents of upper GI bleed due to SSRIs, NSAIDs, and their combination found that SSRIs increased the risk by 1.73 [371] to 2.36 times [372], NSAIDs by 2.55 times [371], and the combination of SSRIs and NSAIDs by 4.02 [371] to 6.33 times [372].

d) The release of serotonin by [platelets](#) is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs and NSAIDs have been associated with an increased risk of bleeding [373].

3.5.1.FF] Nialamide

- 1) Interaction Effect: CNS toxicity or [serotonin syndrome](#) (hypertension, hyperthermia, myoclonus, mental status changes)
- 2) Summary: Concurrent administration or overlapping therapy with [fluvoxamine](#) and a monoamine oxidase (MAO) inhibitor may result in CNS toxicity or [serotonin syndrome](#), a hyperserotonergic state characterized by symptoms such as restlessness, myoclonus, changes in mental status, hyperreflexia, diaphoresis, shivering, and tremor. Serious, even fatal, reactions have been reported with concomitant use of selective serotonin reuptake inhibitors and MAO inhibitors[161][162][163][164]. Concomitant use is not recommended.
- 3) Severity: major
- 4) Onset: rapid
- 5) Substantiation: probable
- 6) Clinical Management: Concurrent use of [fluvoxamine](#) and a MAO inhibitor should be avoided. Wait at least two weeks after discontinuing an MAO inhibitor before initiating therapy with [fluvoxamine](#). Wait at least two weeks after discontinuing [fluvoxamine](#) before initiating therapy with a MAO inhibitor.
- 7) Probable Mechanism: serotonin reuptake inhibition
- 8) Literature Reports

a)) Concomitant use of serotonin specific reuptake inhibitors and monoamine oxidase inhibitors can produce a toxic reaction known as [serotonin syndrome](#) [157]. [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)) A 26-year old woman who had been taking [isocarboxazid](#) for eight weeks stopped taking the drug for 11 days before beginning therapy with [sertraline](#). After a single 100 mg [sertraline](#) dose, the patient became restless and developed leg twitches. The patient was later admitted to the emergency room with diaphoresis, [tachycardia](#), hyperreflexia, and various neuromuscular disturbances. After treatment with [diazepam](#) and [propranolol](#) the patient did not improve. The patient was then given two 4 mg doses of [cyproheptadine](#) an hour apart, with notable improvement in symptoms after the second dose [158].

c)) A drug interaction occurred in a 61-year old woman whose regimen of [sertraline](#) 100 mg twice daily was added to a regimen of [lithium](#), [phenelzine](#), [thioridazine](#), and [doxepin](#). Three hours after taking the first [sertraline](#) dose, the patient was found in a semicomatose state, with elevated body temperature, increased pulse, increased respiration rate, and a blood pressure of 140/110 mm Hg. After transportation to the hospital, the patient was misdiagnosed as having [neuroleptic malignant syndrome](#) (NMS) which was later changed to [serotonin syndrome](#) due to a reaction between [sertraline](#) and [phenelzine](#). The authors suggest that monoamine oxidase inhibitor (MAOI) therapy should be discontinued for at least two weeks before initiation of therapy with a selective serotonin reuptake inhibitor (SSRI) and that before starting a MAOI, SSRI therapy should be discontinued for at least five half-lives of the parent drug and any active metabolites [159].

d)) Two case reports suggested a possible interaction between [fluoxetine](#) and [selegiline](#) [160]. 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.FG] Niflumic Acid

1)) Interaction Effect: an increased risk of bleeding

2)) Summary: Caution is recommended with the concomitant use of NSAIDs and antidepressants, including SSRIs due to an increased risk of [intracranial hemorrhage](#)[367] and [gastrointestinal bleeding](#) [371][372][368][369]. Bleeding events have included [epistaxis](#), ecchymosis, [hematoma](#), [petechiae](#), and life-threatening hemorrhages [374][373][375][376]. When an SSRI and an NSAID are given concurrently, monitor the patient for signs of increased bleeding.

3)) Severity: major

4)) Onset: unspecified

5)) Substantiation: established

6)) Clinical Management: Use caution if NSAIDs and SSRIs are coadministered. Concomitant use of NSAIDs and SSRIs may cause an increased risk of [intracranial hemorrhage](#)[367] and [gastrointestinal bleeding](#) [368][369]. When an SSRI and an NSAID are given concurrently, monitor the patient for signs of increased bleeding.

7)) Probable Mechanism: depletion of [platelet](#) serotonin by SSRI; additive effects

8)) Literature Reports

a) Concomitant use of NSAIDs and antidepressants, including tricyclic antidepressants, SSRIs, serotonin-norepinephrine reuptake inhibitors, and MAOIs, resulted in a 60% increased risk of [intracranial hemorrhage](#) within 30 days of concomitant use compared with antidepressant use alone. There was no significant difference between the antidepressant drug classes and the increased risk; however, there was an increased risk associated with male patients compared with female patients [367].

b) 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. Combined use of an SSRI and NSAIDs or low-dose [aspirin](#) increased the risk to 12.2 and 5.2 times, 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 [370].

c) Two metaanalyses of incidents of upper GI bleed due to SSRIs, NSAIDs, and their combination found that SSRIs increased the risk by 1.73 [371] to 2.36 times [372], NSAIDs by 2.55 times [371], and the combination of SSRIs and NSAIDs by 4.02 [371] to 6.33 times [372].

d) The release of serotonin by [platelets](#) is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs and NSAIDs have been associated with an increased risk of bleeding [373].

3.5.1.FH] Nimesulide

1) Interaction Effect: an increased risk of bleeding

2) Summary: Caution is recommended with the concomitant use of NSAIDs and antidepressants, including SSRIs due to an increased risk of [intracranial hemorrhage](#)[367] and [gastrointestinal bleeding](#) [371][372][368][369]. Bleeding events have included [epistaxis](#), ecchymosis, [hematoma](#), [petechiae](#), and life-threatening hemorrhages [374][373][375][376]. When an SSRI and an NSAID are given concurrently, monitor the patient for signs of increased bleeding.

3) Severity: major

4) Onset: unspecified

5) Substantiation: established

6) Clinical Management: Use caution if NSAIDs and SSRIs are coadministered. Concomitant use of NSAIDs and SSRIs may cause an increased risk of [intracranial hemorrhage](#)[367] and [gastrointestinal bleeding](#) [368][369]. When an SSRI and an NSAID are given concurrently, monitor the patient for signs of increased bleeding.

7) Probable Mechanism: depletion of [platelet](#) serotonin by SSRI; additive effects

8) Literature Reports

a) Concomitant use of NSAIDs and antidepressants, including tricyclic antidepressants, SSRIs, serotonin-norepinephrine reuptake inhibitors, and MAOIs, resulted in a 60% increased risk of [intracranial hemorrhage](#) within 30 days of concomitant use compared with antidepressant use alone. There was no significant difference between the antidepressant drug classes and the increased risk; however, there was an increased risk associated with male patients compared with female patients [367].

b)) 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. Combined use of an SSRI and NSAIDs or low-dose [aspirin](#) increased the risk to 12.2 and 5.2 times, 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 [370].

c)) Two metaanalyses of incidents of upper GI bleed due to SSRIs, NSAIDs, and their combination found that SSRIs increased the risk by 1.73 [371] to 2.36 times [372], NSAIDs by 2.55 times [371], and the combination of SSRIs and NSAIDs by 4.02 [371] to 6.33 times [372].

d)) The release of serotonin by [platelets](#) is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs and NSAIDs have been associated with an increased risk of bleeding [373].

3.5.1.FI] Nimesulide Beta Cyclodextrin

1)) Interaction Effect: an increased risk of bleeding

2)) Summary: Caution is recommended with the concomitant use of NSAIDs and antidepressants, including SSRIs due to an increased risk of [intracranial hemorrhage](#)[367] and [gastrointestinal bleeding](#) [371][372][368][369]. Bleeding events have included [epistaxis](#), ecchymosis, [hematoma](#), [petechiae](#), and life-threatening hemorrhages [374][373][375][376]. When an SSRI and an NSAID are given concurrently, monitor the patient for signs of increased bleeding.

3)) Severity: major

4)) Onset: unspecified

5)) Substantiation: established

6)) Clinical Management: Use caution if NSAIDs and SSRIs are coadministered. Concomitant use of NSAIDs and SSRIs may cause an increased risk of [intracranial hemorrhage](#)[367] and [gastrointestinal bleeding](#) [368][369]. When an SSRI and an NSAID are given concurrently, monitor the patient for signs of increased bleeding.

7)) Probable Mechanism: depletion of [platelet](#) serotonin by SSRI; additive effects

8)) Literature Reports

a)) Concomitant use of NSAIDs and antidepressants, including tricyclic antidepressants, SSRIs, serotonin-norepinephrine reuptake inhibitors, and MAOIs, resulted in a 60% increased risk of [intracranial hemorrhage](#) within 30 days of concomitant use compared with antidepressant use alone. There was no significant difference between the antidepressant drug classes and the increased risk; however, there was an increased risk associated with male patients compared with female patients [367].

b)) 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. Combined use of an SSRI and NSAIDs or low-dose [aspirin](#) increased the risk to 12.2 and 5.2 times, 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 [370].

c) Two metaanalyses of incidents of upper GI bleed due to SSRIs, NSAIDs, and their combination found that SSRIs increased the risk by 1.73 [371] to 2.36 times [372], NSAIDs by 2.55 times [371], and the combination of SSRIs and NSAIDs by 4.02 [371] to 6.33 times [372].

d) The release of serotonin by [platelets](#) is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs and NSAIDs have been associated with an increased risk of bleeding [373].

3.5.1.FJ] [Nimodipine](#)

1) Interaction Effect: increased [nimodipine](#) serum levels

2) Summary: Use of [fluvoxamine](#), a CYP3A4 inhibitor[22], together with [nimodipine](#), a CYP3A4 substrate, may result in increased [nimodipine](#) plasma concentrations and an increased risk of [nimodipine](#) related side effects. [Increased blood pressure](#) monitoring and dose adjustments of [nimodipine](#) may be warranted during coadministration [266].

3) Severity: moderate

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Concomitant use of [fluvoxamine](#), a CYP3A4 inhibitor[22], and [nimodipine](#), a CYP3A4 substrate, may result in increased [nimodipine](#) plasma concentrations. If coadministration is required, monitoring of blood pressure is recommended and dose adjustments of [nimodipine](#) may be warranted [266].

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

3.5.1.FK] [Olanzapine](#)

1) Interaction Effect: an increased risk of [olanzapine](#) adverse effects

2) Summary: Fluvoxamine inhibits cytochrome P450 1A2 enzymes and may inhibit [olanzapine](#) elimination[364]. The clinical significance of this interaction is unknown since [olanzapine](#) is metabolized by multiple enzyme systems.

3) Severity: moderate

4) Onset: delayed

5) Substantiation: probable

6) Clinical Management: Monitor patients for excessive [olanzapine](#) adverse effects (orthostatic hypotension, [tachycardia](#), transaminase elevations, seizures).

7) Probable Mechanism: inhibition of [olanzapine](#) elimination

8) Literature Reports

a) A patient experienced elevated [olanzapine](#) plasma levels during coadministration of [fluvoxamine](#). The patient was taking [fluvoxamine](#) and [olanzapine](#) for several months for [schizophrenia](#) and secondary depression. She appeared to move rigidly, had a slight tremor of both hands and mydriasis. [Olanzapine](#) concentration was 120 mcg/L and [fluvoxamine](#) concentration was 70 mcg/L. [Olanzapine](#) was decreased in increments from 15 mg/day to 5 mg/day. Fourteen days after the last decrease in dose, [olanzapine](#) plasma levels were 38 mcg/L. Tremor and rigidity disappeared, however, mydriasis persisted. [Fluvoxamine](#) was replaced by [paroxetine](#) which resulted in [paroxetine](#) concentration of 0.027 mg/L and [olanzapine](#) concentration of 22 mcg/L [362].

b) Addition of [fluvoxamine](#) to [olanzapine](#) therapy may result in olanzapine-induced side effects or intoxication. Eight chronic schizophrenic patients were being treated for not less than 3 months

with 10-20 mg/day of [olanzapine](#). The dose of [olanzapine](#) was unchanged for not less than 8 weeks prior to the study and remained stable throughout the study period. [Fluvoxamine](#) 100 mg/day was added to [olanzapine](#) treatment at the start of the study (week 0) and continued for 8 weeks. [Olanzapine](#) concentrations increased during [fluvoxamine](#) treatment 1.58-fold from week 0 to week 1, 1.42-fold from week 0 to week 4, and 1.81-fold from week 0 to week 8. Percentage change from week 0 to week 8 ranged from 12% to 112%. Mean concentrations of the N-demethylated metabolite were not significantly changed. Even though all eight patients had higher [olanzapine](#) blood serum concentrations on week 8 than on week 1, the ratio of increase of [olanzapine](#) blood serum concentrations from week 0 to week 8 did not correlate significantly with [fluvoxamine](#) serum levels (p greater than 0.05). This study confirmed that the addition of [fluvoxamine](#) to a stable dose of [olanzapine](#) increased [olanzapine](#) concentrations in the blood serum. Combined [olanzapine](#) and [fluvoxamine](#) should be used cautiously and controlled clinically and by therapeutic drug monitoring to avoid olanzapine-induced side effects or intoxication [363].

3.5.1.FL] Ospemifene

- 1J) Interaction Effect: increased ospemifene exposure and increased risk of adverse events
- 2J) Summary: The concomitant use of ospemifene (a CYP3A4 and CYP2C9 substrate) and a dual CYP3A4 and CYP2C9 inhibitor may increase the exposure of ospemifene. If ospemifene is used concomitantly with a CYP3A4 and CYP2C9 inhibitor, closely monitor ospemifene levels[165] and adjust the ospemifene dosage as required.
- 3J) Severity: major
- 4J) Onset: unspecified
- 5J) Substantiation: theoretical
- 6J) Clinical Management: If ospemifene (a CYP3A4 and CYP2C9 substrate) is used concomitantly with a dual CYP3A4 and CYP2C9 inhibitor, closely monitor patient for increased adverse effects from ospemifene[165] and adjust the ospemifene dosage as required.
- 7J) Probable Mechanism: inhibition of CYP3A4- and CYP2C9-mediated metabolism of ospemifene

3.5.1.FM] Oxaprozin

- 1J) Interaction Effect: an increased risk of bleeding
- 2J) Summary: Caution is recommended with the concomitant use of NSAIDs and antidepressants, including SSRIs due to an increased risk of [intracranial hemorrhage](#)[367] and [gastrointestinal bleeding](#) [371][372][368][369]. Bleeding events have included [epistaxis](#), ecchymosis, [hematoma](#), [petechiae](#), and life-threatening hemorrhages [374][373][375][376]. When an SSRI and an NSAID are given concurrently, monitor the patient for signs of increased bleeding.
- 3J) Severity: major
- 4J) Onset: unspecified
- 5J) Substantiation: established
- 6J) Clinical Management: Use caution if NSAIDs and SSRIs are coadministered. Concomitant use of NSAIDs and SSRIs may cause an increased risk of [intracranial hemorrhage](#)[367] and [gastrointestinal bleeding](#) [368][369]. When an SSRI and an NSAID are given concurrently, monitor the patient for signs of increased bleeding.
- 7J) Probable Mechanism: depletion of [platelet](#) serotonin by SSRI; additive effects
- 8J) Literature Reports

aJ) Concomitant use of NSAIDs and antidepressants, including tricyclic antidepressants, SSRIs, serotonin-norepinephrine reuptake inhibitors, and MAOIs, resulted in a 60% increased risk of [intracranial hemorrhage](#) within 30 days of concomitant use compared with antidepressant use alone. There was no significant difference between the antidepressant drug classes and the

increased risk; however, there was an increased risk associated with male patients compared with female patients [367].

b) 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. Combined use of an SSRI and NSAIDs or low-dose [aspirin](#) increased the risk to 12.2 and 5.2 times, 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 [370].

c) Two metaanalyses of incidents of upper GI bleed due to SSRIs, NSAIDs, and their combination found that SSRIs increased the risk by 1.73 [371] to 2.36 times [372], NSAIDs by 2.55 times [371], and the combination of SSRIs and NSAIDs by 4.02 [371] to 6.33 times [372].

d) The release of serotonin by [platelets](#) is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs and NSAIDs have been associated with an increased risk of bleeding [373].

3.5.1.FN] [Oxycodone](#)

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

2) Summary: Coadministration of [oxycodone](#) and [fluvoxamine](#) has resulted in the development of [serotonin syndrome](#) in a 70-year-old woman. Presenting symptoms included confusion, nausea, fever, clonus, hyperreflexia, and [tachycardia](#). Caution is advised if [fluvoxamine](#) and [oxycodone](#) are coadministered. Monitor patients for signs and symptoms of [serotonin syndrome](#) ([tachycardia](#), [hyperthermia](#), myoclonus, mental status changes)[388].

3) Severity: major

4) Onset: delayed

5) Substantiation: probable

6) Clinical Management: Concomitant administration of [fluvoxamine](#) and [oxycodone](#) may increase the risk of developing [serotonin syndrome](#). If these agents are coadministered, monitor patients for symptoms of [serotonin syndrome](#) ([tachycardia](#), [hyperthermia](#), myoclonus, mental status changes).

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

8) Literature Reports

a) Concurrent administration of [oxycodone](#) and [fluvoxamine](#) resulted in a [serotonin syndrome](#) in a 70-year-old woman. The patient was receiving [fluvoxamine](#) 200 mg and [doxepin](#) 50 mg for several months for treatment of depression. Subsequent to a fall, the patient was started on slow-release oral [oxycodone](#) 40 mg twice daily, and 2 days later, short-acting oral [oxycodone](#) 10 mg, to be used on an "as needed" basis, was added to her regimen. After a dose of about 60 mg [oxycodone](#) taken over 24 hours, the patient presented to the emergency department in a state of confusion, with symptoms including nausea, fever, clonus, hyperreflexia, and shivering. The patient also had mydriasis, transient [atrial fibrillation](#), [tachycardia](#), and an elevated [creatinine kinase](#) level. [Fluvoxamine](#), [doxepin](#), and [oxycodone](#) were discontinued and the patient was treated with 5 doses of oral [acetaminophen](#) 1,000 mg over the next 2 days. The patient's neurologic and cardiovascular symptoms improved steadily over the next 48 hours. Prior to discharge, [doxepin](#) therapy was re-initiated with no apparent adverse effects. However, patient was not rechallenged

with either [fluvoxamine](#) or [oxycodone](#) while she was in the hospital. According to the Naranjo probability scale, the interaction falls into the probable category [388].

3.5.1.FO| Oxyphenbutazone

- 1) Interaction Effect: an increased risk of bleeding
- 2) Summary: Caution is recommended with the concomitant use of NSAIDs and antidepressants, including SSRIs due to an increased risk of [intracranial hemorrhage](#)[367] and [gastrointestinal bleeding](#) [371][372][368][369]. Bleeding events have included [epistaxis](#), ecchymosis, [hematoma](#), [petechiae](#), and life-threatening hemorrhages [374][373][375][376]. When an SSRI and an NSAID are given concurrently, monitor the patient for signs of increased bleeding.
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: established
- 6) Clinical Management: Use caution if NSAIDs and SSRIs are coadministered. Concomitant use of NSAIDs and SSRIs may cause an increased risk of [intracranial hemorrhage](#)[367] and [gastrointestinal bleeding](#) [368][369]. When an SSRI and an NSAID are given concurrently, monitor the patient for signs of increased bleeding.
- 7) Probable Mechanism: depletion of [platelet](#) serotonin by SSRI; additive effects
- 8) Literature Reports

a) Concomitant use of NSAIDs and antidepressants, including tricyclic antidepressants, SSRIs, serotonin-norepinephrine reuptake inhibitors, and MAOIs, resulted in a 60% increased risk of [intracranial hemorrhage](#) within 30 days of concomitant use compared with antidepressant use alone. There was no significant difference between the antidepressant drug classes and the increased risk; however, there was an increased risk associated with male patients compared with female patients [367].

b) 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. Combined use of an SSRI and NSAIDs or low-dose [aspirin](#) increased the risk to 12.2 and 5.2 times, 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 [370].

c) Two metaanalyses of incidents of upper GI bleed due to SSRIs, NSAIDs, and their combination found that SSRIs increased the risk by 1.73 [371] to 2.36 times [372], NSAIDs by 2.55 times [371], and the combination of SSRIs and NSAIDs by 4.02 [371] to 6.33 times [372].

d) The release of serotonin by [platelets](#) is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs and NSAIDs have been associated with an increased risk of bleeding [373].

3.5.1.FP| Palonosetron

- 1) Interaction Effect: increased risk of [serotonin syndrome](#)
- 2) Summary: Concomitant use of [mirtazapine](#) with other serotonergic agents may increase the risk of [serotonin syndrome](#). Monitor for the emergence of [serotonin syndrome](#); symptoms include mental status changes (eg, agitation, hallucinations, [delirium](#), coma), autonomic instability (eg, [tachycardia](#), labile

blood pressure, dizziness, diaphoresis, flushing, [hyperthermia](#)), neuromuscular abnormalities (eg, tremor, rigidity, myoclonus, hyperreflexia, incoordination), seizures, with or without, gastrointestinal symptoms (eg, nausea, vomiting, diarrhea). Discontinue use of [palonosetron](#) and begin supportive treatment if the patient exhibits signs and symptoms of [serotonin syndrome](#)[342].

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: If concomitant use with other serotonergic drugs is clinically warranted, monitor for the emergence of [serotonin syndrome](#). Discontinue use of [palonosetron](#) and begin supportive treatment if the patient exhibits signs and symptoms of [serotonin syndrome](#)[342].

7) Probable Mechanism: unknown

3.5.1.FQ] Parecoxib

1) Interaction Effect: an increased risk of bleeding

2) Summary: Caution is recommended with the concomitant use of NSAIDs and antidepressants, including SSRIs due to an increased risk of [intracranial hemorrhage](#)[367] and [gastrointestinal bleeding](#) [371][372][368][369]. Bleeding events have included [epistaxis](#), ecchymosis, [hematoma](#), [petechiae](#), and life-threatening hemorrhages [374][373][375][376]. When an SSRI and an NSAID are given concurrently, monitor the patient for signs of increased bleeding.

3) Severity: major

4) Onset: unspecified

5) Substantiation: established

6) Clinical Management: Use caution if NSAIDs and SSRIs are coadministered. Concomitant use of NSAIDs and SSRIs may cause an increased risk of [intracranial hemorrhage](#)[367] and [gastrointestinal bleeding](#) [368][369]. When an SSRI and an NSAID are given concurrently, monitor the patient for signs of increased bleeding.

7) Probable Mechanism: depletion of [platelet](#) serotonin by SSRI; additive effects

8) Literature Reports

a) Concomitant use of NSAIDs and antidepressants, including tricyclic antidepressants, SSRIs, serotonin-norepinephrine reuptake inhibitors, and MAOIs, resulted in a 60% increased risk of [intracranial hemorrhage](#) within 30 days of concomitant use compared with antidepressant use alone. There was no significant difference between the antidepressant drug classes and the increased risk; however, there was an increased risk associated with male patients compared with female patients [367].

b) 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. Combined use of an SSRI and NSAIDs or low-dose [aspirin](#) increased the risk to 12.2 and 5.2 times, 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 [370].

c) Two metaanalyses of incidents of upper GI bleed due to SSRIs, NSAIDs, and their combination found that SSRIs increased the risk by 1.73 [371] to 2.36 times [372], NSAIDs by 2.55 times [371], and the combination of SSRIs and NSAIDs by 4.02 [371] to 6.33 times [372].

d)) The release of serotonin by [platelets](#) is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs and NSAIDs have been associated with an increased risk of bleeding [373].

3.5.1.FR] Pargyline

- 1)) Interaction Effect: an increased risk of [serotonin syndrome](#) ([hypertension](#), [tachycardia](#), [hyperthermia](#), [myoclonus](#), [mental status changes](#))
- 2)) Summary: Concomitant use of [fluvoxamine](#) and an MAOI is contraindicated. Concurrent administration or overlapping therapy with [fluvoxamine](#) and an MAOI may result in [serotonin syndrome](#), a hyperserotonergic state characterized by symptoms such as agitation and hallucinations, myoclonus, changes in mental status, hyperreflexia, diaphoresis, rigidity, and tremor. Serious, even fatal, reactions have been reported with concomitant use of SSRIs and MAOIs. A minimum of 14 days should elapse after discontinuing an MAOI intended to treat psychiatric disorders before initiating therapy with [fluvoxamine](#), and a minimum of 14 days should elapse after discontinuing [fluvoxamine](#) before initiating therapy with an MAOI intended to treat psychiatric disorders[20].
- 3)) Severity: contraindicated
- 4)) Onset: unspecified
- 5)) Substantiation: theoretical
- 6)) Clinical Management: Concurrent use of [fluvoxamine](#) and an MAOI is contraindicated. Wait at least 14 days after discontinuing an MAOI intended to treat psychiatric disorders before initiating [fluvoxamine](#). Wait at least 14 days after discontinuing [fluvoxamine](#) before initiating therapy with an MAOI intended to treat psychiatric disorders[20].
- 7)) Probable Mechanism: additive serotonergic effect

3.5.1.FS] 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[114][115][113]. 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](#). In patients receiving [warfarin](#) and [fluvoxamine](#) concomitantly for 2 weeks, [warfarin](#) plasma concentrations increased by 98% and prothrombin times were prolonged. [Fluvoxamine](#) appears to inhibit several cytochrome P450 isoenzymes which may include 1A2 and 2C9 isozymes, which are responsible for [warfarin](#) metabolism [115][113].
- 3)) Severity: major
- 4)) Onset: delayed
- 5)) Substantiation: probable
- 6)) Clinical Management: When [fluvoxamine](#) 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 [fluvoxamine](#) therapy is initiated or discontinued. Periodically reassess the prothrombin time ratio and INR in patients receiving [fluvoxamine](#) and [anticoagulant therapy](#)[113].
- 7)) Probable Mechanism: unknown
- 8)) Literature Reports

a)) According to a retrospective cohort study (n=234), there was an increased risk of clinically relevant bleeding (hospital admission due to bleeding) in patients receiving [warfarin](#) for [atrial](#)

fibrillation during concomitant SSRI therapy or within 2 weeks following SSRI therapy termination. Patients with a mean age of 72 +/- 7 years receiving **warfarin** plus SSRI (n=117) were matched with randomly selected patients who received **warfarin** only (n=117). SSRI included **fluoxetine**, **citalopram**, **paroxetine**, **sertraline**, **fluvoxamine**, or escitalopram. Nine patients experienced 11 bleeding episodes during 213.9 treatment years in the **warfarin** plus SSRI group, and 10 patients experienced 14 bleedings during 586.4 treatment years in the warfarin-only group. The corresponding total incidences of bleedings were 51.4 and 23.9 per 1000 treatment years, respectively. The hazard ratio for first bleedings during treatment with **warfarin** plus SSRI was 3.49 (95% CI; 1.37 to 8.91, p=0.009) compared with **warfarin** only. The SSRI implicated in patients experiencing bleeding at the time of concomitant administration were **sertraline** or **citalopram**. The addition of an SSRI was not associated with a change in **warfarin** dose or INR (p=0.48 and p=0.31 respectively). The results of the study may be limited by earlier bleeding events, unknown patient adherence, and exclusion of **clopidogrel**, dipyridamol, corticosteroids and anticoagulants other than **warfarin** in the model [114].

b) A population-based, case-controlled study of new coumarin users (acenocoumarol and phenprocoumon) with concomitant selective serotonin reuptake inhibitors (SSRIs) resulted in an increased risk of hospitalization due to nongastrointestinal bleeding. Using national pharmacy and hospitalization records, Netherlands researchers identified 1848 cases that were admitted for abnormal bleeding and compared them with 5818 control subjects also taking coumarins. Median duration of treatment in patients was 220 days (range, 1 to 4690 days). Patients on SSRIs showed greater risk for hospitalization for nongastrointestinal bleeding (adjusted odds ratio (OR) 1.7, 95% confidence interval (CI), 1.1 to 2.5), however, the rate of **gastrointestinal bleeding** (adjusted OR 0.8, 95% CI, 0.4 to 1.5) was not significantly different [115].

c) A hospitalized 80-year-old female was started on intravenous **heparin** and oral **warfarin** therapy due to an **embolic stroke** secondary to **atrial fibrillation** and **mitral stenosis**. Her **warfarin** dose was maintained at 1 mg daily, with her INR between 2.5 and 3. **Fluvoxamine** 25 mg daily was started for depression, and her **warfarin** dose was increased to 1.5 mg daily 3 days later due to worsening of the left **hemiparesis**. Three days later, her INR was 9.96, and a repeat INR to rule out laboratory error was 11.3. **Warfarin** was discontinued, fresh frozen plasma was given, and **fluvoxamine** was discontinued. Six days later, **warfarin** was again started at 1 mg daily, and the INR increased over 4 days to 11.8. The elevated INR was attributed to the persisting effect of **fluvoxamine**. She was eventually stabilized on **warfarin** 1 mg daily with INR values between 2 and 2.5 [116].

3.5.1.FT] **Paroxetine**

1) Interaction Effect: increased **fluvoxamine** exposure and increased risk of **serotonin syndrome**

2) Summary: Concomitant use of **fluvoxamine**, a CYP2D6 substrate[153], with **paroxetine**, a potent CYP2D6 inhibitor, may result in increased concentrations of **fluvoxamine** and may require dosage adjustments of either drug. **Serotonin syndrome** may also result from the concomitant use of **paroxetine** and other SSRIs, such as **fluvoxamine** [152]. If concomitant use is necessary, monitor patients for symptoms of **serotonin syndrome**, including neuromuscular abnormalities, autonomic instability, gastrointestinal symptoms, and mental status changes, especially during treatment initiation and dose increases. **Serotonin syndrome** can be life-threatening. If **serotonin syndrome** develops, discontinue **fluvoxamine** and **paroxetine** and initiate supportive care [153][152].

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Coadministration of [paroxetine](#) and [fluvoxamine](#) is not recommended because it may result in a life-threatening condition called [serotonin syndrome](#). If concomitant use of these 2 SSRIs is necessary, discuss the risks of [serotonin syndrome](#) with the patient and monitor closely for symptoms of [serotonin syndrome](#) (mental status changes, autonomic instability, neuromuscular symptoms, seizures, and gastrointestinal symptoms), especially during treatment initiation and dose increases. Dosage adjustments of either drug may also be necessary, due to CYP2D6 inhibition of [fluvoxamine](#) metabolism by [paroxetine](#)[152]. If [serotonin syndrome](#) develops, discontinue [fluvoxamine](#) and [paroxetine](#) and initiate supportive care [153][152].

7) Probable Mechanism: inhibition of CYP2D6-mediated metabolism of [fluvoxamine](#) by [paroxetine](#); additive serotonergic effect

3.5.1.FU] [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[114][115][113]. 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](#). In patients receiving [warfarin](#) and [fluvoxamine](#) concomitantly for 2 weeks, [warfarin](#) plasma concentrations increased by 98% and prothrombin times were prolonged. [Fluvoxamine](#) appears to inhibit several cytochrome P450 isoenzymes which may include 1A2 and 2C9 isozymes, which are responsible for [warfarin](#) metabolism [115][113].

3) Severity: major

4) Onset: delayed

5) Substantiation: probable

6) Clinical Management: When [fluvoxamine](#) 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 [fluvoxamine](#) therapy is initiated or discontinued. Periodically reassess the prothrombin time ratio and INR in patients receiving [fluvoxamine](#) and [anticoagulant therapy](#)[113].

7) Probable Mechanism: unknown

8) Literature Reports

a) According to a retrospective cohort study (n=234), there was an increased risk of clinically relevant bleeding (hospital admission due to bleeding) in patients receiving [warfarin](#) for [atrial fibrillation](#) during concomitant SSRI therapy or within 2 weeks following SSRI therapy termination. Patients with a mean age of 72 +/- 7 years receiving [warfarin](#) plus SSRI (n=117) were matched with randomly selected patients who received [warfarin](#) only (n=117). SSRI included [fluoxetine](#), [citalopram](#), [paroxetine](#), [sertraline](#), [fluvoxamine](#), or [escitalopram](#). Nine patients experienced 11 bleeding episodes during 213.9 treatment years in the [warfarin](#) plus SSRI group, and 10 patients experienced 14 bleedings during 586.4 treatment years in the [warfarin](#)-only group. The corresponding total incidences of bleedings were 51.4 and 23.9 per 1000 treatment years, respectively. The hazard ratio for first bleedings during treatment with [warfarin](#) plus SSRI was 3.49 (95% CI; 1.37 to 8.91, p=0.009) compared with [warfarin](#) only. The SSRI implicated in patients experiencing bleeding at the time of concomitant administration were [sertraline](#) or [citalopram](#). The addition of an SSRI was not associated with a change in [warfarin](#) dose or INR (p=0.48 and p=0.31 respectively). The results of the study may be limited by earlier bleeding events, unknown patient adherence, and exclusion of [clopidogrel](#), [dipyridamol](#), [corticosteroids](#) and anticoagulants other than [warfarin](#) in the model [114].

b) A population-based, case-controlled study of new coumarin users (acenocoumarol and phenprocoumon) with concomitant selective serotonin reuptake inhibitors (SSRIs) resulted in an increased risk of hospitalization due to nongastrointestinal bleeding. Using national pharmacy and hospitalization records, Netherlands researchers identified 1848 cases that were admitted for abnormal bleeding and compared them with 5818 control subjects also taking coumarins. Median duration of treatment in patients was 220 days (range, 1 to 4690 days). Patients on SSRIs showed greater risk for hospitalization for nongastrointestinal bleeding (adjusted odds ratio (OR) 1.7, 95% confidence interval (CI), 1.1 to 2.5), however, the rate of [gastrointestinal bleeding](#) (adjusted OR 0.8, 95% CI, 0.4 to 1.5) was not significantly different [115].

c) A hospitalized 80-year-old female was started on intravenous [heparin](#) and oral [warfarin](#) therapy due to an [embolic stroke](#) secondary to [atrial fibrillation](#) and [mitral stenosis](#). Her [warfarin](#) dose was maintained at 1 mg daily, with her INR between 2.5 and 3. [Fluvoxamine](#) 25 mg daily was started for depression, and her [warfarin](#) dose was increased to 1.5 mg daily 3 days later due to worsening of the left [hemiparesis](#). Three days later, her INR was 9.96, and a repeat INR to rule out laboratory error was 11.3. [Warfarin](#) was discontinued, fresh frozen plasma was given, and [fluvoxamine](#) was discontinued. Six days later, [warfarin](#) was again started at 1 mg daily, and the INR increased over 4 days to 11.8. The elevated INR was attributed to the persisting effect of [fluvoxamine](#). She was eventually stabilized on [warfarin](#) 1 mg daily with INR values between 2 and 2.5 [116].

3.5.1.FV] [Phenelzine](#)

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

2) Summary: Concomitant use of [fluvoxamine](#) and an MAOI is contraindicated. Concurrent administration or overlapping therapy with [fluvoxamine](#) and an MAOI may result in [serotonin syndrome](#), a hyperserotonergic state characterized by symptoms such as agitation and hallucinations, myoclonus, changes in mental status, hyperreflexia, diaphoresis, rigidity, and tremor. Serious, even fatal, reactions have been reported with concomitant use of SSRIs and MAOIs. A minimum of 14 days should elapse after discontinuing an MAOI intended to treat psychiatric disorders before initiating therapy with [fluvoxamine](#), and a minimum of 14 days should elapse after discontinuing [fluvoxamine](#) before initiating therapy with an MAOI intended to treat psychiatric disorders[20].

3) Severity: contraindicated

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Concurrent use of [fluvoxamine](#) and an MAOI is contraindicated. Wait at least 14 days after discontinuing an MAOI intended to treat psychiatric disorders before initiating [fluvoxamine](#). Wait at least 14 days after discontinuing [fluvoxamine](#) before initiating therapy with an MAOI intended to treat psychiatric disorders[20].

7) Probable Mechanism: additive serotonergic effect

3.5.1.FW] [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[114][115][113]. 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](#). In patients receiving [warfarin](#) and [fluvoxamine](#) concomitantly for 2 weeks, [warfarin](#) plasma concentrations increased by

98% and prothrombin times were prolonged. [Fluvoxamine](#) appears to inhibit several cytochrome P450 isoenzymes which may include 1A2 and 2C9 isozymes, which are responsible for [warfarin](#) metabolism [115][113].

3) Severity: major

4) Onset: delayed

5) Substantiation: probable

6) Clinical Management: When [fluvoxamine](#) 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 [fluvoxamine](#) therapy is initiated or discontinued. Periodically reassess the prothrombin time ratio and INR in patients receiving [fluvoxamine](#) and [anticoagulant therapy](#)[113].

7) Probable Mechanism: unknown

8) Literature Reports

a) According to a retrospective cohort study (n=234), there was an increased risk of clinically relevant bleeding (hospital admission due to bleeding) in patients receiving [warfarin](#) for [atrial fibrillation](#) during concomitant SSRI therapy or within 2 weeks following SSRI therapy termination. Patients with a mean age of 72 +/- 7 years receiving [warfarin](#) plus SSRI (n=117) were matched with randomly selected patients who received [warfarin](#) only (n=117). SSRI included [fluoxetine](#), [citalopram](#), [paroxetine](#), [sertraline](#), [fluvoxamine](#), or escitalopram. Nine patients experienced 11 bleeding episodes during 213.9 treatment years in the [warfarin](#) plus SSRI group, and 10 patients experienced 14 bleedings during 586.4 treatment years in the warfarin-only group. The corresponding total incidences of bleedings were 51.4 and 23.9 per 1000 treatment years, respectively. The hazard ratio for first bleedings during treatment with [warfarin](#) plus SSRI was 3.49 (95% CI; 1.37 to 8.91, p=0.009) compared with [warfarin](#) only. The SSRI implicated in patients experiencing bleeding at the time of concomitant administration were [sertraline](#) or [citalopram](#). The addition of an SSRI was not associated with a change in [warfarin](#) dose or INR (p=0.48 and p=0.31 respectively). The results of the study may be limited by earlier bleeding events, unknown patient adherence, and exclusion of [clopidogrel](#), dipyridamol, corticosteroids and anticoagulants other than [warfarin](#) in the model [114].

b) A population-based, case-controlled study of new coumarin users (acenocoumarol and phenprocoumon) with concomitant selective serotonin reuptake inhibitors (SSRIs) resulted in an increased risk of hospitalization due to nongastrointestinal bleeding. Using national pharmacy and hospitalization records, Netherlands researchers identified 1848 cases that were admitted for abnormal bleeding and compared them with 5818 control subjects also taking coumarins. Median duration of treatment in patients was 220 days (range, 1 to 4690 days). Patients on SSRIs showed greater risk for hospitalization for nongastrointestinal bleeding (adjusted odds ratio (OR) 1.7, 95% confidence interval (CI), 1.1 to 2.5), however, the rate of [gastrointestinal bleeding](#) (adjusted OR 0.8, 95% CI, 0.4 to 1.5) was not significantly different [115].

c) A hospitalized 80-year-old female was started on intravenous [heparin](#) and oral [warfarin](#) therapy due to an [embolic stroke](#) secondary to [atrial fibrillation](#) and [mitral stenosis](#). Her [warfarin](#) dose was maintained at 1 mg daily, with her INR between 2.5 and 3. [Fluvoxamine](#) 25 mg daily was started for depression, and her [warfarin](#) dose was increased to 1.5 mg daily 3 days later due to worsening of the left [hemiparesis](#). Three days later, her INR was 9.96, and a repeat INR to rule out laboratory error was 11.3. [Warfarin](#) was discontinued, fresh frozen plasma was given, and [fluvoxamine](#) was discontinued. Six days later, [warfarin](#) was again started at 1 mg daily, and the INR increased over 4 days to 11.8. The elevated INR was attributed to the persisting effect of [fluvoxamine](#). She was eventually stabilized on [warfarin](#) 1 mg daily with INR values between 2 and 2.5 [116].

3.5.1.FX] 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[114][115][113]. 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](#). In patients receiving [warfarin](#) and [fluvoxamine](#) concomitantly for 2 weeks, [warfarin](#) plasma concentrations increased by 98% and prothrombin times were prolonged. [Fluvoxamine](#) appears to inhibit several cytochrome P450 isoenzymes which may include 1A2 and 2C9 isozymes, which are responsible for [warfarin](#) metabolism [115][113].

3) Severity: major

4) Onset: delayed

5) Substantiation: probable

6) Clinical Management: When [fluvoxamine](#) 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 [fluvoxamine](#) therapy is initiated or discontinued. Periodically reassess the prothrombin time ratio and INR in patients receiving [fluvoxamine](#) and [anticoagulant therapy](#)[113].

7) Probable Mechanism: unknown

8) Literature Reports

a) According to a retrospective cohort study (n=234), there was an increased risk of clinically relevant bleeding (hospital admission due to bleeding) in patients receiving [warfarin](#) for [atrial fibrillation](#) during concomitant SSRI therapy or within 2 weeks following SSRI therapy termination. Patients with a mean age of 72 +/- 7 years receiving [warfarin](#) plus SSRI (n=117) were matched with randomly selected patients who received [warfarin](#) only (n=117). SSRI included [fluoxetine](#), [citalopram](#), [paroxetine](#), [sertraline](#), [fluvoxamine](#), or escitalopram. Nine patients experienced 11 bleeding episodes during 213.9 treatment years in the [warfarin](#) plus SSRI group, and 10 patients experienced 14 bleedings during 586.4 treatment years in the warfarin-only group. The corresponding total incidences of bleedings were 51.4 and 23.9 per 1000 treatment years, respectively. The hazard ratio for first bleedings during treatment with [warfarin](#) plus SSRI was 3.49 (95% CI; 1.37 to 8.91, p=0.009) compared with [warfarin](#) only. The SSRI implicated in patients experiencing bleeding at the time of concomitant administration were [sertraline](#) or [citalopram](#). The addition of an SSRI was not associated with a change in [warfarin](#) dose or INR (p=0.48 and p=0.31 respectively). The results of the study may be limited by earlier bleeding events, unknown patient adherence, and exclusion of [clopidogrel](#), dipyridamol, corticosteroids and anticoagulants other than [warfarin](#) in the model [114].

b) A population-based, case-controlled study of new coumarin users (acenocoumarol and phenprocoumon) with concomitant selective serotonin reuptake inhibitors (SSRIs) resulted in an increased risk of hospitalization due to nongastrointestinal bleeding. Using national pharmacy and hospitalization records, Netherlands researchers identified 1848 cases that were admitted for abnormal bleeding and compared them with 5818 control subjects also taking coumarins. Median duration of treatment in patients was 220 days (range, 1 to 4690 days). Patients on SSRIs showed greater risk for hospitalization for nongastrointestinal bleeding (adjusted odds ratio (OR) 1.7, 95% confidence interval (CI), 1.1 to 2.5), however, the rate of [gastrointestinal bleeding](#) (adjusted OR 0.8, 95% CI, 0.4 to 1.5) was not significantly different [115].

c) A hospitalized 80-year-old female was started on intravenous **heparin** and oral **warfarin** therapy due to an **embolic stroke** secondary to **atrial fibrillation** and **mitral stenosis**. Her **warfarin** dose was maintained at 1 mg daily, with her INR between 2.5 and 3. **Fluvoxamine** 25 mg daily was started for depression, and her **warfarin** dose was increased to 1.5 mg daily 3 days later due to worsening of the left **hemiparesis**. Three days later, her INR was 9.96, and a repeat INR to rule out laboratory error was 11.3. **Warfarin** was discontinued, fresh frozen plasma was given, and **fluvoxamine** was discontinued. Six days later, **warfarin** was again started at 1 mg daily, and the INR increased over 4 days to 11.8. The elevated INR was attributed to the persisting effect of **fluvoxamine**. She was eventually stabilized on **warfarin** 1 mg daily with INR values between 2 and 2.5 [116].

3.5.1.FY] **Phenylbutazone**

1) Interaction Effect: an increased risk of bleeding

2) Summary: Caution is recommended with the concomitant use of NSAIDs and antidepressants, including SSRIs due to an increased risk of **intracranial hemorrhage**[367] and **gastrointestinal bleeding** [371][372][368][369]. Bleeding events have included **epistaxis**, ecchymosis, **hematoma**, **petechiae**, and life-threatening hemorrhages [374][373][375][376]. When an SSRI and an NSAID are given concurrently, monitor the patient for signs of increased bleeding.

3) Severity: major

4) Onset: unspecified

5) Substantiation: established

6) Clinical Management: Use caution if NSAIDs and SSRIs are coadministered. Concomitant use of NSAIDs and SSRIs may cause an increased risk of **intracranial hemorrhage**[367] and **gastrointestinal bleeding** [368][369]. When an SSRI and an NSAID are given concurrently, monitor the patient for signs of increased bleeding.

7) Probable Mechanism: depletion of **platelet** serotonin by SSRI; additive effects

8) Literature Reports

a) Concomitant use of NSAIDs and antidepressants, including tricyclic antidepressants, SSRIs, serotonin-norepinephrine reuptake inhibitors, and MAOIs, resulted in a 60% increased risk of **intracranial hemorrhage** within 30 days of concomitant use compared with antidepressant use alone. There was no significant difference between the antidepressant drug classes and the increased risk; however, there was an increased risk associated with male patients compared with female patients [367].

b) 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. Combined use of an SSRI and NSAIDs or low-dose **aspirin** increased the risk to 12.2 and 5.2 times, 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 [370].

c) Two metaanalyses of incidents of upper GI bleed due to SSRIs, NSAIDs, and their combination found that SSRIs increased the risk by 1.73 [371] to 2.36 times [372], NSAIDs by 2.55 times [371], and the combination of SSRIs and NSAIDs by 4.02 [371] to 6.33 times [372].

d)) The release of serotonin by [platelets](#) is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs and NSAIDs have been associated with an increased risk of bleeding [373].

3.5.1.FZ] [Phenytoin](#)

- 1)) Interaction Effect: an increased risk of [phenytoin](#) toxicity (ataxia, hyperreflexia, [nystagmus](#), tremors)
- 2)) Summary: [Fluvoxamine](#) inhibits several of the isoenzymes of the CYP2C9, CYP1A2, and CYP3A4 (oxidative metabolism). Since [phenytoin](#) is eliminated at least partially via the CYP2C9 pathway, it is possible that coadministration with [fluvoxamine](#) may cause elevations in [phenytoin](#) plasma levels[201].
- 3)) Severity: moderate
- 4)) Onset: delayed
- 5)) Substantiation: probable
- 6)) Clinical Management: Consideration should be given to monitoring of [phenytoin](#) serum levels when [fluvoxamine](#) is added or withdrawn from therapy and dosage adjustments made accordingly. Patients should be counseled to be aware of the potential side effects of [phenytoin](#) toxicity such as drowsiness, ataxia, and [nystagmus](#), and to notify their physician if such side effects occur.
- 7)) Probable Mechanism: decreased oxidative metabolism
- 8)) Literature Reports

a)) During an in vitro study, the inhibitory effects of [fluvoxamine](#) on CYP2C9 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). [Fluvoxamine](#), a strong inhibitor of HPPH, impaired the formation of HPPH, which can lead to an increase in steady-state [phenytoin](#) levels [199].

b)) [Phenytoin](#) intoxication occurred in a patient after administration of [fluvoxamine](#). Serum [phenytoin](#) concentration dramatically increased from 16.6 to 49.1 mcg/mL during treatment with [fluvoxamine](#). [Fluvoxamine](#) may inhibit the metabolism of [phenytoin](#), mediated by CYP2C9 and CYP2C19 enzymes [200].

3.5.1.GA] [Piketopfen](#)

- 1)) Interaction Effect: an increased risk of bleeding
- 2)) Summary: Caution is recommended with the concomitant use of NSAIDs and antidepressants, including SSRIs due to an increased risk of [intracranial hemorrhage](#)[367] and [gastrointestinal bleeding](#) [371][372][368][369]. Bleeding events have included [epistaxis](#), ecchymosis, [hematoma](#), [petechiae](#), and life-threatening hemorrhages [374][373][375][376]. When an SSRI and an NSAID are given concurrently, monitor the patient for signs of increased bleeding.
- 3)) Severity: major
- 4)) Onset: unspecified
- 5)) Substantiation: established
- 6)) Clinical Management: Use caution if NSAIDs and SSRIs are coadministered. Concomitant use of NSAIDs and SSRIs may cause an increased risk of [intracranial hemorrhage](#)[367] and [gastrointestinal bleeding](#) [368][369]. When an SSRI and an NSAID are given concurrently, monitor the patient for signs of increased bleeding.
- 7)) Probable Mechanism: depletion of [platelet](#) serotonin by SSRI; additive effects
- 8)) Literature Reports

a) Concomitant use of NSAIDs and antidepressants, including tricyclic antidepressants, SSRIs, serotonin-norepinephrine reuptake inhibitors, and MAOIs, resulted in a 60% increased risk of [intracranial hemorrhage](#) within 30 days of concomitant use compared with antidepressant use alone. There was no significant difference between the antidepressant drug classes and the increased risk; however, there was an increased risk associated with male patients compared with female patients [367].

b) 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. Combined use of an SSRI and NSAIDs or low-dose [aspirin](#) increased the risk to 12.2 and 5.2 times, 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 [370].

c) Two metaanalyses of incidents of upper GI bleed due to SSRIs, NSAIDs, and their combination found that SSRIs increased the risk by 1.73 [371] to 2.36 times [372], NSAIDs by 2.55 times [371], and the combination of SSRIs and NSAIDs by 4.02 [371] to 6.33 times [372].

d) The release of serotonin by [platelets](#) is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs and NSAIDs have been associated with an increased risk of bleeding [373].

3.5.1.GB| Piperazine

1) Interaction Effect: increased exposure of piperazine

2) Summary: The concomitant use of piperazine (a CYP3A4 substrate) with a CYP3A4 inhibitor may increase the exposure of piperazine and the risk for QT-interval prolongation. If concomitant use is required, [ECG monitoring](#) should be considered. Due to the long half-life of piperazine, caution is advised when administering CYP3A4 inhibitors for up to 3 months after piperazine therapy is discontinued[257].

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: The concomitant use of piperazine (a CYP3A4 substrate) with a CYP3A4 inhibitor may increase the exposure of piperazine and the risk for QT-interval prolongation. If concomitant use is required, [ECG monitoring](#) should be considered. Due to the long half-life of piperazine, caution is advised when administering CYP3A4 inhibitors for up to 3 months after piperazine therapy is discontinued[257].

7) Probable Mechanism: inhibition of CYP3A4-mediated metabolism of piperazine

3.5.1.GC| Pirfenidone

1) Interaction Effect: increased pirfenidone exposure

2) Summary: Coadministration of pirfenidone (a CYP1A2 substrate) and a strong CYP1A2 inhibitor is not recommended as this may substantially increase pirfenidone exposure. In a study (N=50), coadministration of stable doses of [fluvoxamine](#) with a single dose pirfenidone resulted in a 4-fold increase in pirfenidone exposure in nonsmokers and a 7-fold increase in smokers. Use of a strong CYP1A2 inhibitor should be discontinued prior to initiating treatment with pirfenidone. If concomitant use cannot be

avoided, reduce the pirfenidone dosage to 267 mg 3 times daily. Monitor closely for adverse events and consider discontinuation of pirfenidone[331].

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Coadministration of pirfenidone (a CYP1A2 substrate) and a strong CYP1A2 inhibitor is not recommended as this may substantially increase pirfenidone exposure. Use of a strong CYP1A2 inhibitor should be discontinued prior to initiating treatment with pirfenidone. If concomitant use cannot be avoided, reduce the pirfenidone dosage to 267 mg 3 times daily. Monitor closely for adverse events and consider discontinuation of pirfenidone[331].

7) Probable Mechanism: inhibition of CYP1A2-mediated pirfenidone metabolism

8) Literature Reports

a) During drug interaction studies in healthy nonsmokers (n=25) and smokers (n=25), coadministration of [fluvoxamine](#) 50 mg once daily for 3 days, 50 mg twice daily for 3 days, and 50 mg in the morning followed by 100 mg at bedtime for 4 days with single dose pirfenidone resulted in a 4-fold increase in pirfenidone exposure in nonsmokers and a 7-fold increase in smokers [332].

3.5.1.GD) [Piroxicam](#)

1) Interaction Effect: an increased risk of bleeding

2) Summary: Caution is recommended with the concomitant use of NSAIDs and antidepressants, including SSRIs due to an increased risk of [intracranial hemorrhage](#)[367] and [gastrointestinal bleeding](#) [371][372][368][369]. Bleeding events have included [epistaxis](#), ecchymosis, [hematoma](#), [petechiae](#), and life-threatening hemorrhages [374][373][375][376]. When an SSRI and an NSAID are given concurrently, monitor the patient for signs of increased bleeding.

3) Severity: major

4) Onset: unspecified

5) Substantiation: established

6) Clinical Management: Use caution if NSAIDs and SSRIs are coadministered. Concomitant use of NSAIDs and SSRIs may cause an increased risk of [intracranial hemorrhage](#)[367] and [gastrointestinal bleeding](#) [368][369]. When an SSRI and an NSAID are given concurrently, monitor the patient for signs of increased bleeding.

7) Probable Mechanism: depletion of [platelet](#) serotonin by SSRI; additive effects

8) Literature Reports

a) Concomitant use of NSAIDs and antidepressants, including tricyclic antidepressants, SSRIs, serotonin-norepinephrine reuptake inhibitors, and MAOIs, resulted in a 60% increased risk of [intracranial hemorrhage](#) within 30 days of concomitant use compared with antidepressant use alone. There was no significant difference between the antidepressant drug classes and the increased risk; however, there was an increased risk associated with male patients compared with female patients [367].

b) 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. Combined use of an SSRI and NSAIDs or low-dose [aspirin](#) increased the risk to 12.2 and 5.2 times, 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 [370].

c) Two metaanalyses of incidents of upper GI bleed due to SSRIs, NSAIDs, and their combination found that SSRIs increased the risk by 1.73 [371] to 2.36 times [372], NSAIDs by 2.55 times [371], and the combination of SSRIs and NSAIDs by 4.02 [371] to 6.33 times [372].

d) The release of serotonin by [platelets](#) is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs and NSAIDs have been associated with an increased risk of bleeding [373].

3.5.1.GE] Pixantrone

- 1) Interaction Effect: increased exposure of CYP1A2 substrates
- 2) Summary: Concurrent administration of pixantrone (a CYP1A2 inhibitor) and a CYP1A2 substrate may increase the exposure of the CYP1A2 substrate. If concomitant administration is required, use caution and monitor the patient closely[265].
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Concurrent administration of pixantrone (a CYP1A2 inhibitor) and a CYP1A2 substrate may increase the exposure of the CYP1A2 substrate. If concomitant administration is required, use caution and monitor the patient closely[265].
- 7) Probable Mechanism: inhibition of CYP1A2-mediated metabolism by pixantrone

3.5.1.GF] Pomalidomide

- 1) Interaction Effect: increased pomalidomide exposure
- 2) Summary: Concomitant use of pomalidomide (a CYP1A2 substrate) with a strong CYP1A2 inhibitor in the presence of a strong CYP3A and P-gp inhibitor increased the exposure of pomalidomide. Avoid coadministration. If concomitant administration with strong CYP1A2 inhibitors in the presence of strong inhibitors of CYP3A4 and P-gp is required, reduce the pomalidomide dose by 50%[169].
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Concomitant use of pomalidomide (a CYP1A2 substrate) with a strong CYP1A2 inhibitor may increase the exposure of pomalidomide. Avoid coadministration. If concomitant administration with strong CYP1A2 inhibitors in the presence of strong inhibitors of CYP3A4 and P-gp is required, reduce the pomalidomide dose by 50%[169].
- 7) Probable Mechanism: inhibition of CYP1A2-mediated metabolism of pomalidomide
- 8) Literature Reports

a) Coadministration of pomalidomide with [fluvoxamine](#) (a strong CYP1A2 inhibitor) in the presence of [ketoconazole](#) (a strong CYP3A4 and P-gp inhibitor) increased the AUC of pomalidomide by 146% compared to pomalidomide administered alone in healthy subjects (N=12). Coadministration of [ketoconazole](#) increased the AUC of pomalidomide by 19% compared to pomalidomide administered alone in healthy subjects (N=16). The effect of a CYP1A2 inhibitor in the absence of a coadministered CYP3A4 and P-gp inhibitor has not been examined [169].

3.5.1.GG] Pranoprofen

- 1) Interaction Effect: an increased risk of bleeding

2j) Summary: Caution is recommended with the concomitant use of NSAIDs and antidepressants, including SSRIs due to an increased risk of [intracranial hemorrhage](#)[367] and [gastrointestinal bleeding](#) [371][372][368][369]. Bleeding events have included [epistaxis](#), ecchymosis, [hematoma](#), [petechiae](#), and life-threatening hemorrhages [374][373][375][376]. When an SSRI and an NSAID are given concurrently, monitor the patient for signs of increased bleeding.

3j) Severity: major

4j) Onset: unspecified

5j) Substantiation: established

6j) Clinical Management: Use caution if NSAIDs and SSRIs are coadministered. Concomitant use of NSAIDs and SSRIs may cause an increased risk of [intracranial hemorrhage](#)[367] and [gastrointestinal bleeding](#) [368][369]. When an SSRI and an NSAID are given concurrently, monitor the patient for signs of increased bleeding.

7j) Probable Mechanism: depletion of [platelet](#) serotonin by SSRI; additive effects

8j) Literature Reports

aj) Concomitant use of NSAIDs and antidepressants, including tricyclic antidepressants, SSRIs, serotonin-norepinephrine reuptake inhibitors, and MAOIs, resulted in a 60% increased risk of [intracranial hemorrhage](#) within 30 days of concomitant use compared with antidepressant use alone. There was no significant difference between the antidepressant drug classes and the increased risk; however, there was an increased risk associated with male patients compared with female patients [367].

bj) 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. Combined use of an SSRI and NSAIDs or low-dose [aspirin](#) increased the risk to 12.2 and 5.2 times, 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 [370].

cj) Two metaanalyses of incidents of upper GI bleed due to SSRIs, NSAIDs, and their combination found that SSRIs increased the risk by 1.73 [371] to 2.36 times [372], NSAIDs by 2.55 times [371], and the combination of SSRIs and NSAIDs by 4.02 [371] to 6.33 times [372].

dj) The release of serotonin by [platelets](#) is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs and NSAIDs have been associated with an increased risk of bleeding [373].

3.5.1.GH] Prasugrel

1j) Interaction Effect: increased risk of bleeding

2j) Summary: Exercise caution when coadministering a SSRI and an antiplatelet agent as this may increase the risk of bleeding events[139][138].[137]. Bleeding events reported have included [epistaxis](#), ecchymosis, [hematoma](#), [petechiae](#), and life-threatening hemorrhages. Monitor patient for signs of increased bleeding when [fluvoxamine](#) is administered with an antiplatelet agent concomitantly [137].

3j) Severity: major

4j) Onset: unspecified

5j) Substantiation: theoretical

6j) Clinical Management: When [fluvoxamine](#) and an antiplatelet agent are given concurrently, monitor patient for signs of increased bleeding[137].

7J) Probable Mechanism: unknown

8J) Literature Reports

aJ) In a retrospective study of patients over 50 years of age with the diagnosis of acute [myocardial infarction](#) (N=27,058), SSRI use with any antiplatelet therapy significantly increased the risk of bleeding by 1.42-fold compared with [aspirin](#) use alone. Therapy with [aspirin](#), [clopidogrel](#), and an SSRI significantly increased risk by 2.35-fold compared with [aspirin](#) use alone and by 1.57-fold compared with [clopidogrel](#) and [aspirin](#) combination therapy [138].

bJ) In a systematic review and meta-analysis of 22 observational studies, SSRI use was associated with a significant 1.55 fold increase in risk of [upper gastrointestinal bleeding](#) (UGIB). Concomitant use of SSRIs and antiplatelet drugs was associated with a 2.48-fold increase in risk of UGIB (3 studies) [139].

3.5.1.GI] Procarbazine

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

2J) Summary: Concomitant use of [fluvoxamine](#) and an MAOI is contraindicated. Concurrent administration or overlapping therapy with [fluvoxamine](#) and an MAOI may result in [serotonin syndrome](#), a hyperserotonergic state characterized by symptoms such as agitation and hallucinations, myoclonus, changes in mental status, hyperreflexia, diaphoresis, rigidity, and tremor. Serious, even fatal, reactions have been reported with concomitant use of SSRIs and MAOIs. A minimum of 14 days should elapse after discontinuing an MAOI intended to treat psychiatric disorders before initiating therapy with [fluvoxamine](#), and a minimum of 14 days should elapse after discontinuing [fluvoxamine](#) before initiating therapy with an MAOI intended to treat psychiatric disorders[20].

3J) Severity: contraindicated

4J) Onset: unspecified

5J) Substantiation: theoretical

6J) Clinical Management: Concurrent use of [fluvoxamine](#) and an MAOI is contraindicated. Wait at least 14 days after discontinuing an MAOI intended to treat psychiatric disorders before initiating [fluvoxamine](#). Wait at least 14 days after discontinuing [fluvoxamine](#) before initiating therapy with an MAOI intended to treat psychiatric disorders[20].

7J) Probable Mechanism: additive serotonergic effect

3.5.1.GJ] Proglumetacin

1J) Interaction Effect: an increased risk of bleeding

2J) Summary: Caution is recommended with the concomitant use of NSAIDs and antidepressants, including SSRIs due to an increased risk of [intracranial hemorrhage](#)[367] and [gastrointestinal bleeding](#) [371][372][368][369]. Bleeding events have included [epistaxis](#), ecchymosis, [hematoma](#), [petechiae](#), and life-threatening hemorrhages [374][373][375][376]. When an SSRI and an NSAID are given concurrently, monitor the patient for signs of increased bleeding.

3J) Severity: major

4J) Onset: unspecified

5J) Substantiation: established

6J) Clinical Management: Use caution if NSAIDs and SSRIs are coadministered. Concomitant use of NSAIDs and SSRIs may cause an increased risk of [intracranial hemorrhage](#)[367] and [gastrointestinal bleeding](#) [368][369]. When an SSRI and an NSAID are given concurrently, monitor the patient for signs of increased bleeding.

7J) Probable Mechanism: depletion of [platelet](#) serotonin by SSRI; additive effects

8) Literature Reports

a) Concomitant use of NSAIDs and antidepressants, including tricyclic antidepressants, SSRIs, serotonin-norepinephrine reuptake inhibitors, and MAOIs, resulted in a 60% increased risk of [intracranial hemorrhage](#) within 30 days of concomitant use compared with antidepressant use alone. There was no significant difference between the antidepressant drug classes and the increased risk; however, there was an increased risk associated with male patients compared with female patients [367].

b) 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. Combined use of an SSRI and NSAIDs or low-dose [aspirin](#) increased the risk to 12.2 and 5.2 times, 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 [370].

c) Two metaanalyses of incidents of upper GI bleed due to SSRIs, NSAIDs, and their combination found that SSRIs increased the risk by 1.73 [371] to 2.36 times [372], NSAIDs by 2.55 times [371], and the combination of SSRIs and NSAIDs by 4.02 [371] to 6.33 times [372].

d) The release of serotonin by [platelets](#) is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs and NSAIDs have been associated with an increased risk of bleeding [373].

3.5.1.GK] Propionic Acid

1) Interaction Effect: an increased risk of bleeding

2) Summary: Caution is recommended with the concomitant use of NSAIDs and antidepressants, including SSRIs due to an increased risk of [intracranial hemorrhage](#)[367] and [gastrointestinal bleeding](#) [371][372][368][369]. Bleeding events have included [epistaxis](#), ecchymosis, [hematoma](#), [petechiae](#), and life-threatening hemorrhages [374][373][375][376]. When an SSRI and an NSAID are given concurrently, monitor the patient for signs of increased bleeding.

3) Severity: major

4) Onset: unspecified

5) Substantiation: established

6) Clinical Management: Use caution if NSAIDs and SSRIs are coadministered. Concomitant use of NSAIDs and SSRIs may cause an increased risk of [intracranial hemorrhage](#)[367] and [gastrointestinal bleeding](#) [368][369]. When an SSRI and an NSAID are given concurrently, monitor the patient for signs of increased bleeding.

7) Probable Mechanism: depletion of [platelet](#) serotonin by SSRI; additive effects

8) Literature Reports

a) Concomitant use of NSAIDs and antidepressants, including tricyclic antidepressants, SSRIs, serotonin-norepinephrine reuptake inhibitors, and MAOIs, resulted in a 60% increased risk of [intracranial hemorrhage](#) within 30 days of concomitant use compared with antidepressant use alone. There was no significant difference between the antidepressant drug classes and the increased risk; however, there was an increased risk associated with male patients compared with female patients [367].

b)) 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. Combined use of an SSRI and NSAIDs or low-dose [aspirin](#) increased the risk to 12.2 and 5.2 times, 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 [370].

c)) Two metaanalyses of incidents of upper GI bleed due to SSRIs, NSAIDs, and their combination found that SSRIs increased the risk by 1.73 [371] to 2.36 times [372], NSAIDs by 2.55 times [371], and the combination of SSRIs and NSAIDs by 4.02 [371] to 6.33 times [372].

d)) The release of serotonin by [platelets](#) is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs and NSAIDs have been associated with an increased risk of bleeding [373].

3.5.1.GL] [Propranolol](#)

1)) Interaction Effect: bradycardia and hypotension

2)) Summary: [Propranolol](#) serum concentrations may increase significantly during concomitant therapy with [fluvoxamine](#). Elevated [propranolol](#) serum concentrations may be associated with an increased risk of bradycardia and hypotension[136].

3)) Severity: moderate

4)) Onset: delayed

5)) Substantiation: probable

6)) Clinical Management: Carefully monitor heart rate and blood pressure. The [propranolol](#) does may need to be reduced if bradycardia or hypotension develop. Alternatively, use of [atenolol](#), a beta-blocker which does not undergo hepatic metabolism and is not affected by [fluvoxamine](#), may be considered.

7)) Probable Mechanism: reduced beta blocker metabolism

8)) Literature Reports

a)) Coadministration of [propranolol](#) (160 mg per day) and [fluvoxamine](#) (100 mg per day) in healthy volunteers resulted in a mean 5-fold increase in minimum [propranolol](#) serum concentrations. This was associated with a slight reduction in heart rate and blood pressure [134][135].

3.5.1.GM] [Propyphenazone](#)

1)) Interaction Effect: an increased risk of bleeding

2)) Summary: Caution is recommended with the concomitant use of NSAIDs and antidepressants, including SSRIs due to an increased risk of [intracranial hemorrhage](#)[367] and [gastrointestinal bleeding](#) [371][372][368][369]. Bleeding events have included [epistaxis](#), ecchymosis, [hematoma](#), [petechiae](#), and life-threatening hemorrhages [374][373][375][376]. When an SSRI and an NSAID are given concurrently, monitor the patient for signs of increased bleeding.

3)) Severity: major

4)) Onset: unspecified

5)) Substantiation: established

6)) Clinical Management: Use caution if NSAIDs and SSRIs are coadministered. Concomitant use of NSAIDs and SSRIs may cause an increased risk of [intracranial hemorrhage](#)[367] and [gastrointestinal](#)

bleeding [368][369]. When an SSRI and an NSAID are given concurrently, monitor the patient for signs of increased bleeding.

7) Probable Mechanism: depletion of platelet serotonin by SSRI; additive effects

8) Literature Reports

a) Concomitant use of NSAIDs and antidepressants, including tricyclic antidepressants, SSRIs, serotonin-norepinephrine reuptake inhibitors, and MAOIs, resulted in a 60% increased risk of intracranial hemorrhage within 30 days of concomitant use compared with antidepressant use alone. There was no significant difference between the antidepressant drug classes and the increased risk; however, there was an increased risk associated with male patients compared with female patients [367].

b) 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. Combined use of an SSRI and NSAIDs or low-dose aspirin increased the risk to 12.2 and 5.2 times, 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 [370].

c) Two metaanalyses of incidents of upper GI bleed due to SSRIs, NSAIDs, and their combination found that SSRIs increased the risk by 1.73 [371] to 2.36 times [372], NSAIDs by 2.55 times [371], and the combination of SSRIs and NSAIDs by 4.02 [371] to 6.33 times [372].

d) The release of serotonin by platelets is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs and NSAIDs have been associated with an increased risk of bleeding [373].

3.5.1.GN] Proquazone

1) Interaction Effect: an increased risk of bleeding

2) Summary: Caution is recommended with the concomitant use of NSAIDs and antidepressants, including SSRIs due to an increased risk of intracranial hemorrhage[367] and gastrointestinal bleeding [371][372][368][369]. Bleeding events have included epistaxis, ecchymosis, hematoma, petechiae, and life-threatening hemorrhages [374][373][375][376]. When an SSRI and an NSAID are given concurrently, monitor the patient for signs of increased bleeding.

3) Severity: major

4) Onset: unspecified

5) Substantiation: established

6) Clinical Management: Use caution if NSAIDs and SSRIs are coadministered. Concomitant use of NSAIDs and SSRIs may cause an increased risk of intracranial hemorrhage[367] and gastrointestinal bleeding [368][369]. When an SSRI and an NSAID are given concurrently, monitor the patient for signs of increased bleeding.

7) Probable Mechanism: depletion of platelet serotonin by SSRI; additive effects

8) Literature Reports

a) Concomitant use of NSAIDs and antidepressants, including tricyclic antidepressants, SSRIs, serotonin-norepinephrine reuptake inhibitors, and MAOIs, resulted in a 60% increased risk of intracranial hemorrhage within 30 days of concomitant use compared with antidepressant use alone. There was no significant difference between the antidepressant drug classes and the

increased risk; however, there was an increased risk associated with male patients compared with female patients [367].

b) 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. Combined use of an SSRI and NSAIDs or low-dose [aspirin](#) increased the risk to 12.2 and 5.2 times, 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 [370].

c) Two metaanalyses of incidents of upper GI bleed due to SSRIs, NSAIDs, and their combination found that SSRIs increased the risk by 1.73 [371] to 2.36 times [372], NSAIDs by 2.55 times [371], and the combination of SSRIs and NSAIDs by 4.02 [371] to 6.33 times [372].

d) The release of serotonin by [platelets](#) is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs and NSAIDs have been associated with an increased risk of bleeding [373].

3.5.1.GO] [Ramelteon](#)

- 1) Interaction Effect: increased [ramelteon](#) plasma concentrations with increased risk of side effects
- 2) Summary: Concurrent administration of [fluvoxamine](#) and [ramelteon](#) is contraindicated due to significantly increased [ramelteon](#) plasma concentrations with concurrent [fluvoxamine](#) use[22][172].
- 3) Severity: contraindicated
- 4) Onset: delayed
- 5) Substantiation: probable
- 6) Clinical Management: Concurrent administration of [fluvoxamine](#) and [ramelteon](#) is contraindicated[22][172].
- 7) Probable Mechanism: inhibition of CYP1A2-mediated [ramelteon](#) metabolism by [fluvoxamine](#)
- 8) Literature Reports

a) [Fluvoxamine](#), a strong CYP1A2 inhibitor, significantly increases [ramelteon](#) plasma concentrations when used concurrently. When a single dose of [ramelteon](#) 16 mg was coadministered to subjects who received [fluvoxamine](#) 100 mg twice daily for 3 days prior, the [ramelteon](#) AUC and Cmax increased approximately 190-fold and 70-fold, respectively [22][172].

3.5.1.GP] [Rasagiline](#)

- 1) Interaction Effect: an increased risk of [serotonin syndrome](#) ([hypertension](#), [tachycardia](#), [hyperthermia](#), [myoclonus](#), [mental status changes](#))
- 2) Summary: Concomitant use of [fluvoxamine](#) and an MAOI is contraindicated. Concurrent administration or overlapping therapy with [fluvoxamine](#) and an MAOI may result in [serotonin syndrome](#), a hyperserotonergic state characterized by symptoms such as agitation and hallucinations, myoclonus, changes in mental status, hyperreflexia, diaphoresis, rigidity, and tremor. Serious, even fatal, reactions have been reported with concomitant use of SSRIs and MAOIs. A minimum of 14 days should elapse after discontinuing an MAOI intended to treat psychiatric disorders before initiating therapy with [fluvoxamine](#), and a minimum of 14 days should elapse after discontinuing [fluvoxamine](#) before initiating therapy with an MAOI intended to treat psychiatric disorders[20].
- 3) Severity: contraindicated

- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Concurrent use of [fluvoxamine](#) and an MAOI is contraindicated. Wait at least 14 days after discontinuing an MAOI intended to treat psychiatric disorders before initiating [fluvoxamine](#). Wait at least 14 days after discontinuing [fluvoxamine](#) before initiating therapy with an MAOI intended to treat psychiatric disorders[20].
- 7) Probable Mechanism: additive serotonergic effect

3.5.1.GQ| 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[114][115][113]. 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](#). In patients receiving [warfarin](#) and [fluvoxamine](#) concomitantly for 2 weeks, [warfarin](#) plasma concentrations increased by 98% and prothrombin times were prolonged. [Fluvoxamine](#) appears to inhibit several cytochrome P450 isoenzymes which may include 1A2 and 2C9 isozymes, which are responsible for [warfarin](#) metabolism [115][113].
- 3) Severity: major
- 4) Onset: delayed
- 5) Substantiation: probable
- 6) Clinical Management: When [fluvoxamine](#) 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 [fluvoxamine](#) therapy is initiated or discontinued. Periodically reassess the prothrombin time ratio and INR in patients receiving [fluvoxamine](#) and [anticoagulant therapy](#)[113].
- 7) Probable Mechanism: unknown
- 8) Literature Reports

a) According to a retrospective cohort study (n=234), there was an increased risk of clinically relevant bleeding (hospital admission due to bleeding) in patients receiving [warfarin](#) for [atrial fibrillation](#) during concomitant SSRI therapy or within 2 weeks following SSRI therapy termination. Patients with a mean age of 72 +/- 7 years receiving [warfarin](#) plus SSRI (n=117) were matched with randomly selected patients who received [warfarin](#) only (n=117). SSRI included [fluoxetine](#), [citalopram](#), [paroxetine](#), [sertraline](#), [fluvoxamine](#), or escitalopram. Nine patients experienced 11 bleeding episodes during 213.9 treatment years in the [warfarin](#) plus SSRI group, and 10 patients experienced 14 bleedings during 586.4 treatment years in the warfarin-only group. The corresponding total incidences of bleedings were 51.4 and 23.9 per 1000 treatment years, respectively. The hazard ratio for first bleedings during treatment with [warfarin](#) plus SSRI was 3.49 (95% CI; 1.37 to 8.91, p=0.009) compared with [warfarin](#) only. The SSRI implicated in patients experiencing bleeding at the time of concomitant administration were [sertraline](#) or [citalopram](#). The addition of an SSRI was not associated with a change in [warfarin](#) dose or INR (p=0.48 and p=0.31 respectively). The results of the study may be limited by earlier bleeding events, unknown patient adherence, and exclusion of [clopidogrel](#), dipyridamol, corticosteroids and anticoagulants other than [warfarin](#) in the model [114].

b) A population-based, case-controlled study of new coumarin users (acenocoumarol and phenprocoumon) with concomitant selective serotonin reuptake inhibitors (SSRIs) resulted in an

increased risk of hospitalization due to nongastrointestinal bleeding. Using national pharmacy and hospitalization records, Netherlands researchers identified 1848 cases that were admitted for abnormal bleeding and compared them with 5818 control subjects also taking coumarins. Median duration of treatment in patients was 220 days (range, 1 to 4690 days). Patients on SSRIs showed greater risk for hospitalization for nongastrointestinal bleeding (adjusted odds ratio (OR) 1.7, 95% confidence interval (CI), 1.1 to 2.5), however, the rate of [gastrointestinal bleeding](#) (adjusted OR 0.8, 95% CI, 0.4 to 1.5) was not significantly different [115].

c) A hospitalized 80-year-old female was started on intravenous [heparin](#) and oral [warfarin](#) therapy due to an [embolic stroke](#) secondary to [atrial fibrillation](#) and [mitral stenosis](#). Her [warfarin](#) dose was maintained at 1 mg daily, with her INR between 2.5 and 3. [Fluvoxamine](#) 25 mg daily was started for depression, and her [warfarin](#) dose was increased to 1.5 mg daily 3 days later due to worsening of the left [hemiparesis](#). Three days later, her INR was 9.96, and a repeat INR to rule out laboratory error was 11.3. [Warfarin](#) was discontinued, fresh frozen plasma was given, and [fluvoxamine](#) was discontinued. Six days later, [warfarin](#) was again started at 1 mg daily, and the INR increased over 4 days to 11.8. The elevated INR was attributed to the persisting effect of [fluvoxamine](#). She was eventually stabilized on [warfarin](#) 1 mg daily with INR values between 2 and 2.5 [116].

3.5.1.GR| [Rivaroxaban](#)

- 1) Interaction Effect: increased risk of bleeding
- 2) Summary: Use caution with concomitant use of rivaroxaban and a serotonin [norepinephrine](#) reuptake inhibitor or SSRI, as additive effects on bleeding may occur. If signs or symptoms of blood loss occur following coadministration, promptly evaluate the patient and consider whether blood replacement is needed, as bleeding may be serious or fatal[210].
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Use caution with concomitant use of rivaroxaban and a serotonin [norepinephrine](#) reuptake inhibitor or SSRI, as additive effects on bleeding may occur. If signs or symptoms of blood loss occur following coadministration, promptly evaluate the patient and consider whether blood replacement is needed, as bleeding may be serious or fatal[210].
- 7) Probable Mechanism: additive effects on bleeding

3.5.1.GS| [Rizatriptan](#)

- 1) Interaction Effect: an increased risk of [serotonin syndrome](#)
- 2) Summary: There have been case reports of weakness, hyperreflexia, and incoordination following concomitant use of [sumatriptan](#), a 5-hydroxytryptamine-1 (5HT-1) agonist, and a serotonin specific reuptake inhibitor (SSRI)[225]. Because [rizatriptan](#) is a 5HT 1B/1D receptor agonist, a similar interaction between SSRIs and [rizatriptan](#) may occur [226]. 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](#) [118].
- 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](#) [224].

3.5.1.GT] [Rofecoxib](#)

1) Interaction Effect: an increased risk of bleeding

2) Summary: Caution is recommended with the concomitant use of NSAIDs and antidepressants, including SSRIs due to an increased risk of [intracranial hemorrhage](#)[367] and [gastrointestinal bleeding](#) [371][372][368][369]. Bleeding events have included [epistaxis](#), ecchymosis, [hematoma](#), [petechiae](#), and life-threatening hemorrhages [374][373][375][376]. When an SSRI and an NSAID are given concurrently, monitor the patient for signs of increased bleeding.

3) Severity: major

4) Onset: unspecified

5) Substantiation: established

6) Clinical Management: Use caution if NSAIDs and SSRIs are coadministered. Concomitant use of NSAIDs and SSRIs may cause an increased risk of [intracranial hemorrhage](#)[367] and [gastrointestinal bleeding](#) [368][369]. When an SSRI and an NSAID are given concurrently, monitor the patient for signs of increased bleeding.

7) Probable Mechanism: depletion of [platelet](#) serotonin by SSRI; additive effects

8) Literature Reports

a) Concomitant use of NSAIDs and antidepressants, including tricyclic antidepressants, SSRIs, serotonin-norepinephrine reuptake inhibitors, and MAOIs, resulted in a 60% increased risk of [intracranial hemorrhage](#) within 30 days of concomitant use compared with antidepressant use alone. There was no significant difference between the antidepressant drug classes and the increased risk; however, there was an increased risk associated with male patients compared with female patients [367].

b) 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. Combined use of an SSRI and NSAIDs or low-dose [aspirin](#) increased the risk to 12.2 and 5.2 times, 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 [370].

c) Two metaanalyses of incidents of upper GI bleed due to SSRIs, NSAIDs, and their combination found that SSRIs increased the risk by 1.73 [371] to 2.36 times [372], NSAIDs by 2.55 times [371], and the combination of SSRIs and NSAIDs by 4.02 [371] to 6.33 times [372].

d)) The release of serotonin by [platelets](#) is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs and NSAIDs have been associated with an increased risk of bleeding [373].

3.5.1.GU] Roflumilast

1)) Interaction Effect: increased roflumilast exposure

2)) Summary: Use caution when coadministering [fluvoxamine](#) and roflumilast. Roflumilast is extensively metabolized via CYP, and concomitant administration of a dual CYP3A4/1A2 inhibitor such as [fluvoxamine](#) has been demonstrated to increase roflumilast plasma concentrations, potentially increasing the risk of adverse events due to roflumilast. In an open-label crossover study of 16 healthy volunteers, concomitant oral administration of [fluvoxamine](#) 50 mg daily for 14 days and a single dose of roflumilast 500 mcg resulted in increased roflumilast Cmax and AUC values of 12% and 156%, respectively, and a 210% reduction and 52% increase in Cmax and AUC of roflumilast N-oxide (active metabolite), respectively[198]. If given concomitantly, monitor for increased roflumilast side effects including new or worsening signs and symptoms of depression, suicidality, weight loss, diarrhea, nausea and headache.

3)) Severity: moderate

4)) Onset: unspecified

5)) Substantiation: established

6)) Clinical Management: Use caution when coadministering [fluvoxamine](#) and roflumilast. Concomitant administration of dual CYP3A4/1A2 enzyme inhibitors, such as [fluvoxamine](#), increased roflumilast plasma concentrations[198], and may increase roflumilast side effects. If given concomitantly, monitor for increased roflumilast side effects including new or worsening signs and symptoms of depression, suicidality, weight loss, diarrhea, nausea and headache.

7)) Probable Mechanism: inhibition of CYP3A4 and CYP1A2 isoenzymes by [fluvoxamine](#), resulting in increased exposure of roflumilast

3.5.1.GV] Ropivacaine

1)) Interaction Effect: increased plasma levels of [ropivacaine](#)

2)) Summary: [Ropivacaine](#) is metabolized in the liver by the cytochrome P450 1A2 (CYP1A2) enzyme system to 3-hydroxyropivacaine, the major metabolite. Drugs which inhibit CYP1A2, such as [fluvoxamine](#), can potentially interact with the metabolism of [ropivacaine](#). This would result in decreased renal clearance and increased plasma concentrations of [ropivacaine](#)[95][96].

3)) Severity: moderate

4)) Onset: rapid

5)) Substantiation: probable

6)) Clinical Management: Care must be taken to monitor the patient for signs of local anesthetic toxicity with the coadministration of [ropivacaine](#) and [fluvoxamine](#).

7)) Probable Mechanism: inhibition by [fluvoxamine](#) of cytochrome P450 1A2-mediated [ropivacaine](#) metabolism

8)) Literature Reports

a)) In a randomized, three-way crossover study, 12 healthy volunteers received a single dose of [ropivacaine](#) 40 mg as an intravenous infusion alone or combined with either oral [fluvoxamine](#) 25 mg or [ketoconazole](#) 100 mg twice daily for two days. The combined therapy with [ropivacaine](#) and [ketoconazole](#) demonstrated no clinically significant differences in the pharmacokinetic measurements obtained. The authors theorized that cytochrome P450 3A4 (CYP3A4) inhibition, as measured by [ketoconazole](#), has little effect on the pharmacokinetics of [ropivacaine](#). However, CYP1A2 inhibition, as measured by [fluvoxamine](#), may result in a clinically relevant drug

interaction with repeated administration. In the presence of [fluvoxamine](#), [ropivacaine](#) total plasma clearance decreased by 68% (from 354 mL/min to 112 mL/min). The observed reduction in the total plasma clearance after [fluvoxamine](#) arises from a decrease in 3-hydroxyropivacaine formation, which is likely mediated by CYP1A2. Additionally, the half-life of [ropivacaine](#) increased from 1.9 hours to 3.6 hours when given with [fluvoxamine](#). The reduction in [ropivacaine](#) clearance during [fluvoxamine](#) administration is likely to be of minor relevance when [ropivacaine](#) is given as a single dose. However, repeated administration of [ropivacaine](#) in a patient also receiving [fluvoxamine](#) may result in toxic [ropivacaine](#) plasma concentrations [93].

b) Inhibition of cytochrome P450 1A2 (CYP1A2) by [fluvoxamine](#) considerably reduced elimination of [ropivacaine](#). The eight patients in this randomized, double-blind, cross-over, four phase study ingested [erythromycin](#) 1500 mg daily for 6 days, [fluvoxamine](#) 100 mg for 5 days, both [erythromycin](#) and [fluvoxamine](#), or placebo. Each subject received [ropivacaine](#) 0.6 mg/kg IV over 30 minutes as a single dose. [Fluvoxamine](#) increased both the AUC (p less than 0.001) of [ropivacaine](#) 3.7-fold, prolonged the half-life from 2.3 to 7.4 h (p less than 0.01), and decreased clearance 77% (p less than 0.001) when compared with placebo. [Fluvoxamine](#) increased the AUC of 2,6-pipecoloxylidide (PPX), a [ropivacaine](#) metabolite, 2.5-fold (p less than 0.001) and the Cmax of PPX 2.8-fold (p less than 0.001) and decreased the plasma levels of 3-OH-ropivacaine to below the limit of quantitation. [Erythromycin](#) had minor effects on the pharmacokinetics of [ropivacaine](#). The combination of [fluvoxamine](#) and [erythromycin](#), however, when compared with [fluvoxamine](#) alone, further increased the AUC of [ropivacaine](#) by 50% (p less than 0.01), and prolonged the half-life from 7.4 to 11.9 h (p less than 0.01). The author concludes that fluvoxamine-induced cytochrome P450 1A2 inhibition considerably reduces elimination of [ropivacaine](#). Coadministration of [fluvoxamine](#) and [erythromycin](#) increases plasma [ropivacaine](#) levels further by decreasing its clearance [94].

3.5.1.GW] Safinamide

- 1) Interaction Effect: Risk of [serotonin syndrome](#)
- 2) Summary: Concomitant use of serotonergic agents with safinamide (a MAOI-type B) is contraindicated due to the potential for [serotonin syndrome](#). Use of serotonergic agents within 14 days of discontinuing a MAOI is also contraindicated[219].
- 3) Severity: contraindicated
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Concomitant use of serotonergic agents with safinamide (a MAOI-type B) is contraindicated due to the potential for [serotonin syndrome](#). Use of serotonergic agents within 14 days of discontinuing a MAOI is also contraindicated[219].
- 7) Probable Mechanism: Additive serotonergic effects

3.5.1.GX] Salicylic Acid

- 1) Interaction Effect: an increased risk of bleeding
- 2) Summary: Caution is recommended with the concomitant use of NSAIDs and antidepressants, including SSRIs due to an increased risk of [intracranial hemorrhage](#)[367] and [gastrointestinal bleeding](#) [371][372][368][369]. Bleeding events have included [epistaxis](#), ecchymosis, [hematoma](#), [petechiae](#), and life-threatening hemorrhages [374][373][375][376]. When an SSRI and an NSAID are given concurrently, monitor the patient for signs of increased bleeding.
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: established

6j) Clinical Management: Use caution if NSAIDs and SSRIs are coadministered. Concomitant use of NSAIDs and SSRIs may cause an increased risk of [intracranial hemorrhage](#)[367] and [gastrointestinal bleeding](#) [368][369]. When an SSRI and an NSAID are given concurrently, monitor the patient for signs of increased bleeding.

7j) Probable Mechanism: depletion of [platelet](#) serotonin by SSRI; additive effects

8j) Literature Reports

aj) Concomitant use of NSAIDs and antidepressants, including tricyclic antidepressants, SSRIs, serotonin-norepinephrine reuptake inhibitors, and MAOIs, resulted in a 60% increased risk of [intracranial hemorrhage](#) within 30 days of concomitant use compared with antidepressant use alone. There was no significant difference between the antidepressant drug classes and the increased risk; however, there was an increased risk associated with male patients compared with female patients [367].

bj) 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. Combined use of an SSRI and NSAIDs or low-dose [aspirin](#) increased the risk to 12.2 and 5.2 times, 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 [370].

cj) Two metaanalyses of incidents of upper GI bleed due to SSRIs, NSAIDs, and their combination found that SSRIs increased the risk by 1.73 [371] to 2.36 times [372], NSAIDs by 2.55 times [371], and the combination of SSRIs and NSAIDs by 4.02 [371] to 6.33 times [372].

dj) The release of serotonin by [platelets](#) is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs and NSAIDs have been associated with an increased risk of bleeding [373].

3.5.1.GY] [Salsalate](#)

1j) Interaction Effect: an increased risk of bleeding

2j) Summary: Caution is recommended with the concomitant use of NSAIDs and antidepressants, including SSRIs due to an increased risk of [intracranial hemorrhage](#)[367] and [gastrointestinal bleeding](#) [371][372][368][369]. Bleeding events have included [epistaxis](#), ecchymosis, [hematoma](#), [petechiae](#), and life-threatening hemorrhages [374][373][375][376]. When an SSRI and an NSAID are given concurrently, monitor the patient for signs of increased bleeding.

3j) Severity: major

4j) Onset: unspecified

5j) Substantiation: established

6j) Clinical Management: Use caution if NSAIDs and SSRIs are coadministered. Concomitant use of NSAIDs and SSRIs may cause an increased risk of [intracranial hemorrhage](#)[367] and [gastrointestinal bleeding](#) [368][369]. When an SSRI and an NSAID are given concurrently, monitor the patient for signs of increased bleeding.

7j) Probable Mechanism: depletion of [platelet](#) serotonin by SSRI; additive effects

8j) Literature Reports

aj) Concomitant use of NSAIDs and antidepressants, including tricyclic antidepressants, SSRIs, serotonin-norepinephrine reuptake inhibitors, and MAOIs, resulted in a 60% increased risk

of [intracranial hemorrhage](#) within 30 days of concomitant use compared with antidepressant use alone. There was no significant difference between the antidepressant drug classes and the increased risk; however, there was an increased risk associated with male patients compared with female patients [367].

b) 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. Combined use of an SSRI and NSAIDs or low-dose [aspirin](#) increased the risk to 12.2 and 5.2 times, 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 [370].

c) Two metaanalyses of incidents of upper GI bleed due to SSRIs, NSAIDs, and their combination found that SSRIs increased the risk by 1.73 [371] to 2.36 times [372], NSAIDs by 2.55 times [371], and the combination of SSRIs and NSAIDs by 4.02 [371] to 6.33 times [372].

d) The release of serotonin by [platelets](#) is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs and NSAIDs have been associated with an increased risk of bleeding [373].

3.5.1.GZ| [Selegiline](#)

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

2) Summary: Concomitant use of [fluvoxamine](#) and an MAOI is contraindicated. Concurrent administration or overlapping therapy with [fluvoxamine](#) and an MAOI may result in [serotonin syndrome](#), a hyperserotonergic state characterized by symptoms such as agitation and hallucinations, myoclonus, changes in mental status, hyperreflexia, diaphoresis, rigidity, and tremor. Serious, even fatal, reactions have been reported with concomitant use of SSRIs and MAOIs. A minimum of 14 days should elapse after discontinuing an MAOI intended to treat psychiatric disorders before initiating therapy with [fluvoxamine](#), and a minimum of 14 days should elapse after discontinuing [fluvoxamine](#) before initiating therapy with an MAOI intended to treat psychiatric disorders[20].

3) Severity: contraindicated

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Concurrent use of [fluvoxamine](#) and an MAOI is contraindicated. Wait at least 14 days after discontinuing an MAOI intended to treat psychiatric disorders before initiating [fluvoxamine](#). Wait at least 14 days after discontinuing [fluvoxamine](#) before initiating therapy with an MAOI intended to treat psychiatric disorders[20].

7) Probable Mechanism: additive serotonergic effect

3.5.1.HA| [Selexipag](#)

1) Interaction Effect: increased risk of bleeding

2) Summary: Exercise caution when coadministering a SSRI and an antiplatelet agent as this may increase the risk of bleeding events[139][138].[137]. Bleeding events reported have included [epistaxis](#), [ecchymosis](#), [hematoma](#), [petechiae](#), and life-threatening hemorrhages. Monitor patient for signs of increased bleeding when [fluvoxamine](#) is administered with an antiplatelet agent concomitantly [137].

3) Severity: major

- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: When [fluvoxamine](#) and an antiplatelet agent are given concurrently, monitor patient for signs of increased bleeding[137].
- 7) Probable Mechanism: unknown
- 8) Literature Reports

a) In a retrospective study of patients over 50 years of age with the diagnosis of acute [myocardial infarction](#) (N=27,058), SSRI use with any antiplatelet therapy significantly increased the risk of bleeding by 1.42-fold compared with [aspirin](#) use alone. Therapy with [aspirin](#), [clopidogrel](#), and an SSRI significantly increased risk by 2.35-fold compared with [aspirin](#) use alone and by 1.57-fold compared with [clopidogrel](#) and [aspirin](#) combination therapy [138].

b) In a systematic review and meta-analysis of 22 observational studies, SSRI use was associated with a significant 1.55 fold increase in risk of [upper gastrointestinal bleeding](#) (UGIB). Concomitant use of SSRIs and antiplatelet drugs was associated with a 2.48-fold increase in risk of UGIB (3 studies) [139].

3.5.1.HB| [Sertraline](#)

- 1) Interaction Effect: increased risk of [serotonin syndrome](#)
- 2) Summary: Coadministration 2 SSRIs may result in an increased risk of [serotonin syndrome](#). Monitor patients closely for [serotonin syndrome](#), especially during treatment initiation and dose increases. Symptoms of [serotonin syndrome](#) include neuromuscular abnormalities (eg, hyperreflexia, tremor, and ataxia), autonomic instability (eg, [tachycardia](#), diaphoresis, and [hyperthermia](#)), gastrointestinal symptoms (eg, nausea, vomiting, diarrhea), or mental status changes (eg, agitation and confusion). Discontinue both drugs immediately if these symptoms occur and initiate supportive therapy[213].
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Coadministration 2 SSRIs may result in an increased risk of [serotonin syndrome](#). Monitor patients closely for [serotonin syndrome](#), especially during treatment initiation and dose increases. Symptoms of [serotonin syndrome](#) include neuromuscular abnormalities (eg, hyperreflexia, tremor, and ataxia), autonomic instability (eg, [tachycardia](#), diaphoresis, and [hyperthermia](#)), gastrointestinal symptoms (eg, nausea, vomiting, diarrhea), or mental status changes (eg, agitation and confusion). Discontinue both drugs immediately if these symptoms occur and initiate supportive therapy[213].
- 7) Probable Mechanism: additive serotonergic effects

3.5.1.HC| [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[329].
- 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 [328].

3.5.1.HD) [Simvastatin](#)

- 1) Interaction Effect: increased plasma concentrations of selected statins and increased risk for [myopathy](#) and [rhabdomyolysis](#)
- 2) Summary: Coadministration of [fluvoxamine](#) with selected statins may result in increased plasma levels of the statin drug and an increased risk for [myopathy](#). Monitor the patient and consider lowering the dosage of the statin drug[188].
- 3) Severity: moderate
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Coadministration of [fluvoxamine](#) with selected statins may result in increased plasma levels of the statin drug and an increased risk for [myopathy](#). Monitor the patient for unexplained muscle pain, tenderness, and weakness, and consider lowering the dosage of the statin drug[188].
- 7) Probable Mechanism: inhibition of CYP3A4-mediated statin metabolism

3.5.1.HE) [Sodium Salicylate](#)

- 1) Interaction Effect: an increased risk of bleeding
- 2) Summary: Caution is recommended with the concomitant use of NSAIDs and antidepressants, including SSRIs due to an increased risk of [intracranial hemorrhage](#)[367] and [gastrointestinal bleeding](#) [371][372][368][369]. Bleeding events have included [epistaxis](#), ecchymosis, [hematoma](#), [petechiae](#), and life-threatening hemorrhages [374][373][375][376]. When an SSRI and an NSAID are given concurrently, monitor the patient for signs of increased bleeding.
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: established
- 6) Clinical Management: Use caution if NSAIDs and SSRIs are coadministered. Concomitant use of NSAIDs and SSRIs may cause an increased risk of [intracranial hemorrhage](#)[367] and [gastrointestinal bleeding](#) [368][369]. When an SSRI and an NSAID are given concurrently, monitor the patient for signs of increased bleeding.
- 7) Probable Mechanism: depletion of [platelet](#) serotonin by SSRI; additive effects
- 8) Literature Reports

a) Concomitant use of NSAIDs and antidepressants, including tricyclic antidepressants, SSRIs, serotonin-norepinephrine reuptake inhibitors, and MAOIs, resulted in a 60% increased risk of [intracranial hemorrhage](#) within 30 days of concomitant use compared with antidepressant use alone. There was no significant difference between the antidepressant drug classes and the increased risk; however, there was an increased risk associated with male patients compared with female patients [367].

b) 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. Combined use of an SSRI and NSAIDs or low-dose [aspirin](#) increased the risk to 12.2 and 5.2 times, 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 [370].

c) Two metaanalyses of incidents of upper GI bleed due to SSRIs, NSAIDs, and their combination found that SSRIs increased the risk by 1.73 [371] to 2.36 times [372], NSAIDs by 2.55 times [371], and the combination of SSRIs and NSAIDs by 4.02 [371] to 6.33 times [372].

d) The release of serotonin by [platelets](#) is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs and NSAIDs have been associated with an increased risk of bleeding [373].

3.5.1.HF] 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[307][308][309][310]. A patient exhibited a syndrome resembling sedative/[hypnotic intoxication](#) after adding St. John's Wort to [paroxetine](#) therapy [311]. St. John's Wort is thought to inhibit serotonin reuptake and may have mild monoamine oxidase inhibitory activity [312][313], 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 [302].

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 [303].

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 [304].

d)) A 28-year-old male developed a manic syndrome following comedication with St. John's Wort and [sertraline](#). The patient was also on [testosterone](#) replacement therapy following [bilateral orchidectomy](#) 2 years earlier, but [testosterone](#) levels were subtherapeutic. The patient was prescribed [sertraline](#) 50 milligrams daily for depression following a 2 week trial of St. John's Wort per patient preference (dose not specified). Before [sertraline](#) was started, the patient was instructed to discontinue St. John'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 [305].

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 [306].

3.5.1.HG] [Sulfinpyrazone](#)

1)) Interaction Effect: increased risk of bleeding

2) Summary: Exercise caution when coadministering a SSRI and an antiplatelet agent as this may increase the risk of bleeding events[139][138].[137]. Bleeding events reported have included [epistaxis](#), ecchymosis, [hematoma](#), [petechiae](#), and life-threatening hemorrhages. Monitor patient for signs of increased bleeding when [fluvoxamine](#) is administered with an antiplatelet agent concomitantly [137].

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: When [fluvoxamine](#) and an antiplatelet agent are given concurrently, monitor patient for signs of increased bleeding[137].

7) Probable Mechanism: unknown

8) Literature Reports

a) In a retrospective study of patients over 50 years of age with the diagnosis of acute [myocardial infarction](#) (N=27,058), SSRI use with any antiplatelet therapy significantly increased the risk of bleeding by 1.42-fold compared with [aspirin](#) use alone. Therapy with [aspirin](#), [clopidogrel](#), and an SSRI significantly increased risk by 2.35-fold compared with [aspirin](#) use alone and by 1.57-fold compared with [clopidogrel](#) and [aspirin](#) combination therapy [138].

b) In a systematic review and meta-analysis of 22 observational studies, SSRI use was associated with a significant 1.55 fold increase in risk of [upper gastrointestinal bleeding](#) (UGIB). Concomitant use of SSRIs and antiplatelet drugs was associated with a 2.48-fold increase in risk of UGIB (3 studies) [139].

3.5.1.HH| [Sulindac](#)

1) Interaction Effect: an increased risk of bleeding

2) Summary: Caution is recommended with the concomitant use of NSAIDs and antidepressants, including SSRIs due to an increased risk of [intracranial hemorrhage](#)[367] and [gastrointestinal bleeding](#) [371][372][368][369]. Bleeding events have included [epistaxis](#), ecchymosis, [hematoma](#), [petechiae](#), and life-threatening hemorrhages [374][373][375][376]. When an SSRI and an NSAID are given concurrently, monitor the patient for signs of increased bleeding.

3) Severity: major

4) Onset: unspecified

5) Substantiation: established

6) Clinical Management: Use caution if NSAIDs and SSRIs are coadministered. Concomitant use of NSAIDs and SSRIs may cause an increased risk of [intracranial hemorrhage](#)[367] and [gastrointestinal bleeding](#) [368][369]. When an SSRI and an NSAID are given concurrently, monitor the patient for signs of increased bleeding.

7) Probable Mechanism: depletion of [platelet](#) serotonin by SSRI; additive effects

8) Literature Reports

a) Concomitant use of NSAIDs and antidepressants, including tricyclic antidepressants, SSRIs, serotonin-norepinephrine reuptake inhibitors, and MAOIs, resulted in a 60% increased risk of [intracranial hemorrhage](#) within 30 days of concomitant use compared with antidepressant use alone. There was no significant difference between the antidepressant drug classes and the increased risk; however, there was an increased risk associated with male patients compared with female patients [367].

b) 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. Combined use of an SSRI and NSAIDs or low-dose [aspirin](#) increased the risk to 12.2 and 5.2 times, 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 [370].

c) Two metaanalyses of incidents of upper GI bleed due to SSRIs, NSAIDs, and their combination found that SSRIs increased the risk by 1.73 [371] to 2.36 times [372], NSAIDs by 2.55 times [371], and the combination of SSRIs and NSAIDs by 4.02 [371] to 6.33 times [372].

d) The release of serotonin by [platelets](#) is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs and NSAIDs have been associated with an increased risk of bleeding [373].

3.5.1.HI] [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 a triptan, such as [sumatriptan](#), and a serotonin specific reuptake inhibitor (SSRI), such as [fluvoxamine](#)[117]. 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](#) [118].

3) Severity: major

4) Onset: delayed

5) Substantiation: probable

6) Clinical Management: Coadministration of a triptan, such as [sumatriptan](#), and an SSRI, such as [fluvoxamine](#), 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.HJ] [Tacrine](#)

1) Interaction Effect: an increase in the plasma concentration of [tacrine](#)

2) Summary: Two studies involving healthy volunteers and single doses of [tacrine](#) found that [fluvoxamine](#) inhibited the metabolism of [tacrine](#), causing an increase in the area under the concentration-time curve (AUC) of [tacrine](#) and three of its metabolites. Fluvoxamine inhibits cytochrome P450 1A2 enzymes, and these same enzymes are responsible for [tacrine](#) metabolism. Whether this interaction would be present in Alzheimer's patients receiving multiple [tacrine](#) doses is not known[391][392].

3) Severity: moderate

4) Onset: rapid

5) Substantiation: probable

6) Clinical Management: While the exact clinical implication of this drug interaction is uncertain, monitor patients receiving [tacrine](#) and [fluvoxamine](#) concurrently for excessive [tacrine](#) adverse effects, including cholinergic effects. Also monitor liver function for increased [hepatotoxicity](#).

7J) Probable Mechanism: inhibition of cytochrome P450 1A2 enzymes by [fluvoxamine](#)

8J) Literature Reports

aJ) A randomized, double-blind, two-period cross-over study involving 14 healthy male volunteers investigated the influence of [fluvoxamine](#) on the pharmacokinetics of a single-dose of [tacrine](#). Study subjects received either [fluvoxamine](#) 100 mg or placebo once daily for six days, and a single dose of [tacrine](#) 40 mg was coadministered on day 6. The [tacrine](#) area under the concentration-time curve (AUC) increased from 27 ng/hr/mL to 224 ng/hr/mL in the presence of [fluvoxamine](#). Maximum concentration (C_{max}) of [tacrine](#) also increased from 7 ng/mL to 39 ng/mL during the [fluvoxamine](#) period. No significant changes in the time to reach C_{max} (t_{max}) and the half-life of [tacrine](#) were observed. The AUC values of three [tacrine](#) metabolites were also significantly increased, but to a lesser extent than the AUC of [tacrine](#). Whether these same results are seen in Alzheimer's patients receiving multiple doses of [tacrine](#) is not known [389].

bJ) Eighteen healthy male volunteers participated in an open, randomized crossover study to establish whether [fluvoxamine](#) in clinically relevant doses was able to inhibit the formation of [tacrine](#) metabolites. Volunteers received [tacrine](#) 40 mg as a single dose and [fluvoxamine](#) 50 mg or 100 mg once daily for five days, followed by a dose of [tacrine](#) 20 mg. [Fluvoxamine](#) reduced the apparent oral clearance of [tacrine](#) by 85%. Specifically, [fluvoxamine](#) reduced the formation of 1- and 2-hydroxytacrine, but the formation of 4-hydroxytacrine was not affected. Whether the inhibition of these metabolites reduced tacrine-induced [hepatotoxicity](#) requires further investigation [390].

3.5.1.HKJ [Tamoxifen](#)

1J) Interaction Effect: decreased [tamoxifen](#) efficacy

2J) Summary: Coadministration of [tamoxifen](#) with a potent CYP2D6 inhibitor may inhibit the CYP2D6-mediated metabolism of [tamoxifen](#) to its active metabolite, endoxifen[333]. Variations in endoxifen concentrations may result, which may reduce the antitumoral efficacy of [tamoxifen](#) and increase the risk of [breast cancer relapse](#) [335][337][338]. A retrospective analysis revealed a 1.9-fold higher [breast cancer](#) recurrence rate in patients receiving a CYP2D6 inhibitor concomitantly with [tamoxifen](#) than in those who received [tamoxifen](#) alone [334]. Monitor patients receiving a CYP2D6 inhibitor concomitantly with [tamoxifen](#) closely for loss of [tamoxifen](#) efficacy.

3J) Severity: major

4J) Onset: unspecified

5J) Substantiation: theoretical

6J) Clinical Management: Monitor patients receiving a CYP2D6 inhibitor concomitantly with [tamoxifen](#) closely for loss of [tamoxifen](#) efficacy. Coadministration of [tamoxifen](#) with a potent CYP2D6 inhibitor may affect [tamoxifen](#) efficacy by inhibiting the CYP2D6-mediated metabolism of [tamoxifen](#) to its active metabolite, endoxifen[333].

7J) Probable Mechanism: inhibition of CYP2D6-mediated [tamoxifen](#) metabolism to endoxifen (its active metabolite)

8J) Literature Reports

aJ) 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 [334].

b) The use of CYP2D6 inhibitors should be avoided in [breast cancer](#) patients receiving [tamoxifen](#) due to the risk of substantially reduced plasma concentrations of the antiestrogenic [tamoxifen](#) metabolite, endoxifen. In a prospective randomized trial, 256 postmenopausal [breast cancer](#) patients receiving [tamoxifen](#) were genotyped and grouped according to CYP2D6 metabolism and medication history. Adjusted analysis showed that decreased metabolizers ($n=65$) had significantly worse relapse-free survival (hazard ratio 1.74; 95% confidence interval (CI), 1.1 to 2.74; $p=0.017$), disease-free survival (hazard ratio 1.6; 95% CI, 1.06 to 2.43; $p=0.027$), and shorter time to recurrence (hazard ratio 1.91; 95% CI, 1.05 to 3.45; $p=0.034$) compared with extensive metabolizers ($n=115$). The greatest risk of [breast cancer relapse](#) was found in the poor metabolizer group (hazard ratio 3.12; 95% CI, 1.37 to 7.55; $p=0.007$) [335]. Decreased metabolizers had either one or two CYP2D6*4 alleles or was receiving a CYP2D6 inhibitor together with [tamoxifen](#) (regardless of genotype), and extensive metabolizers did not have a *4 allele and were not receiving a CYP2D6 inhibitor [336].

3.5.1.HL] Tapentadol

- 1) Interaction Effect: increased risk of [serotonin syndrome](#) ([hypertension](#), [hyperthermia](#), myoclonus, mental status changes)
- 2) Summary: Concurrent use of tapentadol and a selective serotonin reuptake inhibitor (SSRI) may result in [serotonin syndrome](#), which may be life-threatening. Symptoms of [serotonin syndrome](#) may include restlessness, hallucinations, loss of coordination, fast heart beat, rapid changes in blood pressure, increased body temperature, overreactive reflexes, nausea, vomiting, and diarrhea[378].
- 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[378].
- 7) Probable Mechanism: additive serotonergic effect

3.5.1.HM] Tasimelteon

- 1) Interaction Effect: increased tasimelteon exposure and increased risk of tasimelteon adverse events
- 2) Summary: Concomitant use of tasimelteon (a CYP1A2 substrate) with a strong CYP1A2 inhibitor may result in a potentially large increase in tasimelteon exposure and greater risk of related adverse events. When tasimelteon was coadministered with the strong CYP1A2 inhibitor, [fluvoxamine](#) (50 mg), tasimelteon AUC and Cmax increased by 7- and 2-fold, respectively. Therefore, avoid coadministration[267]. If concomitant administration is required, use caution and monitor the patient closely.
- 3) Severity: major
- 4) Onset: unspecified

- 5) Substantiation: theoretical
- 6) Clinical Management: Avoid coadministration of tasimelteon with a strong CYP1A2 inhibitor. Concomitant use of tasimelteon (a CYP1A2 substrate) with a strong CYP1A2 inhibitor may result in a potentially large increase in tasimelteon exposure and greater risk of related adverse events[267]. If concomitant administration is required, use caution and monitor the patient closely.
- 7) Probable Mechanism: inhibition of CYP1A2-mediated metabolism of tasimelteon
- 8) Literature Reports

a) Coadministration of tasimelteon with [fluvoxamine](#), after [fluvoxamine](#) 50 mg/day for 6 days alone, increased tasimelteon AUC and Cmax by 7- and 2-fold, respectively [267].

3.5.1.HN] Tenoxicam

- 1) Interaction Effect: an increased risk of bleeding
- 2) Summary: Caution is recommended with the concomitant use of NSAIDs and antidepressants, including SSRIs due to an increased risk of [intracranial hemorrhage](#)[367] and [gastrointestinal bleeding](#) [371][372][368][369]. Bleeding events have included [epistaxis](#), ecchymosis, [hematoma](#), [petechiae](#), and life-threatening hemorrhages [374][373][375][376]. When an SSRI and an NSAID are given concurrently, monitor the patient for signs of increased bleeding.
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: established
- 6) Clinical Management: Use caution if NSAIDs and SSRIs are coadministered. Concomitant use of NSAIDs and SSRIs may cause an increased risk of [intracranial hemorrhage](#)[367] and [gastrointestinal bleeding](#) [368][369]. When an SSRI and an NSAID are given concurrently, monitor the patient for signs of increased bleeding.
- 7) Probable Mechanism: depletion of [platelet](#) serotonin by SSRI; additive effects
- 8) Literature Reports

a) Concomitant use of NSAIDs and antidepressants, including tricyclic antidepressants, SSRIs, serotonin-norepinephrine reuptake inhibitors, and MAOIs, resulted in a 60% increased risk of [intracranial hemorrhage](#) within 30 days of concomitant use compared with antidepressant use alone. There was no significant difference between the antidepressant drug classes and the increased risk; however, there was an increased risk associated with male patients compared with female patients [367].

b) 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. Combined use of an SSRI and NSAIDs or low-dose [aspirin](#) increased the risk to 12.2 and 5.2 times, 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 [370].

c) Two metaanalyses of incidents of upper GI bleed due to SSRIs, NSAIDs, and their combination found that SSRIs increased the risk by 1.73 [371] to 2.36 times [372], NSAIDs by 2.55 times [371], and the combination of SSRIs and NSAIDs by 4.02 [371] to 6.33 times [372].

d)) The release of serotonin by [platelets](#) is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs and NSAIDs have been associated with an increased risk of bleeding [373].

3.5.1.HO| [Terfenadine](#)

- 1)) Interaction Effect: [cardiotoxicity](#) (QT prolongation, [torsades de pointes](#), [cardiac arrest](#))
- 2)) Summary: [Fluvoxamine](#) should not be used in combination with [terfenadine](#). Although there is no direct experience with this combination, [fluvoxamine](#) appears to be a potent inhibitor of the cytochrome P450III A4 isozyme, the enzyme primarily responsible for the metabolism of [terfenadine](#). Inhibition of this enzyme may result in elevated [terfenadine](#) concentrations; increased plasma concentrations of [terfenadine](#) are associated with QT prolongation and [torsades de pointes](#), which can be fatal[288].
- 3)) Severity: contraindicated
- 4)) Onset: rapid
- 5)) Substantiation: probable
- 6)) Clinical Management: Concurrent use of [fluvoxamine](#) and [terfenadine](#) is contraindicated.
- 7)) Probable Mechanism: inhibition by [fluvoxamine](#) of [terfenadine](#) metabolism

3.5.1.HP| [Theophylline](#)

- 1)) Interaction Effect: [theophylline toxicity](#) (nausea, vomiting, palpitations, seizures)
- 2)) Summary: Fluvoxamine-theophylline combination therapy has produced toxic serum concentrations of [theophylline](#)[318][319][320][321]. The reported mechanism of action is [fluvoxamine's](#) inhibitory effect on the hepatic cytochrome P4501A2 (CYP1A2), the microsome responsible for catalyzing [theophylline](#) metabolism [322].
- 3)) Severity: major
- 4)) Onset: delayed
- 5)) Substantiation: established
- 6)) Clinical Management: Careful monitoring of [theophylline](#) serum concentration is required. [Theophylline](#) doses should be reduced to one-third of the usual daily maintenance dose if [fluvoxamine](#) is coadministered. No dose adjustment is necessary for [fluvoxamine](#).
- 7)) Probable Mechanism: decreased [theophylline](#) metabolism
- 8)) Literature Reports

a)) [Fluvoxamine](#) appeared to be responsible for substantially increased serum [theophylline](#) levels and symptoms of [theophylline toxicity](#) in an 11-year-old boy taking sustained-release [theophylline](#) 300 mg twice daily [314]. Both drugs were discontinued, and [theophylline](#) was later reinstated (dose not specified) with no further evidence of toxicity.

b)) An increase in [theophylline](#) plasma concentrations from 13 mg/L to 40 mg/L was found after [fluvoxamine](#) was added to therapy. The patient was an 83-year-old man who was receiving sustained release [theophylline](#) 600 mg per day [315].

c)) [Fluvoxamine](#) 50 mg twice a day given concurrently with [theophylline](#) 1000 mg daily resulted in a [theophylline](#) plasma concentration of 32 mcg/mL and nausea and [tachycardia](#) in a 75-year-old male with normal liver function [316]. [Theophylline](#) clearance was calculated to be 43 mL/h before the addition of [fluvoxamine](#) and 22 mL/h after four doses.

d)) In 12 healthy nonsmoking volunteers with steady-state [fluvoxamine](#) levels, the pharmacokinetics of a single dose of [theophylline](#) 375 mg were evaluated. [Theophylline](#) clearance

decreased three-fold. Therefore, it is recommended that the daily maintenance dose of [theophylline](#) be reduced by two-thirds in a patient also receiving [fluvoxamine](#) [317].

3.5.1.HQI [Thioridazine](#)

- 1) Interaction Effect: an increased risk of [thioridazine](#) toxicity, [cardiotoxicity](#) (QT prolongation, [torsades de pointes](#), [cardiac arrest](#))
- 2) Summary: [Fluvoxamine](#) inhibits the metabolism of [thioridazine](#), possibly through the inhibition of cytochrome P450 2D6 (CYP2D6) resulting in toxicity. The resulting elevated levels of [thioridazine](#) would be expected to enhance the prolongation of the QT interval associated with [thioridazine](#) and may increase the risk of serious, potentially fatal, [cardiac arrhythmias](#), such as torsade de pointes-type [arrhythmias](#)[142].
- 3) Severity: contraindicated
- 4) Onset: rapid
- 5) Substantiation: probable
- 6) Clinical Management: Due to the potential for significant, possibly life-threatening, proarrhythmic effects, concurrent administration of [thioridazine](#) and [fluvoxamine](#) is contraindicated.
- 7) Probable Mechanism: inhibition of cytochrome P450 2D6-mediated [thioridazine](#) metabolism
- 8) Literature Reports

a) The serum concentrations of [thioridazine](#) and its two metabolites, [mesoridazine](#) and [sulfuridazine](#), were evaluated in ten male schizophrenic patients aged 36 to 78 years at three separate time points. All patients were receiving [thioridazine](#) monotherapy for the management of [schizophrenia](#) at a mean dose of 88 mg daily. [Fluvoxamine](#) 50 mg daily was coadministered for one week. Plasma levels of [thioridazine](#) and its metabolites were measured during monotherapy with [thioridazine](#), after one week of concurrent therapy with [thioridazine](#) and [fluvoxamine](#), and two weeks after [fluvoxamine](#) was discontinued. Following one week of combination therapy with [fluvoxamine](#) and [thioridazine](#), [thioridazine](#) levels increased 225%, [mesoridazine](#) levels increased 219%, and [sulfuridazine](#) concentrations rose 258%. Even two weeks after the discontinuation of [fluvoxamine](#), three patients continued to show elevated [thioridazine](#) and metabolite levels. No clinical symptoms were attributed to the interaction between these two agents [140].

b) The metabolism of [thioridazine](#) is inhibited by drugs such as [fluvoxamine](#) due to reduced cytochrome P450 2D6 and 1A2 isozyme activity. The elevated levels of [thioridazine](#) would be expected to enhance the prolongation of the QT interval associated with [thioridazine](#). This, in turn, may increase the risk of serious, potentially fatal, [cardiac arrhythmias](#), such as torsade de pointes-type [arrhythmias](#) [141].

3.5.1.HR| [Tiaprofenic Acid](#)

- 1) Interaction Effect: an increased risk of bleeding
- 2) Summary: Caution is recommended with the concomitant use of NSAIDs and antidepressants, including SSRIs due to an increased risk of [intracranial hemorrhage](#)[367] and [gastrointestinal bleeding](#) [371][372][368][369]. Bleeding events have included [epistaxis](#), [ecchymosis](#), [hematoma](#), [petechiae](#), and life-threatening hemorrhages [374][373][375][376]. When an SSRI and an NSAID are given concurrently, monitor the patient for signs of increased bleeding.
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: established
- 6) Clinical Management: Use caution if NSAIDs and SSRIs are coadministered. Concomitant use of NSAIDs and SSRIs may cause an increased risk of [intracranial hemorrhage](#)[367] and [gastrointestinal](#)

bleeding [368][369]. When an SSRI and an NSAID are given concurrently, monitor the patient for signs of increased bleeding.

7) Probable Mechanism: depletion of platelet serotonin by SSRI; additive effects

8) Literature Reports

a) Concomitant use of NSAIDs and antidepressants, including tricyclic antidepressants, SSRIs, serotonin-norepinephrine reuptake inhibitors, and MAOIs, resulted in a 60% increased risk of intracranial hemorrhage within 30 days of concomitant use compared with antidepressant use alone. There was no significant difference between the antidepressant drug classes and the increased risk; however, there was an increased risk associated with male patients compared with female patients [367].

b) 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. Combined use of an SSRI and NSAIDs or low-dose aspirin increased the risk to 12.2 and 5.2 times, 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 [370].

c) Two metaanalyses of incidents of upper GI bleed due to SSRIs, NSAIDs, and their combination found that SSRIs increased the risk by 1.73 [371] to 2.36 times [372], NSAIDs by 2.55 times [371], and the combination of SSRIs and NSAIDs by 4.02 [371] to 6.33 times [372].

d) The release of serotonin by platelets is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs and NSAIDs have been associated with an increased risk of bleeding [373].

3.5.1.HS] Ticagrelor

1) Interaction Effect: increased risk of bleeding

2) Summary: Exercise caution when coadministering a SSRI and an antiplatelet agent as this may increase the risk of bleeding events[139][138].[137]. Bleeding events reported have included epistaxis, ecchymosis, hematoma, petechiae, and life-threatening hemorrhages. Monitor patient for signs of increased bleeding when fluvoxamine is administered with an antiplatelet agent concomitantly [137].

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: When fluvoxamine and an antiplatelet agent are given concurrently, monitor patient for signs of increased bleeding[137].

7) Probable Mechanism: unknown

8) Literature Reports

a) In a retrospective study of patients over 50 years of age with the diagnosis of acute myocardial infarction (N=27,058), SSRI use with any antiplatelet therapy significantly increased the risk of bleeding by 1.42-fold compared with aspirin use alone. Therapy with aspirin, clopidogrel, and an SSRI significantly increased risk by 2.35-fold compared with aspirin use alone and by 1.57-fold compared with clopidogrel and aspirin combination therapy [138].

b)) In a systematic review and meta-analysis of 22 observational studies, SSRI use was associated with a significant 1.55 fold increase in risk of [upper gastrointestinal bleeding](#) (UGIB). Concomitant use of SSRIs and antiplatelet drugs was associated with a 2.48-fold increase in risk of UGIB (3 studies) [139].

3.5.1.HT] [Ticlopidine](#)

- 1)) Interaction Effect: increased risk of bleeding
- 2)) Summary: Exercise caution when coadministering a SSRI and an antiplatelet agent as this may increase the risk of bleeding events[139][138].[137]. Bleeding events reported have included [epistaxis](#), ecchymosis, [hematoma](#), [petechiae](#), and life-threatening hemorrhages. Monitor patient for signs of increased bleeding when [fluvoxamine](#) is administered with an antiplatelet agent concomitantly [137].
- 3)) Severity: major
- 4)) Onset: unspecified
- 5)) Substantiation: theoretical
- 6)) Clinical Management: When [fluvoxamine](#) and an antiplatelet agent are given concurrently, monitor patient for signs of increased bleeding[137].
- 7)) Probable Mechanism: unknown
- 8)) Literature Reports

a)) In a retrospective study of patients over 50 years of age with the diagnosis of acute [myocardial infarction](#) (N=27,058), SSRI use with any antiplatelet therapy significantly increased the risk of bleeding by 1.42-fold compared with [aspirin](#) use alone. Therapy with [aspirin](#), [clopidogrel](#), and an SSRI significantly increased risk by 2.35-fold compared with [aspirin](#) use alone and by 1.57-fold compared with [clopidogrel](#) and [aspirin](#) combination therapy [138].

b)) In a systematic review and meta-analysis of 22 observational studies, SSRI use was associated with a significant 1.55 fold increase in risk of [upper gastrointestinal bleeding](#) (UGIB). Concomitant use of SSRIs and antiplatelet drugs was associated with a 2.48-fold increase in risk of UGIB (3 studies) [139].

3.5.1.HU] [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[114][115][113]. 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](#). In patients receiving [warfarin](#) and [fluvoxamine](#) concomitantly for 2 weeks, [warfarin](#) plasma concentrations increased by 98% and prothrombin times were prolonged. [Fluvoxamine](#) appears to inhibit several cytochrome P450 isoenzymes which may include 1A2 and 2C9 isozymes, which are responsible for [warfarin](#) metabolism [115][113].
- 3)) Severity: major
- 4)) Onset: delayed
- 5)) Substantiation: probable
- 6)) Clinical Management: When [fluvoxamine](#) 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 [fluvoxamine](#) therapy is initiated or

discontinued. Periodically reassess the prothrombin time ratio and INR in patients receiving [fluvoxamine](#) and [anticoagulant therapy](#)[113].

7) Probable Mechanism: unknown

8) Literature Reports

a) According to a retrospective cohort study (n=234), there was an increased risk of clinically relevant bleeding (hospital admission due to bleeding) in patients receiving [warfarin](#) for [atrial fibrillation](#) during concomitant SSRI therapy or within 2 weeks following SSRI therapy termination. Patients with a mean age of 72 +/- 7 years receiving [warfarin](#) plus SSRI (n=117) were matched with randomly selected patients who received [warfarin](#) only (n=117). SSRI included [fluoxetine](#), [citalopram](#), [paroxetine](#), [sertraline](#), [fluvoxamine](#), or escitalopram. Nine patients experienced 11 bleeding episodes during 213.9 treatment years in the [warfarin](#) plus SSRI group, and 10 patients experienced 14 bleedings during 586.4 treatment years in the warfarin-only group. The corresponding total incidences of bleedings were 51.4 and 23.9 per 1000 treatment years, respectively. The hazard ratio for first bleedings during treatment with [warfarin](#) plus SSRI was 3.49 (95% CI; 1.37 to 8.91, p=0.009) compared with [warfarin](#) only. The SSRI implicated in patients experiencing bleeding at the time of concomitant administration were [sertraline](#) or [citalopram](#). The addition of an SSRI was not associated with a change in [warfarin](#) dose or INR (p=0.48 and p=0.31 respectively). The results of the study may be limited by earlier bleeding events, unknown patient adherence, and exclusion of [clopidogrel](#), dipyridamol, corticosteroids and anticoagulants other than [warfarin](#) in the model [114].

b) A population-based, case-controlled study of new coumarin users (acenocoumarol and phenprocoumon) with concomitant selective serotonin reuptake inhibitors (SSRIs) resulted in an increased risk of hospitalization due to nongastrointestinal bleeding. Using national pharmacy and hospitalization records, Netherlands researchers identified 1848 cases that were admitted for abnormal bleeding and compared them with 5818 control subjects also taking coumarins. Median duration of treatment in patients was 220 days (range, 1 to 4690 days). Patients on SSRIs showed greater risk for hospitalization for nongastrointestinal bleeding (adjusted odds ratio (OR) 1.7, 95% confidence interval (CI), 1.1 to 2.5), however, the rate of [gastrointestinal bleeding](#) (adjusted OR 0.8, 95% CI, 0.4 to 1.5) was not significantly different [115].

c) A hospitalized 80-year-old female was started on intravenous [heparin](#) and oral [warfarin](#) therapy due to an [embolic stroke](#) secondary to [atrial fibrillation](#) and [mitral stenosis](#). Her [warfarin](#) dose was maintained at 1 mg daily, with her INR between 2.5 and 3. [Fluvoxamine](#) 25 mg daily was started for depression, and her [warfarin](#) dose was increased to 1.5 mg daily 3 days later due to worsening of the left [hemiparesis](#). Three days later, her INR was 9.96, and a repeat INR to rule out laboratory error was 11.3. [Warfarin](#) was discontinued, fresh frozen plasma was given, and [fluvoxamine](#) was discontinued. Six days later, [warfarin](#) was again started at 1 mg daily, and the INR increased over 4 days to 11.8. The elevated INR was attributed to the persisting effect of [fluvoxamine](#). She was eventually stabilized on [warfarin](#) 1 mg daily with INR values between 2 and 2.5 [116].

3.5.1.HV] [Tirofiban](#)

1) Interaction Effect: increased risk of bleeding

2) Summary: Exercise caution when coadministering a SSRI and an antiplatelet agent as this may increase the risk of bleeding events[139][138].[137]. Bleeding events reported have included [epistaxis](#), ecchymosis, [hematoma](#), [petechiae](#), and life-threatening hemorrhages. Monitor patient for signs of increased bleeding when [fluvoxamine](#) is administered with an antiplatelet agent concomitantly [137].

3) Severity: major

4) Onset: unspecified

- 5) Substantiation: theoretical
- 6) Clinical Management: When [fluvoxamine](#) and an antiplatelet agent are given concurrently, monitor patient for signs of increased bleeding[137].
- 7) Probable Mechanism: unknown
- 8) Literature Reports

a) In a retrospective study of patients over 50 years of age with the diagnosis of acute [myocardial infarction](#) (N=27,058), SSRI use with any antiplatelet therapy significantly increased the risk of bleeding by 1.42-fold compared with [aspirin](#) use alone. Therapy with [aspirin](#), [clopidogrel](#), and an SSRI significantly increased risk by 2.35-fold compared with [aspirin](#) use alone and by 1.57-fold compared with [clopidogrel](#) and [aspirin](#) combination therapy [138].

b) In a systematic review and meta-analysis of 22 observational studies, SSRI use was associated with a significant 1.55 fold increase in risk of [upper gastrointestinal bleeding](#) (UGIB). Concomitant use of SSRIs and antiplatelet drugs was associated with a 2.48-fold increase in risk of UGIB (3 studies) [139].

3.5.1.HW| [Tizanidine](#)

- 1) Interaction Effect: increased [tizanidine](#) plasma concentrations
- 2) Summary: Concomitant use of [fluvoxamine](#) and [tizanidine](#) is contraindicated. Use of these drugs together has resulted in increased plasma concentrations and half-life of [tizanidine](#)[283],[286]. Concurrent administration of [fluvoxamine](#), a potent CYP1A2 inhibitor, and [tizanidine](#) induced a profound increase in [tizanidine](#) bioavailability. The inhibition of CYP1A2-mediated [tizanidine](#) metabolism provokes clinically significant hypotension and alteration of consciousness [284]. In a retrospective case series, tizanidine-associated adverse events occurred significantly more often in patients treated concomitantly with [fluvoxamine](#) and [tizanidine](#) compared with [tizanidine](#) monotherapy [285].
- 3) Severity: contraindicated
- 4) Onset: rapid
- 5) Substantiation: established
- 6) Clinical Management: The concomitant use of [fluvoxamine](#) and [tizanidine](#) is contraindicated. Use of [tizanidine](#) with [fluvoxamine](#) can increase the plasma concentrations of [tizanidine](#)[283] which may lead to decreased blood pressure, [psychomotor impairment](#), and excessive drowsiness [284].
- 7) Probable Mechanism: inhibition of CYP1A2-mediated [tizanidine](#) metabolism by [fluvoxamine](#)
- 8) Literature Reports

a) In a study of 10 healthy volunteers treated with [fluvoxamine](#) and [tizanidine](#), the half-life, C_{max}, and AUC of [tizanidine](#) increased by 12-fold, 33-fold, and 3-fold, respectively [283].

b) Coadministration of [fluvoxamine](#) with [tizanidine](#) resulted in profound increases in [tizanidine](#) bioavailability due to P450 CYP1A2-mediated inhibition of [tizanidine](#) metabolism and was associated with multiple adverse clinical effects. In a randomized, double-blind, crossover study (4-week wash out period), healthy subjects (n=10) received a 4-day regimen of [fluvoxamine](#) 100 milligrams (mg) or placebo once daily. On day 4, each subject received a single oral dose of [tizanidine](#) 4 mg. Serial blood pharmacokinetic analysis was performed over the next 24 hours, in conjunction with measurement of pharmacodynamic response. When compared with placebo, the presence of [fluvoxamine](#) dramatically increased [tizanidine](#) mean maximum serum concentration (by 1210% (from 2.2 to 26.6 nanograms/milliliter), p=0.000001), mean area under the concentration-time curve (AUC 0-infinity; by 3260%, p=0.000002), and mean elimination half-life from 1.5 hours to 4.3 hours (by 290%, p=0.00004). Pharmacodynamic responses to fluvoxamine-enhanced [tizanidine](#) exposure were also dramatic: mean systolic blood pressure

declined by 35 millimeters mercury (mmHg; from 115 to 79 mmHg), mean diastolic blood pressure decreased by 20 mmHg (from 66 to 46 mmHg), heart rate decreased by 4 beats per minute, and subjectively perceived drowsiness (0-100 visual analogue scale) increased by a mean of 42 points compared with the placebo-tizanidine phase ($p=0.000009$, $p=0.00002$, $p=0.007$, and $p=0.0002$, respectively). During the fluvoxamine-tizanidine phase, all subjects experienced somnolence and dizziness for between 3 and 6 hours after the dose of [tizanidine](#). There was no compensatory tachycardic response to the treatment-associated hypotension [284].

c) In a retrospective case series review of patients treated with [tizanidine](#) ($n=913$), tizanidine-related adverse events occurred with significantly greater frequency in patients treated concurrently with [fluvoxamine](#) and [tizanidine](#) ($n=23$) when compared with [tizanidine](#) monotherapy (26.1% (6/23) versus 5.3%, respectively; p less than 0.0001). Bradycardia occurred in the 6 affected patients, with dizziness, [hypothermia](#), drowsiness, hypotension, and impaired speech occurring in order of descending frequency [285].

3.5.1.HX] Tolfenamic Acid

1) Interaction Effect: an increased risk of bleeding

2) Summary: Caution is recommended with the concomitant use of NSAIDs and antidepressants, including SSRIs due to an increased risk of [intracranial hemorrhage](#)[367] and [gastrointestinal bleeding](#) [371][372][368][369]. Bleeding events have included [epistaxis](#), ecchymosis, [hematoma](#), [petechiae](#), and life-threatening hemorrhages [374][373][375][376]. When an SSRI and an NSAID are given concurrently, monitor the patient for signs of increased bleeding.

3) Severity: major

4) Onset: unspecified

5) Substantiation: established

6) Clinical Management: Use caution if NSAIDs and SSRIs are coadministered. Concomitant use of NSAIDs and SSRIs may cause an increased risk of [intracranial hemorrhage](#)[367] and [gastrointestinal bleeding](#) [368][369]. When an SSRI and an NSAID are given concurrently, monitor the patient for signs of increased bleeding.

7) Probable Mechanism: depletion of [platelet](#) serotonin by SSRI; additive effects

8) Literature Reports

a) Concomitant use of NSAIDs and antidepressants, including tricyclic antidepressants, SSRIs, serotonin-norepinephrine reuptake inhibitors, and MAOIs, resulted in a 60% increased risk of [intracranial hemorrhage](#) within 30 days of concomitant use compared with antidepressant use alone. There was no significant difference between the antidepressant drug classes and the increased risk; however, there was an increased risk associated with male patients compared with female patients [367].

b) 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. Combined use of an SSRI and NSAIDs or low-dose [aspirin](#) increased the risk to 12.2 and 5.2 times, 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 [370].

c) Two metaanalyses of incidents of upper GI bleed due to SSRIs, NSAIDs, and their combination found that SSRIs increased the risk by 1.73 [371] to 2.36 times [372], NSAIDs by 2.55 times [371], and the combination of SSRIs and NSAIDs by 4.02 [371] to 6.33 times [372].

d) The release of serotonin by [platelets](#) is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs and NSAIDs have been associated with an increased risk of bleeding [373].

3.5.1.HY] [Tolmetin](#)

1) Interaction Effect: an increased risk of bleeding

2) Summary: Caution is recommended with the concomitant use of NSAIDs and antidepressants, including SSRIs due to an increased risk of [intracranial hemorrhage](#)[367] and [gastrointestinal bleeding](#) [371][372][368][369]. Bleeding events have included [epistaxis](#), ecchymosis, [hematoma](#), [petechiae](#), and life-threatening hemorrhages [374][373][375][376]. When an SSRI and an NSAID are given concurrently, monitor the patient for signs of increased bleeding.

3) Severity: major

4) Onset: unspecified

5) Substantiation: established

6) Clinical Management: Use caution if NSAIDs and SSRIs are coadministered. Concomitant use of NSAIDs and SSRIs may cause an increased risk of [intracranial hemorrhage](#)[367] and [gastrointestinal bleeding](#) [368][369]. When an SSRI and an NSAID are given concurrently, monitor the patient for signs of increased bleeding.

7) Probable Mechanism: depletion of [platelet](#) serotonin by SSRI; additive effects

8) Literature Reports

a) Concomitant use of NSAIDs and antidepressants, including tricyclic antidepressants, SSRIs, serotonin-norepinephrine reuptake inhibitors, and MAOIs, resulted in a 60% increased risk of [intracranial hemorrhage](#) within 30 days of concomitant use compared with antidepressant use alone. There was no significant difference between the antidepressant drug classes and the increased risk; however, there was an increased risk associated with male patients compared with female patients [367].

b) 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. Combined use of an SSRI and NSAIDs or low-dose [aspirin](#) increased the risk to 12.2 and 5.2 times, 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 [370].

c) Two metaanalyses of incidents of upper GI bleed due to SSRIs, NSAIDs, and their combination found that SSRIs increased the risk by 1.73 [371] to 2.36 times [372], NSAIDs by 2.55 times [371], and the combination of SSRIs and NSAIDs by 4.02 [371] to 6.33 times [372].

d) The release of serotonin by [platelets](#) is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs and NSAIDs have been associated with an increased risk of bleeding [373].

3.5.1.HZ| Toloxatone

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

2) Summary: Concurrent administration or overlapping therapy with [fluvoxamine](#) and a monoamine oxidase (MAO) inhibitor may result in CNS toxicity or [serotonin syndrome](#), a hyperserotonergic state characterized by symptoms such as restlessness, myoclonus, changes in mental status, hyperreflexia, diaphoresis, shivering, and tremor. Serious, even fatal, reactions have been reported with concomitant use of selective serotonin reuptake inhibitors and MAO inhibitors[179][180][181][182]. As a reversible and selective monoamine oxidase inhibitor, tolloxatone 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, caution should be used.

3) Severity: major

4) Onset: rapid

5) Substantiation: probable

6) Clinical Management: Concurrent use of [fluvoxamine](#) and a MAO inhibitor should be avoided. Wait at least two weeks after discontinuing an MAO inhibitor before initiating therapy with [fluvoxamine](#). Wait at least two weeks after discontinuing [fluvoxamine](#) before initiating therapy with a MAO inhibitor.

7) Probable Mechanism: serotonin reuptake inhibition

8) Literature Reports

a) Concomitant use of serotonin specific reuptake inhibitors and monoamine oxidase inhibitors can produce a toxic reaction known as [serotonin syndrome](#) [175]. [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) A 26-year old woman who had been taking [isocarboxazid](#) for eight weeks stopped taking the drug for 11 days before beginning therapy with [sertraline](#). After a single 100 mg [sertraline](#) dose, the patient became restless and developed leg twitches. The patient was later admitted to the emergency room with diaphoresis, [tachycardia](#), hyperreflexia, and various neuromuscular disturbances. After treatment with [diazepam](#) and [propranolol](#) the patient did not improve. The patient was then given two 4 mg doses of [cyproheptadine](#) an hour apart, with notable improvement in symptoms after the second dose [176].

c) A drug interaction occurred in a 61-year old woman whose regimen of [sertraline](#) 100 mg twice daily was added to a regimen of [lithium](#), [phenelzine](#), [thioridazine](#), and [doxepin](#). Three hours after taking the first [sertraline](#) dose, the patient was found in a semicomatose state, with elevated body temperature, increased pulse, increased respiration rate, and a blood pressure of 140/110 mm Hg. After transportation to the hospital, the patient was misdiagnosed as having [neuroleptic malignant syndrome](#) (NMS) which was later changed to [serotonin syndrome](#) due to a reaction between [sertraline](#) and [phenelzine](#). The authors suggest that monoamine oxidase inhibitor (MAOI) therapy should be discontinued for at least two weeks before initiation of therapy with a selective serotonin reuptake inhibitor (SSRI) and that before starting a MAOI, SSRI therapy should be discontinued for at least five half-lives of the parent drug and any active metabolites [177].

d) Two cases reports suggested a possible interaction between [fluoxetine](#) and [selegiline](#) [178]. One case involved a first episode of mania being observed approximately one month after adding [selegiline](#) to [fluoxetine](#) therapy. The patient improved two months after both drugs were discontinued, and no further details were provided. The second case involved diaphoresis,

vasoconstriction, and cyanosis of the hands which occurred in close temporal relationship to adding [fluoxetine](#) and [selegiline](#). Both drugs were discontinued, with relatively quick resolution of symptoms. Rechallenge with [fluoxetine](#) alone occurred without incident.

3.5.1.IA] [Tramadol](#)

1) Interaction Effect: an increased risk of seizures, [serotonin syndrome](#) (hypertension, hyperthermia, myoclonus, mental status changes), opioid toxicity, and increased concentrations of [tramadol](#) and decreased concentrations of [tramadol](#) active metabolite, M1

2) Summary: Caution is advised with concomitant use of [fluvoxamine](#) (serotonergic agent, and CYP2D6 inhibitor) and [tramadol](#). Concomitant use of [tramadol](#) and an agent with serotonergic activity may increase the risk for seizures and [serotonin syndrome](#) even if [tramadol](#) is used within the recommended dosage range. Additionally, concomitant use of [tramadol](#) and CYP2D6 inhibitors, such as [fluvoxamine](#), can decrease metabolism of [tramadol](#) to the active metabolite, M1, potentially causing reduced analgesia. Furthermore, elevated [tramadol](#) concentrations because of inhibition of CYP2D6-mediated metabolism may cause opioid toxicity. If concomitant use of [tramadol](#) and an agent with serotonergic activity is clinically warranted, careful observation of the patient is recommended, particularly during treatment initiation and dose increases[287]. Consider monitoring patients for signs and symptoms of opioid toxicity or decreased analgesic effect of [tramadol](#).

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Concomitant use of [tramadol](#) and an agent with serotonergic activity, such as [fluvoxamine](#), may increase the risk for seizures and [serotonin syndrome](#), even if [tramadol](#) is used within the recommended dosage range. Additionally, opioid toxicity and reduced analgesia may occur. If concomitant use of [tramadol](#) and an agent with serotonergic activity is clinically warranted, careful observation is recommended, particularly during treatment initiation and dose increases[287]. Consider monitoring patients for signs and symptoms of opioid toxicity as well as decreased analgesic effect of [tramadol](#).

7) Probable Mechanism: lowered seizure threshold; additive serotonergic effects; inhibition of CYP2D6-mediated [tramadol](#) metabolism

3.5.1.IB] [Tranylcypromine](#)

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

2) Summary: Concomitant use of [fluvoxamine](#) and an MAOI is contraindicated. Concurrent administration or overlapping therapy with [fluvoxamine](#) and an MAOI may result in [serotonin syndrome](#), a hyperserotonergic state characterized by symptoms such as agitation and hallucinations, myoclonus, changes in mental status, hyperreflexia, diaphoresis, rigidity, and tremor. Serious, even fatal, reactions have been reported with concomitant use of SSRIs and MAOIs. A minimum of 14 days should elapse after discontinuing an MAOI intended to treat psychiatric disorders before initiating therapy with [fluvoxamine](#), and a minimum of 14 days should elapse after discontinuing [fluvoxamine](#) before initiating therapy with an MAOI intended to treat psychiatric disorders[20].

3) Severity: contraindicated

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Concurrent use of [fluvoxamine](#) and an MAOI is contraindicated. Wait at least 14 days after discontinuing an MAOI intended to treat psychiatric disorders before initiating [fluvoxamine](#).

Wait at least 14 days after discontinuing [fluvoxamine](#) before initiating therapy with an MAOI intended to treat psychiatric disorders[20].

7J) Probable Mechanism: additive serotonergic effect

3.5.1.IC] [Trazodone](#)

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

2J) Summary: Both [fluvoxamine](#) 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](#)[22][323]. Close monitoring for signs and symptoms of [serotonin syndrome](#) is warranted if [fluvoxamine](#) and [trazodone](#) are used concurrently, particularly during treatment initiation and dose increases [323]. 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 [120].

3J) Severity: major

4J) Onset: unspecified

5J) Substantiation: theoretical

6J) Clinical Management: Use caution with concomitant administration of [fluvoxamine](#), a selective serotonin reuptake inhibitor, and [trazodone](#), as this may result in additive serotonergic effects and may increase the risk of [serotonin syndrome](#)[22][323]. If coadministration is required, close monitoring is warranted, particularly during treatment initiation and dose increases [323].

7J) Probable Mechanism: additive serotonergic effect

3.5.1.ID] [Treprostinil](#)

1J) Interaction Effect: increased risk of bleeding

2J) Summary: Exercise caution when coadministering a SSRI and an antiplatelet agent as this may increase the risk of bleeding events[139][138].[137]. Bleeding events reported have included [epistaxis](#), ecchymosis, [hematoma](#), [petechiae](#), and life-threatening hemorrhages. Monitor patient for signs of increased bleeding when [fluvoxamine](#) is administered with an antiplatelet agent concomitantly [137].

3J) Severity: major

4J) Onset: unspecified

5J) Substantiation: theoretical

6J) Clinical Management: When [fluvoxamine](#) and an antiplatelet agent are given concurrently, monitor patient for signs of increased bleeding[137].

7J) Probable Mechanism: unknown

8J) Literature Reports

aJ) In a retrospective study of patients over 50 years of age with the diagnosis of acute [myocardial infarction](#) (N=27,058), SSRI use with any antiplatelet therapy significantly increased the risk of bleeding by 1.42-fold compared with [aspirin](#) use alone. Therapy with [aspirin](#), [clopidogrel](#), and an SSRI significantly increased risk by 2.35-fold compared with [aspirin](#) use alone and by 1.57-fold compared with [clopidogrel](#) and [aspirin](#) combination therapy [138].

bJ) In a systematic review and meta-analysis of 22 observational studies, SSRI use was associated with a significant 1.55 fold increase in risk of [upper gastrointestinal bleeding](#) (UGIB).

Concomitant use of SSRIs and antiplatelet drugs was associated with a 2.48-fold increase in risk of UGIB (3 studies) [139].

3.5.1.IE] Triazolam

- 1) Interaction Effect: elevated serum triazolam concentrations
- 2) Summary: Fluvoxamine coadministration (100 mg daily) with alprazolam 1 mg four times daily resulted in a 2-fold increase in alprazolam steady-state plasma concentrations, AUC, Cmax, and half-life. Elevated plasma levels of alprazolam were associated with impaired psychomotor performance and memory. This suggests that fluvoxamine is a potent inhibitor of cytochrome P450 3A4 enzymes, which are responsible for alprazolam metabolism. Because triazolam also relies on CYP3A4 for metabolism, a similar interaction with fluvoxamine seems likely[241].
- 3) Severity: moderate
- 4) Onset: delayed
- 5) Substantiation: probable
- 6) Clinical Management: When triazolam and fluvoxamine are coadministered, monitor patients for benzodiazepine toxicity (sedation, lethargy, slurred speech). Triazolam doses may need to be reduced, or consider switching to a benzodiazepine eliminated by glucuronidation (eg, lorazepam, oxazepam, temazepam).
- 7) Probable Mechanism: inhibition of triazolam metabolism and clearance due to cytochrome P450 3A4 enzyme inhibition

3.5.1.IF] Tryptophan

- 1) Interaction Effect: an increased risk of serotonin syndrome (hypertension, hyperthermia, myoclonus, mental status changes)
- 2) Summary: Potentially life-threatening serotonin syndrome has been reported with SSRIs when used concomitantly with other serotonergic drugs, such as hydroxytryptophan or tryptophan. If coadministration is clinically warranted, monitor for the development of serotonin syndrome, especially during treatment initiation and dose increases[166].
- 3) Severity: major
- 4) Onset: rapid
- 5) Substantiation: theoretical
- 6) Clinical Management: Potentially life-threatening serotonin syndrome has been reported with SSRIs when used concomitantly with other serotonergic drugs, such as hydroxytryptophan or tryptophan. If coadministration is clinically warranted, monitor for the development of serotonin syndrome, especially during treatment initiation and dose increases[166].
- 7) Probable Mechanism: additive serotonergic effect
- 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 [167].

3.5.1.IG] Valdecixib

- 1) Interaction Effect: an increased risk of bleeding
- 2) Summary: Caution is recommended with the concomitant use of NSAIDs and antidepressants, including SSRIs due to an increased risk of intracranial hemorrhage[367] and gastrointestinal bleeding

[371][372][368][369]. Bleeding events have included [epistaxis](#), ecchymosis, [hematoma](#), [petechiae](#), and life-threatening hemorrhages [374][373][375][376]. When an SSRI and an NSAID are given concurrently, monitor the patient for signs of increased bleeding.

3) Severity: major

4) Onset: unspecified

5) Substantiation: established

6) Clinical Management: Use caution if NSAIDs and SSRIs are coadministered. Concomitant use of NSAIDs and SSRIs may cause an increased risk of [intracranial hemorrhage](#)[367] and [gastrointestinal bleeding](#) [368][369]. When an SSRI and an NSAID are given concurrently, monitor the patient for signs of increased bleeding.

7) Probable Mechanism: depletion of [platelet](#) serotonin by SSRI; additive effects

8) Literature Reports

a) Concomitant use of NSAIDs and antidepressants, including tricyclic antidepressants, SSRIs, serotonin-norepinephrine reuptake inhibitors, and MAOIs, resulted in a 60% increased risk of [intracranial hemorrhage](#) within 30 days of concomitant use compared with antidepressant use alone. There was no significant difference between the antidepressant drug classes and the increased risk; however, there was an increased risk associated with male patients compared with female patients [367].

b) 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. Combined use of an SSRI and NSAIDs or low-dose [aspirin](#) increased the risk to 12.2 and 5.2 times, 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 [370].

c) Two metaanalyses of incidents of upper GI bleed due to SSRIs, NSAIDs, and their combination found that SSRIs increased the risk by 1.73 [371] to 2.36 times [372], NSAIDs by 2.55 times [371], and the combination of SSRIs and NSAIDs by 4.02 [371] to 6.33 times [372].

d) The release of serotonin by [platelets](#) is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs and NSAIDs have been associated with an increased risk of bleeding [373].

3.5.1.IH] Vilazodone

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

2) Summary: [Serotonin syndrome](#) has been reported with vilazodone monotherapy and in combination with other serotonergic drugs; coadministration with another serotonergic drug may increase risk for [serotonin syndrome](#)[168]. Increased serotonin levels which may produce additive serotonergic effects can occur if serotonergic agents are taken concurrently. 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 [120]. Therefore, exercise caution with concomitant use of vilazodone and this drug. Monitor for [serotonin syndrome](#) and discontinue use of both vilazodone and the concomitant serotonergic agent immediately if symptoms of [serotonin syndrome](#) emerge [168].

- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: [Serotonin syndrome](#) has been reported with vilazodone monotherapy and in combination with other serotonergic drugs; coadministration with another serotonergic drug may increase risk for [serotonin syndrome](#). Therefore, exercise caution with concomitant use and monitor for [serotonin syndrome](#). Discontinue use of vilazodone and concomitant serotonergic agents immediately if symptoms of [serotonin syndrome](#) emerge[168].
- 7) Probable Mechanism: additive serotonergic effects

3.5.1.II] Vorapaxar

- 1) Interaction Effect: increased risk of bleeding
- 2) Summary: Exercise caution when coadministering a SSRI and an antiplatelet agent as this may increase the risk of bleeding events[139][138].[137]. Bleeding events reported have included [epistaxis](#), ecchymosis, [hematoma](#), [petechiae](#), and life-threatening hemorrhages. Monitor patient for signs of increased bleeding when [fluvoxamine](#) is administered with an antiplatelet agent concomitantly [137].
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: When [fluvoxamine](#) and an antiplatelet agent are given concurrently, monitor patient for signs of increased bleeding[137].
- 7) Probable Mechanism: unknown
- 8) Literature Reports

a) In a retrospective study of patients over 50 years of age with the diagnosis of acute [myocardial infarction](#) (N=27,058), SSRI use with any antiplatelet therapy significantly increased the risk of bleeding by 1.42-fold compared with [aspirin](#) use alone. Therapy with [aspirin](#), [clopidogrel](#), and an SSRI significantly increased risk by 2.35-fold compared with [aspirin](#) use alone and by 1.57-fold compared with [clopidogrel](#) and [aspirin](#) combination therapy [138].

b) In a systematic review and meta-analysis of 22 observational studies, SSRI use was associated with a significant 1.55 fold increase in risk of [upper gastrointestinal bleeding](#) (UGIB). Concomitant use of SSRIs and antiplatelet drugs was associated with a 2.48-fold increase in risk of UGIB (3 studies) [139].

3.5.1.IJ] Vortioxetine

- 1) Interaction Effect: an increased risk of [serotonin syndrome](#) ([hypertension](#), [hyperthermia](#), myoclonus, mental status changes)
- 2) Summary: Vortioxetine is a serotonergic drug; concomitant use with another agent that affects the serotonergic neurotransmitter system may result in an increased risk of [serotonin syndrome](#) and should be approached with caution. [Serotonin syndrome](#) may be life-threatening. 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[393].
- 3) Severity: major
- 4) Onset: unspecified

5J) Substantiation: theoretical

6J) Clinical Management: Concomitant use of vortioxetine with serotonergic agents may increase the risk for [serotonin syndrome](#) and should be undertaken with caution. If concomitant use of vortioxetine with a serotonergic agent is clinically warranted, close monitoring of the patient is recommended, particularly during treatment initiation and dosage increases. If [serotonin syndrome](#) develops, discontinue vortioxetine and concomitant serotonergic agents and initiate supportive care[393].

7J) Probable Mechanism: additive serotonergic effects

3.5.1.IKJ [Warfarin](#)

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 SSRIs and anticoagulants has been associated with an increased risk of bleeding[114][115][113]. 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](#). In patients receiving [warfarin](#) and [fluvoxamine](#) concomitantly for 2 weeks, [warfarin](#) plasma concentrations increased by 98% and prothrombin times were prolonged. [Fluvoxamine](#) appears to inhibit several cytochrome P450 isoenzymes which may include 1A2 and 2C9 isozymes, which are responsible for [warfarin](#) metabolism [115][113].

3J) Severity: major

4J) Onset: delayed

5J) Substantiation: probable

6J) Clinical Management: When [fluvoxamine](#) 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 [fluvoxamine](#) therapy is initiated or discontinued. Periodically reassess the prothrombin time ratio and INR in patients receiving [fluvoxamine](#) and [anticoagulant therapy](#)[113].

7J) Probable Mechanism: unknown

8J) Literature Reports

aJ) 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 [114].

bJ) 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 [115].

c) A hospitalized 80-year-old female was started on intravenous [heparin](#) and oral [warfarin](#) therapy due to an [embolic stroke](#) secondary to [atrial fibrillation](#) and [mitral stenosis](#). Her [warfarin](#) dose was maintained at 1 mg daily, with her INR between 2.5 and 3. [Fluvoxamine](#) 25 mg daily was started for depression, and her [warfarin](#) dose was increased to 1.5 mg daily 3 days later due to worsening of the left [hemiparesis](#). Three days later, her INR was 9.96, and a repeat INR to rule out laboratory error was 11.3. [Warfarin](#) was discontinued, fresh frozen plasma was given, and [fluvoxamine](#) was discontinued. Six days later, [warfarin](#) was again started at 1 mg daily, and the INR increased over 4 days to 11.8. The elevated INR was attributed to the persisting effect of [fluvoxamine](#). She was eventually stabilized on [warfarin](#) 1 mg daily with INR values between 2 and 2.5 [116].

3.5.1.IL] Ziprasidone

- 1) Interaction Effect: increased risk for [serotonin syndrome](#) ([hypertension](#), [hyperthermia](#), myoclonus, mental status changes)
- 2) Summary: [Serotonin syndrome](#) has been reported with [ziprasidone](#) monotherapy and in combination with other serotonergic drugs[278][279]; coadministration with another serotonergic drug may increase risk for [serotonin syndrome](#). Therefore, exercise caution with concomitant use.
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: [Serotonin syndrome](#) has been reported with [ziprasidone](#) monotherapy and in combination with other serotonergic drugs[278][279]; coadministration with another serotonergic drug may increase risk for [serotonin syndrome](#). Therefore, exercise caution with concomitant use.
- 7) Probable Mechanism: Additive serotonergic effect

3.5.1.IM] Zolmitriptan

- 1) Interaction Effect: an increased risk of [serotonin syndrome](#)
- 2) Summary: Concurrent use of a triptan and an SSRI has resulted in life-threatening [serotonin syndrome](#). Onset of symptoms is usually rapid, occurring within minutes to hours of initiation or dose escalation of a serotonergic agent[324]. 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](#) [118]. Discontinue use of [zolmitriptan](#) if [serotonin syndrome](#) is suspected [324].
- 3) Severity: major
- 4) Onset: rapid
- 5) Substantiation: probable
- 6) Clinical Management: Life-threatening [serotonin syndrome](#) has been reported with coadministration of triptans and SSRIs[324]. Consider potential intermittent use of triptans in patients who receive SSRIs

and closely monitor patients receiving both medications for symptoms of [serotonin syndrome](#) [118]. Discontinue [zolmitriptan](#) if [serotonin syndrome](#) is suspected [324].

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

8) Literature Reports

a) The pharmacokinetics of a single 10 mg dose of [zolmitriptan](#) were not altered by four weeks of [fluoxetine](#) 20 mg daily pretreatment in healthy volunteers. The effects of [zolmitriptan](#) on blood pressure were also not changed by [fluoxetine](#) therapy [325].

3.5.1.IN] [Zolpidem](#)

1) Interaction Effect: decreased [zolpidem](#) clearance and increased exposure

2) Summary: Concomitant use of [fluvoxamine](#), a potent CYP1A2 inhibitor, and moderate CYP3A4 and CYP2C9 inhibitor[232][22], together with [zolpidem](#), a CYP3A4, CYP2C9, and CYP1A2 substrate, significantly increased [zolpidem](#) Cmax, AUC, and half-life (150% increased exposure) in a pharmacokinetic trial with healthy volunteers (n=20) [232]. Concomitant therapy with [fluvoxamine](#) may increase the risk of zolpidem-related side effects and dose adjustments may be warranted during coadministration.

3) Severity: moderate

4) Onset: rapid

5) Substantiation: established

6) Clinical Management: Concomitant use of [fluvoxamine](#) and [zolpidem](#) increased [zolpidem](#) exposure by approximately 150%[232]. Concomitant therapy may increase the risk of zolpidem-related side effects and dose adjustments may be warranted during coadministration.

7) Probable Mechanism: inhibition of CYP3A4-, CYP2C9, and CYP1A2-mediated metabolism of [zolpidem](#) by [fluvoxamine](#)

8) Literature Reports

a) The [zolpidem](#) Cmax, total AUC, and half-life were significantly increased after pretreatment with [fluvoxamine](#) in a pharmacokinetic trial with 20 healthy male volunteers (22 to 30 years old). Participants were given a single dose of [zolpidem](#) 5 mg (day 1), followed by 6 days of [fluvoxamine](#) 100 mg/day (days 2 to 7), and a second dose of [zolpidem](#) 5 mg together with [fluvoxamine](#) 100 mg on day 8. The mean Cmax of [zolpidem](#) was 56.4 +/- 25.6 nanograms (ng)/mL on day 1 and 67.3 +/- 25.8 ng/mL after pretreatment with [fluvoxamine](#) (p=0.005; 90% CI, 1.10 to 1.37), and the [zolpidem](#) AUC(0 to infinity) increased by approximately 150% from 200.9 +/- 116.8 ng x hr/mL to 512 +/- 354.6 ng x hr/mL after pretreatment (p less than 0.0001; 90% CI, 2.14 to 2.71). The half-life was 2.24 +/- 0.8 hours with [zolpidem](#) alone compared with 4.99 +/- 2.92 hours with concomitant [fluvoxamine](#) (p less than 0.0001). Chronic use of concomitant [zolpidem](#) and [fluvoxamine](#) might lead to enhanced adverse effects associated with [zolpidem](#) [232].

3.5.2] Drug-Food Combinations

3.5.2.A] [Grapefruit Juice](#)

1) Interaction Effect: increased [fluvoxamine](#) exposure

2) Summary: Grapefruit juice significantly increased [fluvoxamine](#) exposure when co-administered to healthy volunteers (n=10), in a randomized, placebo-controlled crossover study. Compared with baseline, grapefruit juice produced a 1.3-fold increase in the serum mean concentration of [fluvoxamine](#), by 33 nanograms/milliliter (ng/mL; plus/minus 10 to 44 ng/mL) (p=0.049) and increased the [fluvoxamine](#) mean area under the concentration-time curve from 550 ng hours/mL to 881 ng hours/mL (p=0.014)[407].

3) Severity: minor

- 4) Onset: rapid
- 5) Substantiation: probable
- 6) Clinical Management: Counsel patients to avoid grapefruit juice while taking [fluvoxamine](#). Orange juice may be substituted as it provides the same basic nutrients but is not known to inhibit drug metabolism.
- 7) Probable Mechanism: inhibition of intestinal CYP3A4 and P-glycoprotein-mediated [fluvoxamine](#) metabolism
- 8) Literature Reports

a) Grapefruit juice significantly increased exposure to [fluvoxamine](#), when co-administered to healthy volunteers. In a randomized, crossover study, healthy men (n=10) received 250 milliliters of either regular-strength grapefruit juice or water 3 times daily for 5 days. On day 6, oral [fluvoxamine](#) 75 milligrams was given to each subject along with the grapefruit juice or water regimen. Serial blood sampling then occurred over the next 24 hours. After 2 weeks, subjects crossed over to the opposing study arm. Compared with baseline, grapefruit juice produced a 1.3-fold increase in the mean serum concentration of [fluvoxamine](#), by 33 nanograms/milliliter (ng/mL; plus/minus 10 to 44 ng/mL) (p=0.049). In 8 subjects, the [fluvoxamine](#) mean area under the concentration-time curve increased from 550 ng hours/mL to 881 ng hours/mL (p=0.014); additionally, 2 subjects showed a rebound increase in [fluvoxamine](#) plasma concentration at 24 hours after [fluvoxamine](#) administration [406].

3.5.4] Drug-Tobacco Combinations

3.5.4.A] Tobacco

- 1) Interaction Effect: decreased exposure of CYP1A2 substrates
- 2) Summary: Cigarette smoking releases polycyclic aromatic hydrocarbons that induce CYP1A2 substrate metabolism[409][419], which may reduce CYP1A2 substrate bioavailability. Advise patients to stop smoking during treatment with a CYP1A2 substrate due to the potential reduction in efficacy [408]. If CYP1A2 substrate therapy is required in patients who smoke, consider monitoring for reduced efficacy [409] and adjusting the CYP1A2 substrate dosage if needed [410].
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: CYP1A2 substrate bioavailability may be reduced with tobacco smoking. Advise patients to stop smoking during treatment due to the potential reduction in CYP1A2 substrate efficacy[408]. If therapy with a CYP1A2 substrate is required in patients who smoke, consider monitoring for reduced efficacy [409] and adjusting the CYP1A2 substrate dosage if needed [410].
- 7) Probable Mechanism: induction of CYP1A2-mediated metabolism by tobacco smoke
- 8) Literature Reports

a) Smoking 7 to 12 cigarettes/day produced maximum enzyme induction and a significantly lower mean [clozapine](#) concentration/dose (C/D) ratio in smokers than in nonsmokers (2.8 vs 6 nanograms/mL/mg/day), and similarly with [olanzapine](#) C/D ratio in another study (6.1 vs 12.8 nanograms/mL/mg/day). Smoking more than 12 cigarettes/day did not produce any further induction nor lower C/D ratio of [clozapine](#) or [olanzapine](#) [411].

b) Among patients treated with [mirtazapine](#) 30 mg/day for 4 weeks, smokers had significantly lower concentrations of S(+)-[mirtazapine](#) (23 vs 39 nmol/L) and [mirtazapine](#) S(+)/R(-) ratio (0.28 vs 0.37) than nonsmokers. These effects from smoking remained significant after multivariate analysis [410].

c) In patients receiving stable [clozapine](#) 100 mg/day, heavy smokers (30 or more cigarettes/day) had a significantly higher mean plasma [clozapine](#) concentration coefficient of variation (CV) than smokers (30% vs 16%); however, no difference was seen in patients receiving stable [clozapine](#) 300 or 600 mg/day in a study of patients with [schizophrenia](#) or [schizoaffective disorder](#) (N=47) [412].

d) In a study of patients receiving an average [clozapine](#) dose of 304 mg/day (N=18), [clozapine](#) and norclozapine (active metabolite) plasma concentrations were significantly lower in smokers (median of 25 cigarettes or 4 pipes/day) compared with nonsmokers. The [clozapine](#) plasma concentration in smokers was a significant 3.2-fold lower and norclozapine was 2.3-fold lower compared with plasma concentration in nonsmokers [413].

e) Induction of CYP1A2 activity by cigarette smoking significantly reduced [olanzapine](#) plasma concentrations and clinical effectiveness in smokers (10 to 40 cigarettes/day), compared with nonsmokers in a study of adults with thought disorder (N=17). After 15 days of [olanzapine](#) 10 mg/day, the dose-corrected steady-state [olanzapine](#) plasma concentration (C:D) ratio was about 5-fold lower in smokers compared with nonsmokers (1.56 vs 7.9 nanograms/mL/mg). At the same time, Brief Psychiatric Rating Scale total scores were significantly higher for nonsmokers than for smokers (30.4% vs 12.5%) and were positively correlated with the steady-state plasma [olanzapine](#) C:D ratio. Smoking induced a significant 6-fold higher level of CYP1A2 activity in smokers compared with nonsmokers and the index was closely correlated with the steady-state plasma [olanzapine](#) C:D ratio[414].

f) Cigarette smoking appears to release polycyclic aromatic hydrocarbons that induce CYP1A2 substrate metabolism. In vivo blood clearance and urine metabolite data from [caffeine](#) demethylation has clearly demonstrated the link between CYP1A2 activity and cigarette smoking, which may have clinical consequences when cigarette smoking occurs with [theophylline](#), [caffeine](#), [tacrine](#), [imipramine](#), [haloperidol](#), [pentazocine](#), [propranolol](#), or [flecainide](#) therapy [409].

g) In a study of healthy volunteers (N=14), chronically-exposed passive smokers had a significantly higher mean [theophylline](#) clearance of 60.1 mL/kg/hr compared with 40.9 mL/kg/hr for the nonsmokers. [415]. However, in another study of volunteers (N=5), intense, short-term (5 days) passive smoking did not effect [theophylline](#) disposition [416]. It was concluded that the short duration of exposure to tobacco smoke explained the lack of effect.

h) A retrospective study of patients with [schizophrenia](#) (N=50) revealed that cigarette smokers (more than 1 pack/day) had significantly lower plasma concentrations of [haloperidol](#) (16.83 vs 28.8 nanograms/mL) and reduced [haloperidol](#) (active metabolite; 16.76 vs 34.23 nanograms/mL) and significantly increased [haloperidol](#) oral clearance (1.58 vs 1.1 L/min) compared with nonsmokers [417].

i) The administration of oral [imipramine](#) 3.5 mg/kg to smokers (15 cigarettes/day) resulted in significantly lower mean plasma levels of combined [imipramine](#) and desmethylinipramine when compared with nonsmokers (160 vs 290 nanograms/mL) [418].

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) [Fluvoxamine](#) Maleate

1) Therapeutic

a) A reduction in the severity of recurrent and persistent ideas, thoughts, impulses, or images indicates efficacy. The change from baseline in the Yale Brown Obsessive Compulsive Scale (Y-BOCS) total score may be used to assess therapeutic response in patients with [obsessive compulsive disorder](#).

2) Toxic

a) Physical Findings

1) Monitor for clinical worsening, suicidality, and unusual changes in behavior, at treatment initiation, during the first few months of therapy, and with dose changes, particularly in children and adolescents, and in young adults [40][22].

2) Monitor for changes in seizure frequency [40][22].

3) Monitor weight and growth determinations in children and adolescents regularly, throughout duration of use[40][22].

4.2] Patient Instructions

A) [Fluvoxamine](#) (By mouth)

[Fluvoxamine](#)

Treats [obsessive-compulsive disorder](#) (OCD). This medicine is a type of antidepressant called an SSRI.

When This Medicine Should Not Be Used:

This medicine is not right for everyone. Do not use it if you had an [allergic reaction](#) to [fluvoxamine](#).

How to Use This Medicine:

Long Acting Capsule, Tablet

Take your medicine as directed. Your dose may need to be changed several times to find what works best for you. Take this medicine at bedtime, unless your doctor tells you otherwise.

Swallow the extended-release capsule whole. Do not crush, break, or chew it.

This medicine should come with a Medication Guide. Ask your pharmacist for a copy if you do not have one.

Missed dose: Take a dose as soon as you remember. If it is almost time for your next dose, wait until then and take a regular dose. Do not take extra medicine to make up for a missed dose.

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

Drugs and Foods to Avoid:

Ask your doctor or pharmacist before using any other medicine, including over-the-counter medicines, vitamins, and herbal products.

Do not use [fluvoxamine](#) with [alosectron](#), [pimozide](#), [ramelteon](#), [thioridazine](#), or [tizanidine](#). Do not use [fluvoxamine](#) and an MAO inhibitor within 14 days of each other.

Some medicines can affect how [fluvoxamine](#) works. Tell your doctor if you are using the following:

Buspirone, carbamazepine, clozapine, diazepam, fentanyl, lithium, methadone, metoprolol, mexiletine, omeprazole, phenytoin, propranolol, St John's wort, tacrine, theophylline, tramadol, or tryptophan supplements

A sedative, other medicine to treat depression, triptan medicine to treat migraine headaches, a diuretic (water pill), an NSAID pain or arthritis medicine (such as aspirin, celecoxib, diclofenac, ibuprofen, naproxen), or a blood thinner (such as warfarin)

Do not drink alcohol while you are using this medicine.

Warnings While Using This Medicine:

Tell your doctor if you are pregnant or breastfeeding, or if you have liver disease, bleeding problems, glaucoma, epilepsy or seizures, heart disease, or you had a heart attack. Tell your doctor if you smoke. For some children, teenagers, and young adults, this medicine may increase mental or emotional problems. This may lead to thoughts of suicide and violence. Talk with your doctor right away if you have any thoughts or behavior changes that concern you. Tell your doctor if you or anyone in your family has a history of bipolar disorder or suicide attempts.

This medicine may cause the following problems:

Serotonin syndrome (may be life-threatening when used with certain other medicines)

Higher risk of bleeding problems

Low sodium levels in the blood

Do not stop using this medicine suddenly. Your doctor will need to slowly decrease your dose before you stop it completely.

This medicine may make you dizzy or drowsy. Do not drive or do anything that could be dangerous until you know how this medicine affects you.

This medicine may cause decreased appetite and weight loss. Your child's height and weight will be measured to make sure your child is growing properly.

Keep all medicine out of the reach of children. Never share your medicine with anyone.

Possible Side Effects While Using This Medicine:

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

Allergic reaction: Itching or hives, swelling in your face or hands, swelling or tingling in your mouth or throat, chest tightness, trouble breathing

Anxiety, restlessness, fever, sweating, muscle spasms, nausea, vomiting, diarrhea, seeing or hearing things that are not there

Blistering, peeling, red skin rash

Confusion, weakness, and muscle twitching

Eye pain, vision changes, seeing halos around lights

Fast, pounding, or uneven heartbeat

Feeling more excited or energetic than usual

Headache, trouble concentrating, memory problems, unsteadiness

Seizures

Unusual behavior, thoughts of hurting yourself or others, panic, trouble sleeping

Unusual bleeding or bruising

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

Constipation, stomach upset

Dizziness, unusual drowsiness or sleepiness

Loss of appetite, weight loss

Sexual problems

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

4.3] Place In Therapy

A) **Fluvoxamine** Maleate

1) **Obsessive Compulsive Disorder**

a) The immediate-release formulation of **fluvoxamine** maleate is indicated for the treatment of obsessions and compulsions in patients with OCD aged 8 years and older [40]. The extended-release formulation of **fluvoxamine** maleate is indicated for the treatment of **obsessive compulsive disorder** (OCD) in adult patients; efficacy of **fluvoxamine** maleate extended-release capsules has not been evaluated in pediatric patients [22].

1) Immediate-release Formulation

a) The efficacy of fluvoxamine immediate-release tablets for long-term use was demonstrated in a maintenance study (n=114) in adults with obsessive compulsive disorder (OCD) [22].

b) A 10-week study (n=49) demonstrated that immediate-release fluvoxamine and behavior therapy were more efficacious for treating obsessive compulsive disorder (OCD) compared to placebo and behavior therapy [23].

c) Immediate-release fluvoxamine was significantly more effective than placebo in children (8 years or older) and adolescents with obsessive compulsive disorder (OCD) in a 10-week, double-blind study in 120 children with at least a 6-month history of OCD [25].

2) Extended-release Formulation

a) Treatment with extended-release fluvoxamine maleate at once-daily doses of 100 to 300 milligrams was safe and led to clinical improvement in adult patients with obsessive-compulsive disorder compared to placebo in a 12-week, multicenter, randomized, double-blind study (n=253) [24].

2) **Social Anxiety Disorder**

a) In a randomized, double-blind, multicenter, placebo-controlled study (n=300), patients with generalized **social anxiety disorder** (GSAD) who received **fluvoxamine** extended-release (ER) demonstrated a significantly greater reduction in the mean Liebowitz Social Anxiety Scale (LSAS) total score from baseline compared with patients who received placebo [34], with a trend towards continued clinical benefit with **fluvoxamine** ER compared to placebo in a 12-week double-blind extension phase of this study [35].

3) Depression

a)] 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. [Fluvoxamine](#) does not have any major therapeutic benefits over other SSRIs; however, discontinuation of therapy among patients treated with [fluvoxamine](#) appeared higher than for other SSRIs during clinical trials. Gastrointestinal symptoms and drowsiness/sedation were more common especially early in therapy than with other SSRIs. Ultimately, the selection of an SSRI is dependent on clinical judgement and response of patients to previous therapy [451].

b)] 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 of 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% responded 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 [452].

See Drug Consult reference: Class Comparison: SSRIs and Serotonin [Norepinephrine](#) Reuptake Inhibitors (SNRIs) (Selected)

4.4] Mechanism of Action / Pharmacology

A)] [Fluvoxamine](#) Maleate

1)] Mechanism of Action

a)] [Fluvoxamine](#) maleate is a potent selective serotonin (5-HT) reuptake inhibitor (SSRI) belonging to the 2-aminoethyl oxime ethers of aralkylketones series and is unrelated to other SSRIs and [clomipramine](#). In [obsessive compulsive disorder](#) the clinical effect is presumed to be from its specific inhibition of serotonin reuptake in brain neurons. In-vitro studies have shown that [fluvoxamine](#) maleate has no significant affinity for histaminergic, alpha or beta adrenergic, muscarinic, or dopaminergic receptors [113][435].

2)] Review Articles

a)] [Fluvoxamine](#) is a compound in the series of 2-aminoethyloxime ethers of aralkylketones. The drug acts as an antidepressant and has no structural similarities to tricyclic antidepressants. [Fluvoxamine](#) is a potent selective inhibitor of presynaptic serotonin (5-hydroxytryptamine or 5-HT) reuptake [441]. Following a single dose of [fluvoxamine](#), the serotonin turnover in the rat forebrain was reduced [441]. Also, in the raphe nuclei the intraneuronal and extraneuronal concentrations of serotonin decreased and increased, respectively [442]. In vitro and in vivo experiments demonstrated that [fluvoxamine](#) fails to facilitate noradrenergic neurotransmission, similar to other specific inhibitors of serotonin uptake [443][444]. Unlike the tricyclic antidepressants, [fluvoxamine](#) demonstrates a very low in vitro affinity for alpha-1, alpha-2, beta-1, [dopamine](#)-2, [histamine](#)-1, serotonin-1, serotonin-2 or muscarinic receptors [445][446]. In vitro and in vivo studies have not demonstrated any monoamine oxidase inhibitor activity [447][446].

b)] The exact relationship of serotonin uptake inhibition and its effects on depression are not known. It is proposed that [fluvoxamine's](#) antidepressant activity is initiated by enhanced serotonergic input to other neuronal systems in the brain. This may lead to primary and secondary changes in receptors and rates of firing and rates of release of neurotransmitters which may result in remission of depressive symptoms [448].

c) The effects of treatment with [fluvoxamine](#) on [platelet](#) and plasma serotonin were studied in 11 drug-free patients with [major depression](#) (Celeda et al, 1992). Single-dose [fluvoxamine](#) (50 mg) was without effect on serotonin, whereas treatment with 100 to 150 mg/day for 12 weeks reduced both [platelet](#) (-89%) and plasma (-60%) serotonin. Patients who responded to the treatment at 6 weeks had significantly lower pretreatment values of [platelet](#) serotonin than the rest. This suggests that "low serotonin" patients may respond more rapidly to [fluvoxamine](#). [Platelet](#) serotonin and Hamilton Depression Scale scores correlated significantly during treatment. These data demonstrate a marked action of [fluvoxamine](#) as a serotonin reuptake inhibitor at therapeutic doses and confirm that this mechanism is relevant for its efficacy as an antidepressant.

d) [Fluvoxamine](#) does not have significant effects on central [norepinephrine](#) function in human depressed patients, as determined by measurement of MHPG, VMA, NMN, and HVA in urine and NE in plasma [449].

e) The possible relationship between plasma tryptophan (Trp) to large neutral amino acid (LNAA) ratio, thought to reflect brain serotonin (5-HT) formation, was estimated in 47 patients with [major depression](#) (unipolar and bipolar) before and after 6 weeks of [fluvoxamine](#). The authors found a significant difference between responders (n=39) and nonresponders (n=8) for Trp/LNAA ratio, whereas no difference emerged between the two groups for the mean plasma steady-state [fluvoxamine](#) levels. These data suggest that a specific plasma amino acid profile may be a useful indicator of good clinical response to [fluvoxamine](#) [450].

4.5] Therapeutic Uses

4.5.1] FDA Uses

4.5.1.A] [Fluvoxamine](#) Maleate

4.5.1.A.1] [Obsessive-compulsive disorder](#)

FDA Labeled Indication

a) Overview

FDA Approval: Adult, yes; [Pediatric, yes \(8 years or older, immediate-release only\)](#)

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:

Indication

[Fluvoxamine](#) extended-release is indicated for the treatment of [obsessive compulsive disorder](#) (OCD) in adults; efficacy has not been evaluated in pediatric patients [1].

Immediate-release [fluvoxamine](#) is indicated for the treatment of obsessions and compulsions in patients with OCD aged 8 years or older [20].

Evidence (Adult)

Immediate-release [fluvoxamine](#) significantly reduced [relapse](#) rate compared with placebo in a randomized withdrawal study in 114 patients who initially responded to initial [fluvoxamine](#) therapy [22].

The addition of immediate-release [fluvoxamine](#) to [behavioral therapy](#) was significantly more effective in reducing obsessions (Y-BOCS total and Y-BOCS obsession subtotal) than behavior therapy and placebo in a short-term randomized trial (N=49). After 10 weeks, both groups had significant improvements on the Structured Clinical Interview (SCID), Yale-Brown Obsessive-Compulsive Scale (Y-BOCS), Hamilton Depression Scale (HAM-D), Clinical Anxiety Scale (CAS), Global Assessment Scale (GAS), and the Clinical Global Improvement Scale (CGIS) [23].

Extended-release [fluvoxamine](#) significantly reduced Y-BOCS total scores (mean baseline, approximately 26.5; -8.5 vs -5.6), as well as obsession (39.6% vs 24.4% change) and compulsion (34.3% vs 24.8% change) Y-BOCS subtotals, compared with placebo in a 12-week, randomized trial (N=253). Mean daily dose at endpoint was [fluvoxamine](#) 271 mg/day. More patients discontinued treatment due to adverse events in the [fluvoxamine](#) group (19% vs 6%) [24].

Evidence (Pediatric)

Immediate-release [fluvoxamine](#) was significantly more effective than placebo in reduction of Children's Yale-Brown Obsessive Compulsive Scale score in children (8 years or older) with at least a 6-month history of [obsessive compulsive disorder](#) (OCD) in a 10-week study (N=120) [25].

Guidelines

Serotonin reuptake inhibitors, including [fluvoxamine](#), and [cognitive behavioral therapy](#) are safe and effective first-line treatment of [obsessive-compulsive disorder](#) [21].

See Drug Consult reference: Class Comparison: SSRIs and Serotonin [Norepinephrine](#) Reuptake Inhibitors (SNRIs) (Selected)

4.5.2] Non FDA Uses

4.5.2.A] [Fluvoxamine](#) Maleate

4.5.2.A.1] Alcoholism

a) Overview

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

Efficacy: Adult, Evidence is inconclusive

Recommendation: Adult, Class IIb

Strength of Evidence: Adult, Category B

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

b) Summary:

Adverse effects limit the usefulness of [fluvoxamine](#) for treating alcoholism [5].

c) Adult:

1j) Adverse effects limit the usefulness of [fluvoxamine](#) for treating alcoholism. Results of open-label and placebo-controlled trials of [fluvoxamine](#) as an adjunct to [relapse](#) prevention psychotherapy in alcoholics were reported [5]. In the open trial, 16 inpatient alcoholics began a 12-week treatment program, with 10 patients dropping out during the first 4 weeks of treatment. In the controlled trial, 8 of 10 patients on [fluvoxamine](#) dropped out during the first 4 weeks of treatment, compared with only 1 of 9 patients on placebo. Baseline patient characteristics did not explain the baseline differential attrition in the controlled trial, although the placebo-treated patients are more alcohol-dependent. In both trials, patients taking [fluvoxamine](#) complained of a variety of adverse effects, which they identified as the basis for early termination of treatment. The most commonly reported adverse effects were nausea, headache, and sedation. More severe effects included [hepatitis](#) (1), depigmenting [dermatitis](#) (1), and focal seizures (1).

4.5.2.A.2] [Autistic 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 adults, [fluvoxamine](#) was more effective than placebo for improving symptoms of [autism](#) [6].

c) Adult:

1j) In a 12-week, placebo-controlled trial (n=30), [fluvoxamine](#) was more effective than placebo for reducing repetitive thoughts/behavior and aggression and for improving some aspects of social interaction and language usage. Patients assigned to [fluvoxamine](#) were initially treated with 50 milligrams (mg) per day which was adjusted to a maximum of 300 mg daily over 3 weeks; the dosage was 276 mg versus 283 mg in patients treated with [fluvoxamine](#) versus placebo, respectively, at the conclusion of the study. Using the Clinical Global Impression Scale, [fluvoxamine](#) was statistically superior to placebo (p less than 0.001); statistically significant differences were also noted for other assessment scales. In addition, 4 of 15 patients treated with [fluvoxamine](#) showed clinically significant improvements in social functioning, including full-time employment (n=1), participation in a wedding (n=1), and a move from a group home to a supervised apartment (n=2). Adverse effects were mild and did NOT require treatment discontinuation. Based on the positive results obtained in these adult patients with [autism](#), further study is required in children and adolescents with [autism](#) [6].

4.5.2.A.3] [Body dysmorphic 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:

[Fluvoxamine](#) produced a significant response in patients with [body dysmorphic disorder](#) in an open-label study (n=30) [7].

c) Adult:

1) In a 16-week, open-label study, [fluvoxamine](#) appeared effective in the treatment of [body dysmorphic disorder](#) (BDD). After establishing the diagnosis of BDD, patients (n=30, 21 females) were treated with [fluvoxamine](#) 50 milligrams (mg) daily with increases to 150 mg twice daily by day 9, if tolerated. Using an intent-to-treat analysis, it was found that there were statistically significant (p less than 0.001) decreases in the Brown Assessment of Beliefs Scale (BABS), 66%; the Yale-Brown Obsessive Compulsive Scale modified for BDD (BDD-YBOCS), 46.6%; the Hamilton Rating Scale for Depression (HAM-D), 38%; and the Montgomery-Asberg Depression Rating Scale (MADRS), 38%; at study endpoint. Additionally, the Clinical Global Impressions Scale (CGI) rated 63% of patients as responders. Five of 7 delusional patients were responders; and response was not related to initial severity of illness. The mean dose of [fluvoxamine](#) was 238.3 mg/day (range 50-300 mg/day) and the mean response time was 6.1 weeks (range, 1 to 16 weeks). Only 60% of the patients completed the study (reasons for dropouts not stated). This preliminary study suggests that [fluvoxamine](#) is effective for BDD, but blinded, placebo-controlled studies are needed to determine efficacy [7].

4.5.2.A.4] Compulsive buying

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:

Treatment with [fluvoxamine](#) did not alter the buying behavior of subjects prone to compulsive buying in a randomized, placebo-controlled trial (n=37) [8].

c) Adult:

1) Results of a prospective, randomized, double-blind, placebo- controlled study demonstrated no benefit with [fluvoxamine](#) therapy in the number of shopping episodes, amount of time spent shopping, amount of money spent, or number of items purchased in 37 subjects with compulsive buying disorder. Forty-two subjects entered the study beginning with a 1-week single-blind placebo lead-in. Five subjects who experienced more than a 50% improvement in the Yale-Brown Obsessive Compulsive Scale modified for compulsive

buying (YBOCS-CB) scores after this first week were excluded. Seventy-four percent of the 42 enrolled patients were diagnosed with comorbid psychiatric disorders. Subjects were randomized to placebo or daily [fluvoxamine](#) 50 milligrams (mg) increased weekly up to 300 mg according to subject response and tolerance. The average dose of [fluvoxamine](#) was 215 mg. The most commonly reported adverse events with [fluvoxamine](#) therapy were gastrointestinal distress (25%) and insomnia (20%), compared with headache (29%) and sedation (18%) with placebo. Each of the efficacy variables, YBOCS-CB, Global Assessment of Functioning (GAF), and Hamilton Rating Scale for Depression (HAM-D) improved with time for both treatment groups, yet no difference between treatment groups was observed [8].

4.5.2.A.5] Compulsive gambling

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, open study, [fluvoxamine](#) reduced pathological gambling [28].

c) Adult:

1) Of 10 patients who completed 8 weeks of [fluvoxamine](#) therapy, total abstinence of gambling was achieved in 7. Sixteen patients began treatment with placebo for 8 weeks but 4 and 2 were terminated due to noncompliance and lack of efficacy, respectively. The remaining patients received [fluvoxamine](#); the mean [fluvoxamine](#) dose was 220 milligrams/day at study endpoint. The Yale-Brown scale gambling behavior scores were reduced by 25%, and 7 of 10 patients were considered treatment responders by the clinician-rated Clinical Global Impression scores. While [fluvoxamine](#) appeared effective, this study was small, non-blinded, and of short duration; therefore, a randomized, controlled trial is needed to verify the results [28].

4.5.2.A.6] Depression

a) Overview

FDA Approval: Adult, no; **Pediatric, no**

Efficacy: Adult, Evidence favors efficacy

Recommendation: Adult, Class IIa

Strength of Evidence: Adult, Category B

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

b) Summary:

Fluvoxamine was more effective than placebo during double-blind trials for the treatment of depression [9][10][11].

A single night time dose of fluvoxamine appears to be best tolerated (Siddigui et al, 1985).

c) Adult:

1) Fluvoxamine is effective in the treatment of delusional depression [12]. In a group of 59 patients, 84.2% responded favorably within the six-week study period. The dose of fluvoxamine used was 100 mg daily days 1 through 3; 200 mg daily days 4 through 7; and 300 mg daily from day 8. No other psychotropic drugs were used, except for eight patients who continued to receive maintenance therapy with lithium.

2) Fluvoxamine was effective in the treatment of severely depressed patients in a re-evaluation of a double-blind study of fluvoxamine, imipramine, and placebo in 308 patients [9]. Improvement was superior in severely depressed patients to that of moderately depressed patients, which in turn was superior to mildly depressed patients. Anticholinergic side effects were more common for imipramine, while gastrointestinal effects were more frequent with fluvoxamine.

3) Fluvoxamine was safe and effective for treating depression during a 6-week, large-scale, open trial of 5625 depressed patients [10]. All patients were started on fluvoxamine 50 to 100 milligrams at night, increasing after the first week, if necessary, to a maximum of 300 milligrams per day. Of the original 5625 patients admitted, 73% completed the study. In 6.4% (358 patients), withdrawal was not considered to be drug related. Other reasons for withdrawal included adverse effects in 16.2% (912 patients) and lack of efficacy in 2.1% (117 patients). The most commonly reported adverse effect was nausea (12.7%), followed by headache (5%), dizziness (4.5%), and somnolence (3.8%).

4) Fluvoxamine produced a more significant reduction in the global score of the Hamilton Rating Scale of Depression than placebo during a 4-week, double-blind study of 41 patients with depression [11]. Patients randomized to receive fluvoxamine started at doses of 100 milligrams/day and were increased to 150 milligrams/day after 3 days. A significant reduction in the partial scores connected with anxiety and depression was observed in the fluvoxamine-treated patients after 7 days of therapy when compared with baseline scores. This trend became greater during the course of the treatment. Placebo-treated patients demonstrated a reduction in anxiety-related scores during the first 7 days; however, this disappeared over the course of treatment. The most commonly reported adverse effects associated with fluvoxamine therapy were nausea, vomiting, tremor, dry mouth, and increased salivation; however, they were only slightly-to-moderately severe and usually resolved by the end of the study.

5) An uncontrolled, non-randomized study of fluvoxamine 100 milligrams/day in 16 depressed HIV-1-infected patients revealed that fluvoxamine should not be used as first line treatment in this clinical setting. Good efficacy was reported in 6 patients, whereas the other 10 discontinued the drug due to severe adverse effects (acute total insomnia, gastrointestinal disturbance, aggressive and impulsive behavior, and excessive sedation) [13].

4.5.2.A.7] Eating disorder

a) Overview

FDA Approval: Adult, no; Pediatric, no

Efficacy: Adult, Evidence favors efficacy

Recommendation: Adult, Class IIa

Strength of Evidence: Adult, Category B

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

b) Summary:

In small open-label and larger double-blind, placebo-controlled trials, [fluvoxamine](#) has been effective for reducing the number of binge-eating episodes and for [bulimia nervosa](#) (Aynso-Gutierrez et al, 1994), [15][16].

c) Adult:

1) In a 9-week study, [fluvoxamine](#) effectively reduced the frequency of binges in patients with [binge-eating disorder](#). In this double-blind, flexible-dose study (n=85), patients were randomly assigned to placebo or [fluvoxamine](#) 50 milligrams (mg) daily titrated to a maximum dose of 300 mg daily. [Fluvoxamine](#) compared to placebo resulted in a significant reduction in frequency of binges (p=0.006), Clinical Global Impression severity scale score (p=0.002), and body mass index (p=0.04). Of the 67 patients who completed 9 weeks of treatment, 15 and 12 were in remission (no binges) or markedly improved (75% or greater improvement) in the [fluvoxamine](#) and placebo groups, respectively (p=0.04). Significantly more patients treated with [fluvoxamine](#) than placebo discontinued treatment due to adverse effects (p=0.03); however, none of the adverse effects were serious. Of interest, the placebo response was between 42% and 44% which suggests that a conservative approach should be used in offering drug therapy for this disorder [16].

2) [Fluvoxamine](#) was effective in the treatment of 20 patients with [bulimia nervosa](#) when used in doses of 50 to 150 mg per day for eight weeks (Aynso-Gutierrez et al, 1994). Four patients showed drowsiness and 3 insomnia.

3) In an uncontrolled, non-randomized study, 15 women with [bulimia nervosa](#) were administered 4 months of combined cognitive-behavioral and nutritional therapy along with either [fluvoxamine](#) 300 milligrams (mg) per day or amineptine 300 mg/day. Bulimic Investigation Test symptoms and gravity improved significantly and equally in both groups, whereas Eating Disorders Inventory scores and depression and anxiety according to the Hamilton Rating Scale for Depression and Anxiety decreased, but not significantly. Body mass index was normal before therapy and did not change during treatment. These preliminary results need to be validated in larger and better designed studies [15].

4.5.2.A.8] [Fibromyalgia](#)

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:

[Fluvoxamine](#) may be helpful for patients with [fibromyalgia](#) [17].

c) Adult:

1) [Fluvoxamine](#) was equally effective to [amitriptyline](#) in reducing pain associated with [fibromyalgia](#). In an open-label, uncontrolled study, 68 Japanese patients with [fibromyalgia](#) received either [amitriptyline](#) at a mean dose of 20 milligrams (mg)/day or [fluvoxamine](#) at a mean dose of 25 mg/day for 4 weeks. Patients evaluated pain relief by means of a visual analog scale and efficacy was defined as a decrease in pain by at least 50%. At 4 weeks, 50% of patients in the [amitriptyline](#) group and 41% of patients in the [fluvoxamine](#) group reported effective relief of pain (p=NS). Drowsiness was the most commonly reported adverse event with [amitriptyline](#) treatment and nausea was most frequently reported with [fluvoxamine](#). The authors hypothesize that because the efficacy of [amitriptyline](#) for the treatment of fibromyalgia-related pain has been established in previous, controlled trials and because [fluvoxamine](#) showed similar efficacy to [amitriptyline](#) in this open-label study; [fluvoxamine](#) may be helpful for patients with [fibromyalgia](#) [17].

4.5.2.A.9] Hypochondriasis

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:

[Fluvoxamine](#) may be beneficial in the treatment of [hypochondriasis](#) [18].

c) Adult:

1) The results of one study suggest that [fluvoxamine](#) may be a beneficial treatment in reducing symptoms of patients with [hypochondriasis](#). In a small, 12-week, open-label study, patients with at least a moderate [hypochondriasis](#) rating on the Heightened Illness Concern Severity Scale (HICSS) received daily divided doses of [fluvoxamine](#) (50 milligrams (mg) initially, increased every 7 days to a maximum dose of 300 mg by the sixth week) for 10 weeks following a 2-week placebo run-in phase. Response was defined as a clinician-rated change in score of "much improved" or "very much improved" on the Clinical Global Impressions (CGI) scale. In the intent-to-treat analysis, 57.1% of patients responded to [fluvoxamine](#) treatment. In patients who completed 6 or more weeks of treatment, 72.7% were responders and mean scores on the HICSS were significantly reduced from baseline to endpoint (5 vs 3.64, p=0.001). [Fluvoxamine](#) was generally well tolerated. Further, well- controlled studies are needed to substantiate these findings [18].

4.5.2.A.10] Migraine; Prophylaxis

See Drug Consult reference: Migraine -- Recommendations for Prophylaxis in Adults

4.5.2.A.11] Mixed anxiety and depressive 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:

Fluvoxamine was effective for treating depression accompanied by an anxiety disorder in a small, open-label study (n=30) [14].

c) Adult:

1) Eighteen (60%) of 30 patients achieved a score of 2 or less on the Clinical Global Impressions-Improvement (CGI-I) scale for both anxiety and depression. All patients had **major depression** with at least 1 comorbid anxiety disorder. **Fluvoxamine** was initiated at 50 milligrams (mg)/day and was titrated to 200 mg/day as needed and tolerated; the mean dose was 143 mg/day at 12 weeks (study endpoint). Twenty (67%) and 23 (77%) patients showed a response on the CGI-I depression and CGI-I anxiety scales at endpoint, respectively. Twelve patients withdrew from the study before 12 weeks. This small open study suggests that **fluvoxamine** is effective for treating depression accompanied by an anxiety disorder, but these results must be confirmed in a controlled clinical trial [14].

4.5.2.A.12] 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:

SSRIs, including **fluvoxamine**, may confer a protective effect against first MI [19].

c) Adult:

1) In a case-control study comprised of 653 cases of **first myocardial infarction** (MI) and 2990 control subjects, results indicated that selective serotonin reuptake inhibitors (SSRIs) may confer a protective effect against first MI. The subjects in this study were smokers, between the ages of 30 to 65 years, with a first MI hospitalized between September 1995 and December 1997. The four SSRIs investigated in this study were **fluoxetine**, **fluvoxamine**, **paroxetine**,

and [sertraline](#); doses taken by participants were not stated. The odds ratio of patients who were taking SSRIs having a first MI compared to controls (after adjustment for potential confounders) was 0.35 (95% CI 0.18, 0.68; p less than 0.01). The authors suggested that this effect was possibly attributable to an inhibitory effect on serotonin-mediated [platelet](#) activation or amelioration of other factors associated with increased risk for MI in depression [19].

4.5.2.A.13] [Panic 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:

In uncontrolled or placebo-controlled studies, [fluvoxamine](#) was effective for treating [panic disorder](#) in patients with and without depression [26][27].

c) Adult:

1) [Fluvoxamine](#) was effective for treating [panic disorder](#) complicated by depression. In an 8-week, open-label, flexible-dose trial, [fluvoxamine](#) was administered to 17 patients. Thirteen patients had [panic disorder with agoraphobia](#); 14 patients had an additional anxiety disorder; 15 patients had a [major depressive disorder](#); and 5 patients also had [obsessive-compulsive disorder](#). [Fluvoxamine](#) was initiated at 40 milligrams per day, increased to 100 milligrams on day 5 and to 150 milligrams on day 9. The dose was increased at 50 milligram intervals each week until side effects occurred; the maximum dose of 300 milligrams was reached; or panic attack and depression resolved. Fifteen patients completed the study. One patient dropped out due to side effects and one for unknown reasons. The most common adverse events were nausea, insomnia, anxiety/restlessness, headache, drowsiness and dry mouth. At the study's end (at a mean [fluvoxamine](#) dose of 213 milligrams), there was a statistically significant difference from baseline in the number of panic attacks, anticipatory anxiety, general anxiety, depression and a self-rating of disability; however, [fluvoxamine](#) did NOT affect [agoraphobia](#) avoidance [26].

2) [Fluvoxamine](#) was superior to [cognitive therapy](#) (CT) and placebo (PL) in the treatment of seventy-five outpatients with moderate-to-severe [panic disorder](#). CT subjects also showed improvement but the degree of improvement was not different from that of PL patients. [Fluvoxamine](#) also produced improvement earlier than CT; at week 4, 57% of [fluvoxamine](#) patients were rated moderately improved or better compared to 40% for the CT group and 22% for the PL group. At the same time point, 43% of [fluvoxamine](#) patients were free of panic attacks compared with 25% of CT and 4% of PL patients [27].

3) In a placebo-controlled, double-blind study, [fluvoxamine](#) significantly reduced the number of panic attacks compared to placebo. The severity of attacks was not affected by

[fluvoxamine](#). There was no difference between drug and placebo until 6 weeks of treatment when placebo lost its effect on anxiety, depressive mood, and disability (Hoehn-Saric, 1993).

4.5.2.A.14] [Posttraumatic stress 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:

Open trials suggest that [fluvoxamine](#) may be useful for treating [post-traumatic stress disorder](#) [29][30][31].

c) Adult:

1) Some symptoms of combat-related [post-traumatic stress disorder](#) (PTSD) improved during treatment with [fluvoxamine](#); however, there was a high dropout rate from the study due to side effects and lack of perceived therapeutic benefit. Fifteen Vietnam combat veterans with no other psychiatric diagnosis than PTSD and depression were treated with [fluvoxamine](#), starting at a dose of 50 milligrams (mg) twice daily and increasing to a maximum of 300 mg/day, in an open-label, 14-week study. The study was preceded by a 30-day washout period. The mean daily dose of [fluvoxamine](#) at week 14 was 150 mg. Only 8 patients completed 8 weeks of the study and 5 completed the entire study. In intent-to-treat analysis, scores on intrusion and avoidance scales of the Clinician PTSD Scale (CAPS) showed significant improvement (p less than 0.001), as did scores on the Hamilton Anxiety Scale (p less than 0.001). However, measures of depression showed no significant changes. Hyperarousal scores also were unchanged. Gastrointestinal side effects and dizziness were the most common adverse effects reported [29].

2) In an open, 8-week trial, [fluvoxamine](#) resulted in symptom improvement in 64.2% of civilian patients with [post-traumatic stress disorder](#) (PTSD). Fifteen patients with confirmed PTSD were treated with [fluvoxamine](#) 50 milligrams (mg) daily with adjustment of dose to a maximum of 200 mg daily depending on symptom improvement and side effects. Using assessment scales including the Structured Interview for PTSD, Treatment-Outcome PTSD Scale, and the Duke Global Rating Scale for PTSD, the symptom score improved by 40% to 50%; this difference was clinically and statistically significant. Five patients left the trial early due to adverse effects (n=2) and administrative reasons (n=3); however, 14 of 15 patients were included in the efficacy analysis. Positive results of this and an earlier trial indicate that a double-blind, placebo-controlled trial should be performed with [fluvoxamine](#) for PTSD [30].

3) In an open-label trial, [fluvoxamine](#) improved stress-related symptoms in 10 Vietnam combat veterans with [post-traumatic stress disorder](#). The 12-week study consisted of a drug wash out and DSM-III-R diagnoses screening during weeks 0 to 2, followed by [fluvoxamine](#) 50 milligrams (mg) daily starting at week 2. [Fluvoxamine](#) was increased weekly by 50 mg to a therapeutic dose; the (modal) daily dose was 150 mg, (range 100 to 250 mg daily). Self-report

and clinician ratings of stress-specific and general psychiatric symptomatology improved significantly over the first 6 weeks and continued at this level for the duration of the study. These included the intrusion, avoidance and hyperarousal symptoms of PTSD. The comorbid features of depression and anxiety were also significantly affected; however, hostility was unaffected. The most commonly reported side effects were sedation, headache, nausea, and insomnia [31].

4.5.2.A.15] Prostatic pain

a) Overview

FDA Approval: Adult, no; **Pediatric, no**

Efficacy: Adult, Evidence is inconclusive

Recommendation: Adult, Class IIb

Strength of Evidence: Adult, Category B

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

b) Summary:

[Fluvoxamine](#) reduced pain and normalized urinary flow rates in patients with prostatodynia in a randomized, double-blind, placebo-controlled study (n=42) [32].

c) Adult:

1) [Fluvoxamine](#) treatment was more likely than placebo to reduce pain and normalize urinary flow rates in patients with prostatodynia. In this randomized, double-blind, placebo-controlled study (n=42), patients with at least a one-year history of perigenital pain without local or systemic infection and without local inflammation were assigned to receive placebo or [fluvoxamine](#) for 8 weeks. Treatment medication was initiated at 50 milligrams (mg) daily, then increased by 50 mg every 2 weeks, as needed (median dose, 150 mg; range, 50-300 mg). Patients treated with [fluvoxamine](#) reported significant improvements in pain as compared with placebo-treated patients (p=0.01). Significantly more patients in the [fluvoxamine](#) group showed improvement in urinary flow rate as compared with the placebo group (7 of 8 vs 1 of 6, respectively; p=0.03). Larger studies are needed to address the efficacy of [fluvoxamine](#) for all symptoms of prostatodynia and to identify the optimal dose [32].

4.5.2.A.16] Repetitive self-excoriation

a) Overview

FDA Approval: Adult, no; **Pediatric, no**

Efficacy: Adult, Evidence is inconclusive

Recommendation: Adult, Class III

Strength of Evidence: Adult, Category B

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

b) Summary:

A response rate of 50% was seen in patients treated with [fluvoxamine](#) in an open-label study [33].

c) Adult:

1) In an open, 12-week study, patients with psychogenic [excoriation](#) improved during treatment with [fluvoxamine](#); however, 7 patients withdrew early due to adverse effects (n=4) or unrelated reasons. Response defined as a 30% or greater decrease in the total score on the modified Yale-Brown Obsessive Compulsive Scale (Y-BOCS) was achieved in 50% of enrolled patients. The modified Y-BOCS score was reduced from 17.9 at baseline to 10.9 at termination. Adverse effects were common and included those normally expected with [fluvoxamine](#). This study suggests that [fluvoxamine](#) may be useful for psychogenic [excoriation](#); however, controlled clinical trials are needed to confirm this [33].

4.5.2.A.17] Social phobia

a) Overview

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

Efficacy: Adult, Evidence favors efficacy

Recommendation: Adult, Class IIb

Strength of Evidence: Adult, Category B

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

b) Summary:

In a randomized, double-blind, multicenter, placebo-controlled study (n=300), patients with generalized [social anxiety disorder](#) (GSAD) who received [fluvoxamine](#) controlled-release (CR) demonstrated a significantly greater reduction in the mean Liebowitz Social Anxiety Scale (LSAS) total score from baseline compared with patients who received placebo [34]; there was a trend towards continued clinical benefit with [fluvoxamine](#) ER compared to placebo in a 12-week double-blind extension phase of this study [35].

[Fluvoxamine](#) was superior to placebo for treating [social phobia](#) in a clinical study (n=86) [36].

c) Adult:

1) [Fluvoxamine](#) extended-release (ER) was an effective therapy in the treatment of patients with generalized [social anxiety disorder](#) (GSAD). In a randomized, double-blind, placebo-controlled, multicenter study, patients (n=300) with GSAD and a score of at least 60 on the Liebowitz Social Anxiety Scale (LSAS) received [fluvoxamine](#) ER (initial, 100 milligrams (mg)/day, titrated weekly in 50 mg increments, as needed, to maximum of 300 mg/day; mean dose, 209 mg/day) for 12 weeks. A significantly greater reduction in the mean LSAS total score was observed from baseline to endpoint in the [fluvoxamine](#) ER group as compared with the placebo group (37% vs 28%, respectively; p=0.02). The mean LSAS total score for patients in the [fluvoxamine](#) ER group was significantly more improved as compared with placebo at weeks 4, 8, 10, and 12 (p less than 0.05, all values), but not at week 6 (p=0.066). Reductions on the fear and avoidance subscales of the LSAS were also significantly greater for [fluvoxamine](#) ER-treated patients as compared with placebo-treated patients (p=0.015 and p=0.04, respectively). Additionally, [fluvoxamine](#) ER was superior to placebo in three of four secondary measures including the Clinical Global Impression Improvement

(CGI-I) Scale, CGI-Severity (CGI-S) of Illness Scale, and the Sheehan Disability Scale (SDS) ($p=0.026$, $p=0.022$, and $p=0.036$, respectively). Nausea (47%), headache (35%), insomnia (32%), asthenia (28%), and somnolence (22%) were the most commonly reported adverse events. Adverse effects related to sexual dysfunction were not significantly different between treatment groups, however these effects included abnormal ejaculation, [anorgasmia](#), impotence, and decreased libido [34].

a) In a 12-week double-blind extension of the aforementioned study, there was a trend towards continued clinical benefit with [fluvoxamine](#) ER ($n=56$) compared to placebo ($n=53$) among patients with generalized [social anxiety disorder](#). Patients completing the 12-week acute phase study and achieving at least minimal improvement (ie, a CGI-I score of 3 or less) continued to receive study medications as assigned in the acute phase; the mean [fluvoxamine](#) ER dose in the extension phase was 181 milligrams/day. Notably, the extension phase was not powered to detect statistical significance due to the small number of patients expected to continue into the extension study. At the end of 24 weeks of treatment, the mean LSAS total scores continued to decline in the [fluvoxamine](#) ER group compared to placebo (difference from week 12, -6.3 ± 1.6 for [fluvoxamine](#) ER versus (vs) -1.6 ± 1.6 for placebo; $p=0.109$). Although not statistically significant, greater improvements were seen in the [fluvoxamine](#) ER group compared to placebo for the secondary measures of CGI-S and SDS scores during the 12-week extension. The percentage of responders (ie, score of 1 or 2 on the CGI-I; 80% vs 74%; $p=0.322$) and remitters (ie, score of 1 on the CGI-I; 38% vs 28%; $p=0.318$) was numerically higher in the [fluvoxamine](#) ER group than the placebo group. During the extension phase, 9% (5/56) and 4% (2/53) of [fluvoxamine](#) ER- and placebo-treated patients, respectively, discontinued treatment due to adverse events. Common adverse events occurring more frequently than placebo included sweating (9% vs 4%), nausea (7% vs 2%), and sexual dysfunction (16% vs 5%), with 7% of [fluvoxamine](#) ER-treated patients reporting abnormal ejaculation (0% in the placebo group) [35].

2) [Fluvoxamine](#) was superior to placebo for treating [social phobia](#). Patients diagnosed with DSM-IV [social anxiety disorder](#) were randomly assigned to 12 weeks of double-blind treatment with placebo ($n=44$) or [fluvoxamine](#) 50 milligrams daily ($n=42$) with titration at weekly intervals to a maximum dose of 300 milligrams daily. Response was defined by a score of 1 (very much improved) or 2 (much improved) on the Clinical Global Impression scale (CGI). Of the patients ($n=64$) who completed the full 12 weeks of the study, 53.3% and 23.5% treated with [fluvoxamine](#) and placebo, respectively, were considered responders on the CGI scale ($p=0.01$). In addition, evaluation using specialized [social phobia](#) scales demonstrated significant improvement in the [fluvoxamine](#) versus placebo group (ie, Brief [Social Phobia](#) Scale, p less than 0.01; [Social Phobia](#) Inventory, $p=0.02$; Liebowitz Social Anxiety Scale subscales for work and family life, $p=0.006$ and $p=0.02$). The mean [fluvoxamine](#) dose was 202 milligrams/day at study end. Treatment was withdrawn due to adverse effects in 25% and 9.1% of patients treated with [fluvoxamine](#) and placebo, respectively; nausea and insomnia were the primary adverse effects that led to treatment discontinuation. Treatment benefit was first observed at 6 weeks and continued through week 12 of the study. Comparison of [fluvoxamine](#) with other accepted treatments is needed [36].

3) [Fluvoxamine](#) was effective in a small group of patients who met DSM-III-R criteria for [social phobia](#). Fifteen patients were treated with [fluvoxamine](#) 50 milligrams (mg)/day

with titration to 150 mg/day as needed; treatment was continued for 6 weeks. Five patients discontinued treatment due to adverse effects or difficulty traveling for appointments. Assessment scales including the Hamilton Rating for Anxiety, Brief [Social Phobia Scale](#), Marks-Sheehan Phobia Scale, Fear Questionnaire, and Sheehan Patient Rated Anxiety Scale showed a significant reduction from baseline to week 7. Patients also reported a reduction in anxiety associated with giving a speech at baseline and conclusion of the study. This small, open study suggests that [fluvoxamine](#) is effective for [social anxiety disorder](#) [37].

4.5.2.A.18] [Stereotypy habit disorder](#)

a) Overview

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

Efficacy: Adult, Evidence is inconclusive

Recommendation: Adult, Class IIb

Strength of Evidence: Adult, Category C

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

b) Summary:

Three patients responded to [fluvoxamine](#) with complete cessation of stereotypic behavior in 1 patient [38].

c) Adult:

1) Of 3 elderly women with stereotypic behavior, 2 almost completely stopped the behavior, and 1 had a partial response to [fluvoxamine](#) [38]. Pretreatment assessment with the [Abnormal Involuntary Movement Scales \(AIMS\)](#) yielded a score of 13 to 16. The first patient gnawed on her fingers, clothing, and towels but stopped this behavior after receiving [fluvoxamine](#) 50 milligrams (mg) daily for 4 weeks; the AIMS decreased to 1. Treatment was continued for 10 weeks; this patient remained symptom-free 6 months after stopping [fluvoxamine](#). The second patient had almost complete resolution of chewing on her sweater and finger sucking 3 weeks after increasing [fluvoxamine](#) to 100 mg daily; her AIMS also decreased to 1. The third patient caused constant irritation and infection to her left eyelid due to constantly wiping it with her sleeve. This behavior partially abated after treatment with [fluvoxamine](#) 150 mg daily; the AIMS went from 16 to 7. Therapy was tolerated well by all patients who ranged in age from 81 to 88 years. Since 2 patients maintained a response after treatment withdrawal, this behavior was considered responsive to [fluvoxamine](#) and is likely related to a serotonergic mechanism.

4.5.2.A.19] [Trichotillomania](#)

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:

Fluvoxamine may have beneficial effects in patients with trichotillomania [39].

c) Adult:

1) In a 12-week, open trial, fluvoxamine treatment resulted in some improvement in trichotillomania. Twenty-one patients were treated with fluvoxamine 50 milligrams (mg) daily with dosage adjustment to a maximum of 300 mg daily. Of the 21 patients treated, only 13 completed the entire 12 weeks of treatment. When the data were analyzed including patients completing the study, few statistically significant differences were found in symptoms on the assessment scales; however, when all patients were included, significant differences were found in several symptoms on the assessment scales. One possible explanation for this difference includes early treatment withdrawal in patients with a good response; another possible reason is the assessment scales were NOT well validated for trichotillomania. Since some symptomatic improvement occurred in both groups (completers and non-completers), controlled clinical trials are needed to assess fluvoxamine treatment for trichotillomania [39].

4.5.2.A.20] Wernicke-Korsakoff syndrome**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:

Results of studies have been mixed when fluvoxamine was used for treating alcoholic Korsakoff syndrome. Available studies have included only a few patients; therefore, larger, well-controlled studies may resolve the controversy [3][4].

c) Adult:

1) Fluvoxamine 200 milligrams/day was ineffective in the treatment of alcoholic Korsakoff syndrome in 8 patients who were treated for 4 weeks in a double-blind, placebo-controlled, crossover trial. Fluvoxamine had no cognitive-enhancing effect as measured by a detailed neuropsychological battery on a weekly basis. There was significant impairment in verbal fluency. Two patients developed a major depressive episode in the fluvoxamine group; within 3 days of fluvoxamine discontinuation, their mood returned to normal [3].

2) Fluvoxamine 100 to 200 milligrams/day improved episodic memory in 7 patients with alcohol amnestic disorder (Korsakoff's psychosis) in a 4-week, double-blind, crossover design study. These improvements were significantly correlated with reductions in cerebrospinal fluid 5-HIAA levels, suggesting that facilitation of serotonergic neurotransmission may ameliorate the episodic memory failure in patients with alcohol amnestic disorder (Martin, 1989).

3) Fluvoxamine produced a small but significant improvement in memory performance in 5 alcoholic organic brain syndrome patients during a double-blind, crossover study.

Fluvoxamine 200 milligrams/day for 4 weeks was administered to all patients. Overall improvement in performance was associated with higher levels of fluvoxamine and lower levels of 5-hydroxy-indole-acetic acid (5HIAA), a metabolite of serotonin, in the cerebrospinal fluid [4].

4.6] Comparative Efficacy / Evaluation With Other Therapies

4.6.A] Amineptine

4.6.A.1] Bulimia nervosa

a) Fifteen women with bulimia nervosa were treated with a combined cognitive-behavioral, nutritional and antidepressant therapy (either amineptine 300 milligrams (mg) per day or fluvoxamine 300 mg/day) for 4 months. The combination of psychotherapeutic and pharmacologic therapy showed rapid, good effects and improvement was stable in most of the patients until the end of the observations. Prior to therapy, the patients had high global Eating Disorders Inventory (EDI) scores; these did not change during fluvoxamine therapy and decreased during amineptine administration in some patients (not statistically significant). No statistically significant improvement ($p=0.4$) was found in depression or anxiety in the two groups. The Bulimic Investigation Test Edinburgh (BITE) symptoms and gravity scores improved significantly ($p=0.001$) in both groups and gravity was more significantly ($p=0.05$) improved with amineptine than fluvoxamine. Optimum dosage and duration of treatment for this condition have not been determined. The data of this study are preliminary and the results need to be validated in a larger population over a longer observation period [499].

4.6.B] Amitriptyline

4.6.B.1] Depression

a) SUMMARY: In two clinical studies, amitriptyline and fluvoxamine were equally effective in treating patients with depression [491][492]. A greater percentage of the amitriptyline group discontinued therapy due to side effects [492].

b) In a double-blind, randomized parallel study lasting seven weeks, fluvoxamine (mean dose 175 mg/day) was compared to amitriptyline (mean dose 135 mg/day) in 33 outpatients with moderate degrees of depression. There was no statistically significant difference between the two drugs as judged using the Hamilton Rating Scale for Depression and the Clinical Global Impression Scale. The two drugs had a comparable safety profile, although a greater percentage of the amitriptyline group discontinued therapy due to side effects [492].

c) In another study, amitriptyline was compared to fluvoxamine in a double-blind trial of 56 patients with major depressive disorders. The study lasted 6 weeks and doses of amitriptyline and fluvoxamine escalated from 50 to 300 mg and 100 to 300 mg, respectively. Patients were divided into responders and non-responders based on the Hamilton rating scale for depression and the Montgomery-Asberg depression rating scale. Overall, the drugs were found equally effective, but there was some symptom specificity which might guide the selection of one or the other drug in the clinical setting [491].

4.6.B.2] Fibromyalgia

a) Fluvoxamine was equally effective to amitriptyline in reducing pain associated with fibromyalgia. In an open-label, uncontrolled study, 68 Japanese patients with fibromyalgia received either amitriptyline at a mean dose of 20 milligrams (mg)/day or fluvoxamine at a mean dose of 25 mg/day for 4 weeks. Patients evaluated pain relief by means of a visual analog scale and efficacy was defined as a decrease in pain by at least 50%. At 4 weeks, 50% of patients in the amitriptyline group and 41% of patients in the fluvoxamine group reported effective relief of pain ($p=NS$). Drowsiness was the most commonly reported

adverse event with [amitriptyline](#) treatment and nausea was most frequently reported with [fluvoxamine](#). The authors hypothesize that because the efficacy of [amitriptyline](#) for the treatment of fibromyalgia-related pain has been established in previous, controlled trials and because [fluvoxamine](#) showed similar efficacy to [amitriptyline](#) in this open-label study; [fluvoxamine](#) may be helpful for patients with [fibromyalgia](#) (Nishikai & Akiya).

4.6.C] [Clomipramine](#)

4.6.C.1] [Anxiety](#)

a) [Fluvoxamine](#) and [clomiPRAMINE](#) were comparable in reducing anxiety symptoms in patients with [agoraphobia with panic attacks](#) (APA), [generalized anxiety disorders](#) (GAD), and [obsessive-compulsive disorders](#) (OCD) as classified by DSM-III during a randomized, double-blind study [472]. Of the 50 patients in this study, 39 diagnosed with APA, 5 with GAD, and 6 with OCD. Patients were randomly assigned to receive either [clomiPRAMINE](#), up to 150 milligrams/day, or [fluvoxamine](#), up to 100 milligrams/day, for the 6-week study. Both drugs demonstrated significant improvement in anxiety symptoms after drug therapy when compared to pretreatment.

4.6.C.2] [Cataplexy](#)

a) Both [fluvoxamine](#) and [clomiPRAMINE](#) improved [cataplexy](#), but not [narcolepsy](#), in 18 patients with these diseases during a cross-over study [473]. It was not revealed if either the patients or researchers were blinded to drug therapy. It should be noted that 15 of the 18 patients were receiving [clomiPRAMINE](#) 25 to 100 milligrams/daily at the start of the trial, and may have been accustomed to the adverse effects of [clomiPRAMINE](#). Also, if the patients were not blinded to drug therapy, some patients may have associated more adverse effects with a new drug, [fluvoxamine](#). Patients were randomly allocated to receive [fluvoxamine](#) or [clomiPRAMINE](#) for a 3-week interval. After a 1-week drug-free period, the patients crossed over to the other drug. The daily dosing range for both drugs ranged from 25 to 200 milligrams/day. All patients were clinically assessed by observers on 5 occasions. The observers' impression was that [fluvoxamine](#) caused a moderate reduction in the frequency of attacks of [cataplexy](#) and [sleep paralysis](#) in most subjects. [Fluvoxamine](#) abolished [cataplexy](#) in 4 patients and [sleep paralysis](#) in 2 patients; only 12 of the 18 patients completed the fluvoxamine-treatment period. The observers felt that [clomiPRAMINE](#) was more effective than [fluvoxamine](#) in preventing both [cataplexy](#) and [sleep paralysis](#). [ClomiPRAMINE](#) abolished [cataplexy](#) in 4 patients and [sleep paralysis](#) in 5 patients.

4.6.C.3] [Depression](#)

a) SUMMARY: Several double-blind, short-term studies have demonstrated [fluvoxamine](#) to be as effective as [clomiPRAMINE](#) in the treatment of depression [474][475]. Anticholinergic adverse effects appear to be less common with [fluvoxamine](#) therapy.

b) [Fluvoxamine](#) and [clomiPRAMINE](#) were compared for antidepressant activity in a 6-week, randomized, double-blind study of 43 outpatients with [major depression](#) [474]. Oral [fluvoxamine](#) 100 to 300 milligrams or oral [clomiPRAMINE](#) 50 to 150 milligrams was administered once daily in the evening. Assessments of the HAM-D (Hamilton Rating Scale for Depression) during the study and at the end failed to demonstrate any significant differences in antidepressant activity between the 2 drugs. The incidence of anticholinergic adverse effects were slightly more significant in the clomiPRAMINE-treated group.

c) [ClomiPRAMINE](#) and [fluvoxamine](#) appeared to be equally effective in the treatment of depression for 36 female inpatients during a 4-week, randomized, double-blind study [475]. Patients were randomized to receive either oral [clomiPRAMINE](#) or oral [fluvoxamine](#) 50 milligrams 3 times daily. [Diazepam](#) 10 to 30 mg/day for severe agitation and/or anxiety was the only other psychotropic agent administered. Significant improvements in the Hamilton Rating Scale for Depression, the Clinical Global Impression,

and the [Zung Self-Rating Depression scale](#) were seen in both treatment groups. Anticholinergic adverse effects appeared more frequently in the clomiPRAMINE-treated patients, while gastrointestinal effects were more prevalent in the [fluvoxamine](#) group.

d) [Fluvoxamine](#) and [clomiPRAMINE](#) appeared to have similar clinical efficacy in the treatment of [endogenous depression](#) for 30 unipolar and bipolar inpatients during a 4-week, randomized, double-blind study [474]. Both drugs were administered orally in doses of 150 to 300 milligrams/day in 3 divided doses. At the end of the study, the fluvoxamine-treated patients demonstrated a 73% improvement on the Hamilton Rating Scale for Depression, while the clomiPRAMINE-treated patients had a 62% improvement. In the bipolar patients, 3 of 4 on [fluvoxamine](#) responded, while only 1 of 5 on [clomiPRAMINE](#) demonstrated a good response on the CGI Global Change Scale. Overall, the differences in efficacy between the 2 drugs were not statistically significant. Adverse anticholinergic effects were significantly more prevalent in the clomiPRAMINE-treated group.

e) Both [clomiPRAMINE](#) and [fluvoxamine](#) produced significant improvements on the Hamilton Rating Scale for Depression (HAM-D) in 32 patients with mixed depression during a 4-week, randomized, double-blind study [476]. The average daily dosage was 130 milligrams and 132.8 milligrams for [fluvoxamine](#) and [clomiPRAMINE](#), respectively. The mean percentage improvement on the HAM-D for the fluvoxamine-treated patients was 63.8%, and for the clomiPRAMINE-treated patients it was 66.3%.

4.6.C.4] [Obsessive-compulsive disorder](#)

a) [Fluvoxamine](#) (150 to 125 milligrams/day) and [clomiPRAMINE](#) (100 to 250 milligrams/day) were equally effective in the treatment (10 weeks) of 66 outpatients with [obsessive compulsive disorder](#). Both treatments were well-tolerated. [Fluvoxamine](#) produced fewer anticholinergic adverse effects and caused less sexual dysfunction than [clomiPRAMINE](#), but caused more headache and insomnia [477]. under [OBSESSIVE COMPULSIVE DISORDER](#) add:

b) In a randomized, double-blind study of 26 patients with [obsessive compulsive disorder](#) without comorbid diseases, [fluvoxamine](#) and [clomiPRAMINE](#), each titrated from an initial dose of 50 milligrams (mg) in the evening up to a maximum of 300 mg daily within two weeks, were equally effective (38% improvement over baseline with [fluvoxamine](#) versus 40% for [clomiPRAMINE](#)). Efficacy was assessed according to the Yale-Brown Obsessive Compulsive Scale and Clinical Global Impression Scale. [Fluvoxamine](#) was better tolerated, with less anticholinergic adverse effects while [clomiPRAMINE](#) had a quicker onset of action. Further studies are needed to demonstrate a time-related effect that might differentiate these drugs [478].

4.6.C.5] [Panic disorder](#)

a) [ClomiPRAMINE](#) (10 milligrams (mg) for three days and 20 mg for four days) and [fluvoxamine](#) (50 mg/day for seven days) were both effective in decreasing the hypersensitivity to 35% carbon dioxide, supporting the serotonergic effect of these drugs to decrease panic attacks through modification of carbon dioxide sensitivity. Thirty-nine [panic disorder](#) patients were enrolled in a double-blind, randomized, placebo-controlled study, where each patient was given the 35% carbon dioxide challenge on days 0, 3, and 7. Patients on [clomiPRAMINE](#) and [fluvoxamine](#) showed significant reduction in sensitivity over placebo after seven days as seen by the percent change on a visual analogue for anxiety scale ($p=0.027$) [479].

4.6.D] [Clovexamine](#)

1) Efficacy

a) SUMMARY: Clovoxamine induces only minor electroencephalographic changes in healthy subjects; whereas, changes produced by [fluvoxamine](#) more closely resemble those of [imipramine](#),

including an increase of slow activity. Clovoxamine appears less sedating than [fluvoxamine](#), and may possess mild alerting effects.

b) In computerized electroencephalographic studies involving healthy subjects [494], oral clovoxamine 50 to 125 mg was primarily associated with an increase in very fast beta-activity (predominant 6 hours postdose), suggesting an activating effect of the drug. Although an increase in fast beta-activity was also observed with [fluvoxamine](#) 75 mg, this agent also produced a concomitant increase of slow activity and a decrease of alpha-activity. [Imipramine](#) 75 mg produced the most marked electroencephalographic changes, characterized by a concomitant increase of slow and fast activities and a decrease of alpha-activity. Augmentation of slow activity was, however, less with [fluvoxamine](#) than [imipramine](#), suggesting less sedative properties of the former. Overall, pharmacodynamic data based on both electroencephalographic and psychometric parameters indicated that [imipramine](#) 75 mg produced the most central nervous system changes, followed by [fluvoxamine](#) 75 mg, clovoxamine 125 mg, clovoxamine 75 mg, and clovoxamine 50 mg. Peak effects occurred 4 to 6 hours after clovoxamine and [fluvoxamine](#), compared to 2 to 4 hours following [imipramine](#). Adverse effects were minimal with clovoxamine, with euphoria occurring in a few subjects; in contrast, tiredness was common after [fluvoxamine](#) (50% of subjects) and [imipramine](#) (80%).

c) The results of a further placebo-controlled study in healthy volunteers also suggested a lower propensity of clovoxamine to induce sedation in comparison with [fluvoxamine](#). In doses of 50 mg twice daily (8 am and 6 pm), [fluvoxamine](#) was associated with changes suggestive of enhanced nighttime sedation; fluvoxamine-treated were significantly less refreshed upon awakening and had greater difficulty in achieving morning alertness compared to placebo, and there were trends toward fewer nocturnal awakenings and shorter sleep latency in the [fluvoxamine](#) group. In contrast, these effects were not observed clovoxamine 150 mg daily (100 mg at 8 am and 50 mg at 6 pm); depth of sleep was reduced significantly with clovoxamine compared to placebo [495].

4.6.E] [Desipramine](#)

4.6.E.1] Depression

a) The efficacy of [fluvoxamine](#) was compared to that of [desipramine](#) in a multicenter, double-blind, placebo-controlled six-week flexible dose trial of 90 outpatients with [major depressive disorder](#). Dosage range for each active medication was 100 to 300 milligrams/d. The Montgomery-Asberg Depression Rating Scale, the Hamilton Rating Scale for Depression, and the Clinical Global Impression Scale were used to assess response. There was no significant difference in efficacy among the three treatments until week six, when both active drug groups continued to improve while the placebo group remained at the same level of depression. The authors concluded that 6 weeks was too short a time to identify the differences between active drug and placebo in the patient population [496].

b) An immediate increase in pain threshold (polysynaptic R-III reflex and subjective pain rating to electric shock) was seen in a single-dose, placebo-controlled study comparing [desipramine](#), [fluvoxamine](#), and moclobemide in healthy volunteers (n=10) (Coquoz et al, 1993).

4.6.F] [Dothiepin](#)

4.6.F.1] Depression

a) [Fluvoxamine](#) and dothiepin were comparable in reducing symptoms of depression in 73 patients during a 6-week, double-blind study [454]. The patients were randomized to receive initial starting doses of either [fluvoxamine](#) 100 milligrams or dothiepin 75 milligrams daily. The doses were increased gradually, as tolerated, to a maximum of [fluvoxamine](#) 300 milligrams or dothiepin 225 milligrams/day. At the conclusion

of the study, both drugs demonstrated efficacy in treating depression as measured by the Hamilton Depression Rating Scale (HAMD), Clinical Global Impression, and Clinical Global Improvement scales. There were no significant differences in efficacy between the 2 drugs. Dothiepin was associated with more anticholinergic adverse effects, while **fluvoxamine** was associated with more nausea and vomiting.

b) **Fluvoxamine** (25 to 200 mg/d) was equivalent to dothiepin (25 to 200 mg/d) in efficacy in 52 elderly inpatients with **major depressive disorder**. Patients were treated for 6 weeks with weekly assessments for therapeutic response and presence of adverse effects. The mean dosage during the last 2 weeks of the study was 157 mg/d for **fluvoxamine** and 159 mg/d for dothiepin. Sixty-three percent of **fluvoxamine** patients and 60% of dothiepin patients showed marked improvement at six weeks [455].

4.6.G] **Fluoxetine**

4.6.G.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 [457].

4.6.H] **Flupenthixol**

4.6.H.1] **Depression**

a) Flupenthixol was as effective as **fluvoxamine** in the treatment of depression, and had a more favorable adverse effect profile [490]. In a multicenter trial, 72 patients with depression were randomized to receive either flupenthixol 1 milligram/day (n=36) or **fluvoxamine** 100 milligram/day (n=36) for 4 weeks. Patients were evaluated objectively on days 1, 8, 15, and 29 using the Hamilton Depression Rating Scale, the Clinical Global Impressions Scale, and a self-assessment analog scale. At the end of the first week, the dose was doubled if response was judged to be insufficient. While both drugs were shown to be effective, mean improvement scores were higher at all evaluation times as measured by any of the 3 parameters in the group receiving flupenthixol. At the end of the first week, 89% of the flupenthixol group showed at least minimal improvement, compared with 75% of the **fluvoxamine** group. At the end of the study, all patients receiving flupenthixol had responded to treatment, compared with 83% of the **fluvoxamine** group. Four patients taking **fluvoxamine** were withdrawn due to adverse effects, but no patients receiving flupenthixol were withdrawn.

4.6.I] **Imipramine**

4.6.I.1] **Depression**

a) SUMMARY: **Fluvoxamine** and **imipramine** appear to be equally efficacious in the treatment of depression [464][465][466][467]; (March, 1990)[468].

b) **Fluvoxamine** demonstrated a trend toward superiority over **imipramine** in treating 63 patients with **major depression** during a 4- to 6-week, randomized, placebo-controlled, double-blind study [464]. All drugs were started at 50 milligrams/day, and were gradually increased to a maximum of 300 mg/day. The mean daily dose of **fluvoxamine** at the the end of the study was 207 mg, and 192 mg for **imipramine**. At the end of the study, the total Hamilton Rating Scale for Depression (HAM-D) score had decreased by 75%, 55%, and 6% in the **fluvoxamine**-, **imipramine**-, and placebo-treated groups, respectively. At the end

of the study there were 8, 3, and 1 responders from the [fluvoxamine](#), [imipramine](#), and placebo groups, respectively. Only 1 patient in each active treatment group withdrew from the study because of adverse effects.

c) [Fluvoxamine](#) was comparable to [imipramine](#) in antidepressant activity during a 4-week, double-blind, multicenter study of 151 patients [465]. Drug therapy was administered in twice daily dosing in the range of 100 to 300 milligrams daily for [fluvoxamine](#) and 50 to 200 milligrams daily for [imipramine](#). At the end of the study there was a mean improvement in the Hamilton Rating Scale for Depression (HAM-D) of 67.2% in the fluvoxamine-treated group and a 62.1% improvement in the imipramine-treated group. A similar improvement was detected with both drugs on the Clinical Global Impression Scale. At the end of the study, the mean daily dose of [fluvoxamine](#) was 221 mg and 112 mg for [imipramine](#). A total of 37 patients withdrew from the study prematurely; 19 on [fluvoxamine](#) and 18 on [imipramine](#). The reasons for early withdrawal appeared to be similar between both drugs.

d) [Fluvoxamine](#) and [imipramine](#) were comparable in efficacy for the treatment of depression in 36 patients diagnosed with unipolar or [bipolar depression](#) during a 4- to 6-week, randomized, double-blind study [466]. Both medications were administered at bedtime with a maximal dosage range between 150 to 225 milligrams/day. In the unipolar depressed fluvoxamine-treated patients, 92% were judged "improved" at the end of the study compared to 81% of the [imipramine](#) group. However, the imipramine-treated group appeared to have a higher percent of patients rated as "much" or "very much" improved, 75% compared to 54% of the [fluvoxamine](#) group.

e) A double-blind comparative study of [fluvoxamine](#) and [imipramine](#) was carried out in 20 outpatients with [depressive disorder](#). Patients received randomly-assigned medication over a 4-week period in a dosage range of 50 to 300 mg given in 2 divided doses. There was a significant symptom severity reduction in both groups at the end of 4 weeks, and [fluvoxamine](#) was more effective than [imipramine](#) in reducing suicidal ideas and anxiety/somatic symptoms. Anticholinergic-type adverse reactions predominated for [imipramine](#) and gastrointestinal effects for [fluvoxamine](#) [469].

f) In a 6-week, double-blind, placebo-controlled, variable-dose study assessing the comparative antidepressant efficacy of [fluvoxamine](#) (FLU), [imipramine](#) (IMI), and placebo (PBO), 45 patients with [major depressive disorder](#) were evaluated for response and side effects. Dosage ranged between 100 to 300 milligrams/day for active medications. No statistically significant differences between either the FLU (N=17) and PBO or the FLU and IMI groups were found. Side effects were present in all three groups: IMI(N=18): constipation (83%), dry mouth (55%), and sweating, dizziness, and nausea, all 39%. FLU(N=18): diarrhea, headache, dry mouth, all 41%, nausea (35%), and flatus (29%). PBO(N=18): [pruritus](#) (29%, nausea (23%), headache (18%), asthenia and somnolence, both 12%. This study revealed a high placebo response, with a 50% improvement at week 6. Thus, it is difficult to show differences from active medication unless the study is carried out for a longer time. In addition, the numbers of patients are too small to detect a true difference. Second, patients seemed to either respond or not respond to FLU, while the response to IMI appeared to be more graded. This may reflect a subgroup of depressed patients that have a serotonin-deficient type of depression [468].

g) Other double-blind, placebo-controlled studies comparing [imipramine](#) and [fluvoxamine](#) have only demonstrated slightly more improvement in depression with either drug when compared with placebo [470][471].

4.6.1.2) Adverse Effects

a) SUMMARY: [Fluvoxamine](#) produces less cardiovascular and anticholinergic adverse effects than [imipramine](#); however, nausea and vomiting are more common with [fluvoxamine](#) therapy [460][461][462][463].

b) Adverse effects data was pooled from the results of 10 double-blind, placebo-controlled trials comparing [fluvoxamine](#) (n=222) with [imipramine](#) (n=221) [460]. Anticholinergic effects such as dry mouth, dizziness/syncope, sweating, and abnormal accommodation were much more prevalent in

patients receiving [imipramine](#). Nausea/vomiting was the only adverse effect to be much more prevalent in the fluvoxamine-treated patients.

c) The cardiac effects of tricyclic antidepressants were compared with [fluvoxamine](#). The major cardiac adverse effects observed with tricyclic antidepressants include postural hypotension, heart rate increase, and slight prolongation of the intraventricular conduction time and QT interval. The only cardiac effect observed with [fluvoxamine](#) was a statistically, but not clinically, significant slowing of heart rate [461].

d) [Fluvoxamine](#) produced less [psychomotor impairment](#) than [imipramine](#). [Fluvoxamine](#) was superior to [imipramine](#) 75 milligrams in regards to concentration, reaction time, mood, psychomotor activity, and affectivity. Following the administration of [fluvoxamine](#) 75 milligrams to 10 healthy volunteers, psychometric tests demonstrated a tendency towards an improvement in psychomotor activity, concentration, attention, after-effect, and mood and a significant increase in critical flicker fusion frequency when compared to placebo [462].

4.6.J] [Lithium](#)

4.6.J.1] Depression

a) The rate of recurrence of unipolar [depressive episodes](#) was lower for [fluvoxamine](#) 200 milligrams (mg) per day than [lithium](#) salts 600 to 900 mg/day in a randomized study of 64 unipolar patients. Follow-up continued for 24 months [497]. Further follow-up at 36 months showed no additional recurrences of depression in either the [fluvoxamine](#) or the [lithium](#) group [498]. Due to methodological limitations, further studies are needed.

4.6.K] [Lorazepam](#)

4.6.K.1] Depression

a) [Fluvoxamine](#) (50 to 300 mg/d) was compared with [lorazepam](#) (1 to 6 mg/d) in a multi-center, double-blind, parallel group study in 112 general practice patients with mixed anxiety and depression. Response was assessed over a 6-week period using the Montgomery-Asberg Depression Rating Scale (MADRS) and the Clinical Anxiety Scale (CAS). There were no significant differences between treatments at any point except in an elderly subgroup where anxiety improved more rapidly with [lorazepam](#). There were significant improvements in MADRS and CAS, and global ratings compared with baseline at all subsequent assessments. [Lorazepam](#) produced more sedation while [fluvoxamine](#) produced more nausea and vomiting [493].

4.6.L] [Maprotiline](#)

4.6.L.1] [Schizophrenia](#)

a) [Fluvoxamine](#) was more effective than [maprotiline](#) for improving negative symptoms associated with [schizophrenia](#). Patients entered in this study had [schizophrenia](#) of at least 2 years duration and received more than 1 antipsychotic with anticholinergics (stable dose maintained during study). Patients (n=38) were randomly assigned to [fluvoxamine](#) or [maprotiline](#) 50 milligrams (mg) daily which was increased to 100 mg during the remaining 5 weeks of the study. Thirteen patients left the study within 2 weeks due to personal reasons, side effects, or worsening symptoms; these patients were NOT included in the efficacy analysis. The total score for the Scale for the Assessment of Negative Symptoms was significantly ($p=0.045$) lower in the [fluvoxamine](#) (65.6 to 57.1) versus [maprotiline](#) (80.3 to 78) group; similar results were obtained for the Brief Psychiatric Rating Scale for negative factors. Five (38.5%) patients in the [fluvoxamine](#) group were responders (defined by 20% improvement in total SANS score) versus none

in the [maprotiline](#) group. The authors suggest that the serotonergic versus the antidepressant effect of [fluvoxamine](#) are responsible for the change in negative symptoms. Further study is needed since the sample size was small, and many patients left the study [456].

4.6.M] Mianserin

4.6.M.1] Depression

a) Both [fluvoxamine](#) and mianserin are effective for the treatment of [depressive illness](#) [458]. Efficacy and CNS effects of [fluvoxamine](#) were compared with those of mianserin in depressed outpatients in a 6-week double-blind trial. The study included active treatment with 100 to 300 milligrams/d of [fluvoxamine](#) or 60 to 180 milligrams/d of mianserin. Data from 63 patients (30 [fluvoxamine](#)) showed comparable efficacy at the end of 6 weeks. MADRS scores (Montgomery-Asburg Depression Rating Scale) improved 65.6% with [fluvoxamine](#) and 60.8% with mianserin with no significant differences between treatments at any assessment. Mianserin produced more sedation during the first week of treatment but this difference resolved for the remainder of the study.

b) [Fluvoxamine](#) 50 to 200 milligrams and mianserin 20 to 80 milligrams/d were equivalent in efficacy and tolerability in a study of 57 elderly patients with [major depressive episode](#). Seven of 25 [fluvoxamine](#) patients and 4 of 25 mianserin patients had to leave the study because of intolerable side effects [459].

4.6.N] Milnacipran

4.6.N.1] Depression

a) Although there was no significant difference in efficacy between groups of patients treated with [fluvoxamine](#) or milnacipran when viewed overall, among the subset of severely depressed patients, significantly more who were treated with milnacipran responded to treatment (50% or greater improvement in Hamilton Depression Rating Scale (HDRS) score) than who were treated with [fluvoxamine](#). The groups comprised patients who had been treated with milnacipran (maximum dose 15 milligrams (mg) per day) for at least 22 months (n=102) or with [fluvoxamine](#) (maximum dose 250 mg/day) for the same period (n=90). Overall, 53% of milnacipran-treated patients and 47% of fluvoxamine-treated patients responded to treatment. Among patients with an initial HDRS score of 19 or greater, 69% of those treated with milnacipran and 46% of those treated with [fluvoxamine](#) responded (p=0.046). Scores showing improvement in insomnia and agitation significantly favored milnacipran. There were no significant differences between groups for individual or total adverse events. However, urological adverse events occurred more frequently in the milnacipran group and gastrointestinal symptoms in the [fluvoxamine](#) group. Palpitations occurred only in the milnacipran group (3%) [480].

b) 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](#) [481][482]. 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 [483]; however, this study suffered from methodological problems, the most significant being once-daily dosing of milnacipran, which may not achieve therapeutic levels.

c) 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 [484][482][485]. 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 [482].

d) Comparisons with other similar agents (eg, [sertraline](#)) are lacking.

4.6.O] Oxaprotiline

4.6.O.1] Depression

a) Oxaprotiline appeared to be more efficacious than [fluvoxamine](#) in 71 depressed patients resistant to prior tricyclic antidepressants during a randomized, double-blind, partial crossover study [453]. Patients were randomized to receive either [fluvoxamine](#) or oxaprotiline at a starting dose of 50 mg BID, which was gradually increased to a maximum of 150 mg BID as tolerated. The mean daily doses of oxaprotiline and [fluvoxamine](#) at the end of 4 weeks were 260 mg and 288 mg, respectively. Only 9 of 33 (27%) patients receiving oxaprotiline demonstrated a response, while none of the fluvoxamine-treated patients responded. During the second treatment phase, 55 patients were crossed over to the other drug. The mean daily doses of oxaprotiline and [fluvoxamine](#) at the end of the second phase were 267 mg and 286 mg, respectively. Of the 31 patients completing at least 2 weeks of oxaprotiline therapy, 12 (38%) responded; however, 6 (19%) relapsed within 6 months for a long-term response rate of only 19%. Of the 21 patients completing at least 2 weeks of [fluvoxamine](#) therapy, 2 patients (9%) responded with lasting effects.

4.6.P] Paroxetine

4.6.P.1] Depression

a) [Fluvoxamine](#) and [paroxetine](#) produced similar improvements in depressive symptoms in patients with an initial or recurrent episode of [major depression](#). Adverse effects occurred in 100% and 97% of patients treated with [paroxetine](#) and [fluvoxamine](#), respectively. [Fluvoxamine](#) was associated with a higher incidence of asthenia, dry mouth, somnolence, and insomnia; whereas, [paroxetine](#) caused a higher incidence of headache, nausea, diarrhea, sweating, abnormal dreams, and sexual dysfunction. In this 7-week, randomized, double-blind study, 58 patients were assigned to receive [fluvoxamine](#) 50 milligrams(mg)/day or [paroxetine](#) 20 mg/day initially; the protocol allowed for dosage titration to [fluvoxamine](#) 150 mg/day or [paroxetine](#) 50 mg/day. An additional 10 [fluvoxamine](#)- and 8 paroxetine-treated patients dropped out of the study for various reasons, but all of the patients were included in the intent-to-treat efficacy analysis. Due to the small sample size of this study, only large differences between treatments would be detectable; therefore, larger studies are needed to detect differences in treatment effects between these drugs [486].

b) The pharmacology, pharmacokinetics, adverse effects, drug interactions, efficacy, and dosage and administration of [fluvoxamine](#) (FVX), [sertraline](#) (SRT) and [paroxetine](#) (PRX) were compared in a comprehensive review [487]. All three agents have large volumes of distribution and are highly protein-bound. In contrast to [fluoxetine](#), FVX, SRT, and PRX all have shorter elimination half-lives (approximately 24 hours) and are metabolized to clinically-inactive compounds. Nausea was the most commonly reported adverse effect for all three agents. Other reported adverse effects include sedation, headache, dry mouth, insomnia, sexual dysfunction, and constipation. FVX has been found to be superior to placebo and equivalent to [imipramine](#), [clomipramine](#), [desipramine](#), mianserin, and [maprotiline](#) in the treatment of depression and both FVX and SRT have been shown to be superior to placebo in the treatment of [obsessive-compulsive disorder](#) (OCD). PRX has been found to be superior to placebo and equivalent to [amitriptyline](#), [imipramine](#), [clomipramine](#), and [doxepin](#) in the treatment of depression while SRT has been found to be superior to placebo and equivalent to [amitriptyline](#). Clinical experience has demonstrated all three drugs to be effective in the treatment of depression. They may be especially useful in elderly patients, in those who cannot tolerate alternate treatments, and in those who do not respond to adequate trials of other antidepressant therapies.

4.6.Q] Sertraline

4.6.Q.1] Depression

a) In a small study (n=64), the incidence of recurrent depression was similar between patients treated prophylactically with [sertraline](#) and [fluvoxamine](#). Sixty-four patients entered the study and received either [sertraline](#) 100 milligrams(mg)/day or [fluvoxamine](#) 200 mg/day for 2 years; increases in dose were allowed if depression recurred. During the study period, 7 sertraline-treated and 6 fluvoxamine-treated patients had a new episode of depression (p=0.88). Adverse effects were minor and transient for both treatments. Results of this study suggest that [sertraline](#) and [fluvoxamine](#) were effective for preventing recurrent depression episodes, but are limited by the absence of a placebo control group[488].

b) The pharmacology, pharmacokinetics, adverse effects, drug interactions, efficacy, and dosage of [fluvoxamine](#) (FVX), [sertraline](#) (SRT) and [paroxetine](#) (PRX) were compared in a comprehensive review [489]. All three agents have large volumes of distribution and are highly protein-bound. In comparison to [fluoxetine](#), FVX, SRT, and PRX all have shorter elimination half-lives (approximately 24 hours) and are metabolized to clinically-inactive compounds. These agents, therefore, are less likely than [fluoxetine](#) to interact with other drugs. Nausea was the most commonly reported adverse effect for all three agents. Other reported adverse effects include sedation, headache, dry mouth, insomnia, sexual dysfunction, and constipation. FVX has been found to be superior to placebo and equivalent to [imipramine](#), [clomipramine](#), [desipramine](#), mianserin, and [maprotiline](#) in the treatment of depression and both FVX and SRT have been shown to be superior to placebo in the treatment of [obsessive-compulsive disorder](#) (OCD). PRX has been found to be superior to placebo and equivalent to [amitriptyline](#), [imipramine](#), [clomipramine](#), and [doxepin](#) in the treatment of depression while SRT has been found to be superior to placebo and equivalent to [amitriptyline](#). Clinical experience has demonstrated all three drugs to be effective in the treatment of depression. They may be especially useful in elderly patients, in those who cannot tolerate alternate treatments, and in those who do not respond to adequate trials of other antidepressant therapies.

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