

DRUGDEX-EV 2518

MICROMEDEX

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CITALOPRAM

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0.0] Overview

1) Class

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

Antidepressant

2) Dosing Information

- a) [Citalopram](#) Hydrobromide

1) Adult

- a) discontinue with gradual dose reduction and monitoring for withdrawal symptoms [3]
b) doses above 40 mg/day are not recommended due to the risk for QT prolongation [3]

1) Depression

- a) initial, 20 mg/day ORALLY as a single dose in the morning or evening; dose increases should usually occur in increments of 20 mg at intervals of no less than one week; MAX, 40 mg/day [3]

2) Pediatric

- a) safety and effectiveness in children have not been established [3]

3) Contraindications

- a) [Citalopram](#) Hydrobromide

1)) concomitant use with an MAOI, including [linezolid](#) or IV methylene blue, or use within 14 days of discontinuing an MAOI used to treat psychiatric disorders due to increased risk of [serotonin syndrome](#) [38]

2)) concomitant use with [pimozide](#) [38]

3)) hypersensitivity to [citalopram](#) or any other component of the product [38]

4)) Serious Adverse Effects

a)) [Citalopram](#) Hydrobromide

1)) Cerebrovascular accident

2)) [Myocardial infarction](#)

3)) Prolonged QT interval

4)) [Serotonin syndrome](#)

5)) Suicidal thoughts

6)) Suicide

7)) [Torsades de pointes](#)

5)) Clinical Applications

a)) [Citalopram](#) Hydrobromide

1)) FDA Approved Indications

a)) Depression

1.0) Dosing Information

[Drug Properties](#)

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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

[Citalopram](#)

[Citalopram](#) Hydrobromide

Nitalapram

C)) Physicochemical Properties

1)) Molecular Weight

a) Base: 324.4 [489]; hydrobromide: 405.35 [3]

2) Solubility

a) Sparingly soluble in water and soluble in ethanol [3]

1.2) Storage and Stability

A) Citalopram Hydrobromide

1) Preparation

a) Oral route

1) Citalopram may be taken in the morning or evening, with or without food [3].

2) Allow at least 14 days between discontinuation of an MAOI and initiation of citalopram or between discontinuation of citalopram and initiation of treatment with MAO inhibitors [3].

1.3) Adult Dosage

1.3.1) Normal Dosage

1.3.1.A) Citalopram Hydrobromide

1.3.1.A.1) Oral route

1.3.1.A.1.a) Depression

1) The recommended adult dose of citalopram for the treatment of depression is 20 to 40 mg orally once daily. The initial dose is 20 mg once daily. Dose adjustments in increments of 20 mg should occur at intervals of no less than 1 week. Doses above 40 mg are not recommended due to the risk of QT prolongation. Also, the advantage of a 60-mg dose compared with a 40-mg dose has not been demonstrated [3].

See Drug Consult reference: CLASS COMPARISON: SSRIs AND SEROTONIN NOREPINEPHRINE REUPTAKE INHIBITORS (SNRIs) (SELECTED)

1.3.1.A.1.b) Obsessive-compulsive disorder

1) Citalopram 20 to 60 mg per day was effective for improving symptoms of obsessive-compulsive disorder in a study with 401 patients. There was no statistically significant difference between doses on any measure [15].

1.3.1.A.1.c) Discontinuing Therapy

1) A slow dose reduction with monitoring for withdrawal symptoms is recommended when discontinuing citalopram therapy. Consider resuming the previously prescribed dose and then discontinuing citalopram therapy at a slower rate if withdrawal symptoms occur [3].

1.3.1.A.1.d) Maximum Dose

1j) Daily doses greater than [citalopram](#) 40 mg are not recommended due to the risk for QT prolongation [3].

1.3.1.A.2] [Coronary arteriosclerosis](#) - Depression

a) Results of a randomized, controlled, 12-week, parallel-group, 2 x 2 factorial study indicate that [citalopram](#), along with weekly clinical management, was effective for the treatment of [major depression](#) in patients with [coronary artery disease](#) (CAD). The Canadian Cardiac Randomized Evaluation of Antidepressant and Psychotherapy Efficacy (CREATE) trial enrolled 284 patients with CAD and a diagnosis of [major depression](#) for 4 weeks or longer. All patients had baseline 24-item Hamilton Depression Rating Scale (HAM-D) scores of 20 or higher. Patients underwent two randomizations: 1) 12 weekly sessions of interpersonal psychotherapy (IPT) plus clinical management (to include semi-structured 20- to 25-minute visits addressing information related to depression and medication use, reassurance, and encouragement to adhere to the medication and study protocol) (n=142) or clinical management only (n=142) and 2) 12 weeks of [citalopram](#) 20 to 40 mg daily (n=142) or placebo (n=142). The primary outcome measure was the change in the HAM-D score from baseline to week 12. The secondary outcome measure was the change in scores of the self-rated [Beck Depression Inventory II](#) (BDI-II) from baseline to week 12. At the end of 12 weeks, [citalopram](#) was superior to placebo in reducing depressive symptoms in all efficacy measures. The mean difference between [citalopram](#) and placebo HAM-D score reduction at week 12 was 3.3 points (96.7% confidence interval (CI), 0.80 to 5.85; p=0.005) with an effect size of 0.33. [Citalopram](#) performed better than placebo in the mean HAM-D response, defined as at least a 50% reduction from baseline (52.8% and 40.1%, respectively; p=0.03), remission, defined as a week-12 HAM-D score of 8 or less (35.9% and 22.5%, respectively; p=0.01), and BDI-II score reduction (difference, 3.6 points; 98.3% CI, 0.58 to 6.64; p=0.005; effect size=0.33). There was no significant difference between IPT plus clinical management and clinical management alone, but HAM-D scores favored clinical management (-2.26 points; 96.7% CI, -4.78 to 0.27; p=0.06; effect size, 0.23). There was no difference between IPT plus clinical management and clinical management alone with regard to difference in BDI-II (1.13 points; 98.3% CI, -1.9 to 4.16; p=0.37; effect size=0.11). Cardiovascular events were not commonly reported during the 12-week study. Side effects that were more commonly reported among patients receiving [citalopram](#) compared to placebo included: dizziness, diarrhea, somnolence, sweating, palpitations, and decreased libido [2].

1.3.1.A.3] [Postmenopausal flushing](#)

a) [Citalopram](#) significantly reduced severity and frequency of hot flash symptoms in postmenopausal women when compared with placebo in a randomized, double-blind placebo-controlled study (n=254). After a one-week baseline recording period, eligible postmenopausal women were randomized to placebo (n=83), [citalopram](#) 10 mg daily (n=54), 20 mg daily (n=56) or 30 mg daily (n=55) for 6 weeks. All participants kept daily diaries to rate hot flash intensity from mild to very severe, and to track the number of hot flashes per day. Baseline daily hot flash score was at least 12 (range, 12 to 17), baseline frequency was at least 8 occurrences per day. A proportion of patients in each arm were taking [tamoxifen](#) (ranging from 6% to 11% of patients) or an aromatase inhibitor (AI, ranging from 16% to 18% of patients), and use was not significantly different among treatment arms. Primary endpoint was evaluated among 44 active-treatment patients and 64 placebo patients. [Citalopram](#) reduced hot flash scores, the primary endpoint, by 7 (49%), 7.7 (50%), 10.7 (55%) in the 10-mg, 20-mg, and 30-mg arms, respectively (p less than 0.002 vs baseline) compared with a decrease of 2 (23%) in the placebo arm. The difference between each [citalopram](#) arm versus placebo was statistically significant (p less than 0.001), and the effects between the different [citalopram](#) doses were not significant. The number of daily hot flash occurrences decreased by 3.6 (46%) in the [citalopram](#)

10-mg arm, 3.9 (46%) in the [citalopram](#) 20-mg arm, 4.5 (50%) in the [citalopram](#) 30-mg arm, and 1.4 (20%) in the placebo arm (p less than 0.001 for each [citalopram](#) arm vs placebo). Similar outcomes were observed when results were stratified by whether patients were taking [tamoxifen](#) or an AI. Self-reported adverse events did not vary significantly between [citalopram](#) arms and placebo. One patient randomized to [citalopram](#) 30 mg daily reported Grade 3 insomnia, three reported Grade 3 sedation; one placebo patient reported Grade 2 sedation [1].

1.3.2] Dosage in [Renal Failure](#)

A) [Citalopram](#) Hydrobromide

1) No dose adjustment is necessary in patients with mild to moderate [renal impairment](#). For patients with severe [renal impairment](#), the manufacturer recommends that [citalopram](#) be used cautiously [3].

2) Less than 15% of an oral dose of [citalopram](#) is excreted unchanged in the urine [36] [37]. However, an additional 20% is excreted as metabolites, some of which are pharmacologically active (albeit less than the parent compound) [37] [10]. These data suggest the potential need for dose adjustments in moderate-to-severe [renal impairment](#); however, studies investigating the pharmacokinetics of the drug in these patients are lacking, as are dose recommendations.

1.3.3] Dosage in [Hepatic Insufficiency](#)

A) [Citalopram](#) Hydrobromide

1) The recommended maximum dose for patients with reduced hepatic function is 20 mg once daily [35].

1.3.4] Dosage in Geriatric Patients

A) [Citalopram](#) Hydrobromide

1) The maximum recommended dose for elderly patients over 60 years of age is 20 mg once daily [35].

1.3.6] Dosage in Other Disease States

A) [Citalopram](#) Hydrobromide

1) CYP2C19 Poor Metabolizers or Concomitant Use with CYP2C19 Inhibitors (including [cimetidine](#))

a) The recommended maximum dose for patients who are poor metabolizers of CYP2C19 or who are taking [cimetidine](#) or another CYP2C19 inhibitor is 20 mg orally daily [3].

1.4] Pediatric Dosage

1.4.1] Normal Dosage

1.4.1.A] [Citalopram](#) Hydrobromide

1.4.1.A.1] Oral route

a) The safety and effectiveness of [citalopram](#) in pediatric patients has not been established [3].

2.0] Pharmacokinetics

Drug Concentration Levels ADME

2.2] Drug Concentration Levels

A)] Citalopram Hydrobromide

1)] Peak Concentration

a)] Citalopram displays linear and dose-proportional pharmacokinetics across the dose range of 10 to 60 mg daily in single- and multiple-dose studies [76].

1)] CYP2C19 Poor Metabolizers

a)] Cmax is increased by approximately 68% in CYP2C19 poor metabolizers compared with healthy volunteers [76].

2)] Time to Peak Concentration

a)] Oral: approximately 4 hours [76]

1)] Following a single-dose study, peak plasma concentrations are achieved about 4 hours after the administration of citalopram 40 mg [76].

3)] Area Under the Curve

a)] Citalopram displays linear and dose-proportional pharmacokinetics across the dose range of 10 to 60 mg daily in single- and multiple-dose studies [76].

1)] CYP2C19 Poor Metabolizers

a)] AUC is increased by approximately 107% in CYP2C19 poor metabolizers compared with healthy volunteers [76].

2)] Elderly (60 years and older)

a)] In a single-dose study, the AUC of citalopram increased 30% in subjects age 60 years and older compared with younger volunteers [76].

b)] In a multiple-dose study, the AUC of citalopram was 23% increased in subjects age 60 years and older compared with younger volunteers [76].

2.3] ADME

2.3.1] Absorption

A)] Citalopram Hydrobromide

1) Bioavailability**a) Oral: 80% [76]**

1) The bioavailability of oral citalopram is 80% of an IV dose [76].

2) Effects of Food**a) No effect on systemic availability [76]**

1) Absorption of citalopram is not effected by food [76].

2.3.2] Distribution**A) Distribution Sites****1) Citalopram Hydrobromide****a) Protein Binding**

1) 80% [76]

a) Citalopram is approximately 80% bound to proteins [76].

B) Distribution Kinetics**1) Citalopram Hydrobromide****a) Volume of Distribution**

1) 12 L/kg [76]

a) The volume of distribution of citalopram is approximately 12 L/kg [76].

2.3.3] Metabolism**A) Metabolism Sites and Kinetics****1) Citalopram Hydrobromide**

a) Liver: mainly, via N-demethylation (CYP3A4 and CYP2C19 isoenzymes), deamination, and N-oxidation [76] [392]

1) Citalopram is mainly biotransformed by the liver [76] primarily via N-demethylation, deamination, and N-oxidation [392].

2)) N-demethylation of citalopram occurs primarily via CYP3A4 and CYP2C19 isoenzymes [76].

B)) Metabolites

1)) Citalopram Hydrobromide

a)) Demethylcitalopram (major): active [76]

1)) The major metabolite of citalopram, demethylcitalopram, is present in plasma at approximately one-half the concentration that of the parent drug at steady-state [76].

2)) In vitro studies suggest that citalopram is at least 8 times more potent than the metabolites at inhibition of serotonin reuptake and that they do not contribute significantly to the efficacy of citalopram [76].

b)) Didemethylcitalopram: active [76].

1)) A metabolite of citalopram, didemethylcitalopram, is present in plasma at approximately one-tenth the concentration that of the parent drug at steady-state [76].

2)) In vitro studies suggest that citalopram is at least 8 times more potent than the metabolites at inhibition of serotonin reuptake and that they do not contribute significantly to the efficacy of citalopram [76].

c)) Citalopram-N-oxide: active [76].

1)) Citalopram is metabolized to demethylcitalopram, didemethylcitalopram, citalopram-N-oxide, and a deaminated propionic acid derivative [76].

2)) In vitro studies suggest that citalopram is at least 8 times more potent than the metabolites at inhibition of serotonin reuptake and that they do not contribute significantly to the efficacy of citalopram [76].

d)) Propionic acid metabolite [76]: inactive [393] [392].

1)) Citalopram is metabolized to demethylcitalopram, didemethylcitalopram, citalopram-N-oxide, and a deaminated propionic acid derivative [76]. The propionic acid metabolite of citalopram is not active in serotonin reuptake inhibition [393] [392].

2)) In vitro studies suggest that citalopram is at least 8 times more potent than the metabolites at inhibition of serotonin reuptake and that they do not contribute significantly to the efficacy of citalopram [76].

2.3.4] Excretion

A)) Kidney

1)) Citalopram Hydrobromide

a) Renal Clearance (rate)

1) 20% [76].

a) Renal clearance accounts for approximately 20% of systemic clearance of citalopram [76].

b) Renal Excretion (%)

1) 10% [76].

a) Approximately 10% of an IV dose of citalopram is recovered unchanged in the urine, with an additional 5% as the primary metabolite, demethylcitalopram [76].

B) Feces**1) Citalopram Hydrobromide**

a) Significant [392] [394].

1) Fecal elimination from enterohepatic circulation may be significant [392] [394].

C) Total Body Clearance**1) Citalopram Hydrobromide**

a) 330 mL/min [76].

1) Systemic clearance of citalopram occurs at 330 mL/min [76].

a) Reduced Hepatic Function

1) Systemic clearance following oral administration of citalopram was reduced by 37% in patients with reduced hepatic function compared with healthy volunteers [76].

b) Reduced Renal Function

1) Systemic clearance following oral administration of citalopram was reduced by 17% in patients with reduced renal function compared with healthy volunteers [76].

2.3.5] Elimination Half-life**A) Parent Compound**

1)) Citalopram Hydrobromide**a)) 35 hours [76]**

1)) The mean half-life of citalopram is 35 hours [76].

b)) increased by 30% (steady-state), elderly (60 years and older) [76]

1)) In a single-dose study, the half-life of citalopram was 50% increased and in a multiple-dose study, the steady-state half-life of citalopram was 30% increased in subjects age 60 years and older compared with younger volunteers [76].

c)) doubled, reduced hepatic function [76]

1)) Following oral administration of citalopram, the half-life was doubled in patients with reduced hepatic function compared with healthy volunteers [76].

2.3.6] Extracorporeal Elimination**A)) Hemodialysis****1)) Citalopram Hydrobromide****a)) Dialyzable: No [76]**

1)) Forced diuresis, dialysis, hemoperfusion, and exchange transfusion are unlikely to be of benefit in an overdose since citalopram has such a large volume of distribution [76].

B)) Hemoperfusion**1)) Citalopram Hydrobromide****a)) Dialyzable: No [76]**

1)) Forced diuresis, dialysis, hemoperfusion, and exchange transfusion are unlikely to be of benefit in an overdose since citalopram has such a large volume of distribution [76].

C)) Exchange Transfusion**1)) Citalopram Hydrobromide****a)) Dialyzable: No [76]**

1)) Forced diuresis, dialysis, hemoperfusion, and exchange transfusion are unlikely to be of benefit in an overdose since citalopram has such a large volume of distribution [76].

3.0] Cautions

[Contraindications](#)

[Precautions](#)

[Adverse Reactions](#)

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

[Drug Interactions](#)

3.0.A] Black Box WARNING

Citalopram Hydrobromide

Oral (Tablet; Solution)

Antidepressants increased the risk of suicidal thinking and behavior in children, adolescents, and young adults in short-term studies with major depressive disorder (MDD) and other psychiatric disorders. Short term studies did not show an increase in the risk of suicidality with antidepressants compared with placebo in adults beyond age 24, and there was a reduction in risk with antidepressants compared with placebo in adults aged 65 or older. This risk must be balanced with the clinical need. Monitor patients 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. Not approved for use in pediatric patients [38].

3.1] Contraindications

A) [Citalopram](#) Hydrobromide

- 1) concomitant use with an MAOI, including [linezolid](#) or IV methylene blue, or use within 14 days of discontinuing an MAOI used to treat psychiatric disorders due to increased risk of [serotonin syndrome](#) [38]
- 2) concomitant use with [pimozide](#) [38]
- 3) hypersensitivity to [citalopram](#) or any other component of the product [38]

3.2] Precautions

A) [Citalopram](#) Hydrobromide

- 1) Black Box Warning:
- 2)-- increased risk of suicidality or worsening depression, especially in children, adolescents, and young adults during first few months of therapy or dose adjustments; monitoring recommended and discontinuation may be required [38]
- 3) Cardiovascular:
- 4) -- dose-dependent QT-interval prolongation, including [torsade de pointes](#), has been reported; use of doses greater than 40 mg/day is not recommended; monitoring recommended and discontinuation may be necessary [35]

5)) -- avoid use in patients with congenital [long QT syndrome](#), bradycardia, recent cardiovascular infarction, or uncompensated [heart failure](#) due to an increased risk for QT-interval prolongation; monitoring recommended when therapeutic use is clinically necessary [38]

6)) -- QTc interval persistently greater than 500 milliseconds; discontinue therapy [35]

7)) Endocrine Metabolic:

8)) -- avoid use in patients with hypokalemia or hypomagnesemia; baseline screening and monitoring recommended in patients predisposed to significant electrolyte disturbances due to increased risk of QT-interval prolongation [38]

9)) -- [hyponatremia](#), usually the result of SIADH, has occurred, especially in volume-depleted and elderly patients or with concurrent diuretic therapy; discontinue if symptoms develop [38]

10)) Hematologic:

11)) -- bleeding events, including life-threatening hemorrhages, have been reported with SSRIs and serotonin [norepinephrine](#) reuptake inhibitors; concomitant use of NSAIDs, [aspirin](#), [warfarin](#), and other anticoagulants may increase this risk [38]

12)) Hepatic:

13)) -- limit dose to 20 mg/day in patients with [hepatic impairment](#) due to higher drug exposure and increased risk for QT-interval prolongation [38]

14)) Neurologic:

15)) -- use with caution in patients with history of seizures [38]

16)) Ophthalmic:

17)) -- worsening of [angle-closure glaucoma](#) may occur in patients with anatomically narrow angles without [iridectomy](#) [38]

18)) Psychiatric:

19)) -- antidepressant therapy may trigger a mixed/[manic episode](#) in patients with underlying [bipolar disorder](#); baseline screening recommended [38]

20)) Renal:

21)) -- use with caution in patients with severe [renal impairment](#) [38]

22)) Other:

23)) -- CYP2C19 poor metabolizers are at risk for QT prolongation; use of doses greater than 20 mg/day not recommended [38]

24)) -- life-threatening [serotonin syndrome](#) has been reported, often during concurrent use with other serotonergic drugs (ie, triptans, tricyclic antidepressants, [fentanyl](#), [lithium](#), [tramadol](#), [buspirone](#), tryptophan, St John's wort) or serotonin inhibitors (ie, MAOIs, [linezolid](#), methylene blue); monitoring recommended and discontinue if suspected [38]

25)) -- limit dose in geriatric patients, older than 60 years of age, to 20 mg/day due to higher drug exposure and increased risk for QT-interval prolongation [38]

26)) -- serious withdrawal symptoms upon abrupt discontinuation have been reported; gradual withdrawal and monitoring recommended when possible [38]

27)) -- [hypomania](#) or mania have been reported; use caution in patients with history of mania [38]

28)) Concomitant Use:

29)) -- avoid QT-interval prolonging drugs, including class 1A (eg, [quinidine](#), [procainamide](#)) or class III (eg, [sotalol](#), [amiodarone](#)) antiarrhythmics, antipsychotics (eg, [thioridazine](#), [chlorpromazine](#)), antibiotics (eg, [moxifloxacin](#), [gatifloxacin](#)), or other drug classes (eg, [methadone](#), [levomethadyl acetate](#), [pentamidine](#)) [38]

30)) -- avoid alcohol [38]

3.3] Adverse Reactions

3.3.1] Cardiovascular Effects

3.3.1.A] [Citalopram Hydrobromide](#)

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

a)) Incidence: 0.1% to 1% [3]

b)) Adult Clinical Trials

1)) [Major depression](#) (oral): 0.1% to 1% of patients treated with multiple [citalopram](#) doses of 10 to 80 mg/day during any phase of a trial [3]

2)) [Major depression](#), QT prolongation study (oral): 0.9% vs 0.4% with placebo (decrease of heart rate to less than 50 beats/min with a 25% change from baseline) [3]

3)) Worsening of preexisting bradycardia (pretreatment heart rate 48 to 60 beats/min) has been reported [44] [45] [46]

c)) Adult Case Report

1)) A 60-year-old woman experienced an episode of syncope within 2 weeks of [citalopram](#) initiation. She was found to have [sinus bradycardia](#) (50 beats/min), with a blood pressure of 105/57 mmHg and no evidence of QT prolongation or other [heart abnormalities](#). Her medications at the time of presentation were [omeprazole](#) 20 mg/day, [alprazolam](#) 1 mg as needed for anxiety, and [citalopram](#) 20 mg/day. [Citalopram](#) was discontinued, and 48 hours later, her heart rate was 66 beats/min and her blood pressure was 120/70 mmHg. According to the Naranjo probability scale, her experience was probably caused by [citalopram](#) [47].

3.3.1.A.2] [Hypotension](#)

a)) Incidence: at least 1% [40]

b)) Adult Clinical Trials

1)) [Major depression](#) (oral): at least 1% of patients treated with multiple [citalopram](#) doses of 10 to 80 mg/day during any phase of a trial [40]

3.3.1.A.3] Lightheadedness

- a) Orthostatic dizziness has also been reported in some patients [44] [46] [44].

3.3.1.A.4] Myocardial infarction

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

- b) Adult Clinical Trials

- 1) **Major depression** (oral): 0.1% to 1% of patients treated with multiple **citalopram** doses of 10 to 80 mg/day during any phase of a trial [40]

3.3.1.A.5] Orthostatic hypotension

- a) Incidence: at least 1% [40]

- b) Adult Clinical Trials

- 1) **Major depression** (oral): at least 1% of patients treated with multiple **citalopram** doses of 10 to 80 mg/day during any phase of a trial [40]

3.3.1.A.6] Prolonged QT interval

- a) Incidence: 0.5% to 1.9% [3]

- b) General Information

- 1) Occurs in a dose-dependant manner [3]

- c) Prevention and Management

- 1) Do not exceed **citalopram** 40 mg/day or administer to patients with congenital **long QT syndrome** [3]

- 2) Higher **citalopram** exposure and risk would be expected in CYP2C19 poor metabolizers and patients taking concomitant **cimetidine** or other CYP2C19 inhibitors [3]

- 3) Prior to therapy initiation, correct hypokalemia and hypomagnesemia and monitor periodically for recurrence [3]

- 4) Patients with **congestive heart failure**, **bradyarrhythmias**, or who receive other QT-prolonging drugs should have **ECG monitoring** while receiving **citalopram** [3]

- d) Adult Clinical Trials

- 1) **Major depression**, QT prolongation study (oral): change from baseline in QTcF of greater than 60 milliseconds (msec), 1.9% vs 1.2% with placebo; postdose QTcF of greater than 500 msec, 0.5% vs 0% with placebo [3]

- 2) Healthy volunteers (oral): mean QTc increase was 8.5 milliseconds (msec) with 20 mg/day, 12.6 seconds with 40 mg/day and 18.5 msec with 60 mg/day [3]

- e) Pharmacovigilance Study

- 1) **Citalopram** had a dose-related association with QT prolongation in a pharmacovigilance study of 38,397 patients treated with antidepressants. Review of adults (mean age 58.3 years; 60% female) within a large electronic health record system identified 9777 patients taking **citalopram** with an ECG measured within 14 to 90 days after the prescription issuance. After

adjustment for multiple factors, including age, gender, and history of [myocardial infarction](#), [ventricular arrhythmia](#), or [hypertension](#), a dose response association with QTc prolongation was identified for [citalopram](#). Significant increases in QTc were observed with [citalopram](#) dose escalation from 10 to 20 mg and from 40 to 60 mg. When evaluating the within-patient mean QTc increase with dose escalation, significant QTc increases were observed after a [citalopram](#) dose escalation from 10 to 20 mg (n=59; 7.8 milliseconds) and from 20 to 40 mg (n=107; 10.3 milliseconds) [41].

3.3.1.A.7] Syncope

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

b) Adult Clinical Trials

1) [Major depression](#) (oral): 0.1% to 1% of patients treated with multiple [citalopram](#) doses of 10 to 80 mg/day during any phase of a trial [40]

3.3.1.A.8] Tachycardia

a) Incidence: 0.5% to 1% [3]

b) Adult Clinical Trials

1) [Major depression](#) (oral): at least 1% of patients treated with [citalopram](#) 10 to 80 mg/day during any phase of a trial [3]

2) [Major depression](#), QT prolongation study (oral): 0.5% vs 0.4% with placebo (heart rate increases to over 100 beats/min) [3]

3.3.1.A.9] Torsades de pointes

a) Adult Case Reports and Postmarketing

1) Pharmacovigilance Study

a) A review of the Swedish pharmacovigilance database (SWEDIS) found [citalopram](#) to be the third most common drug implicated in cases of [torsade de pointes](#). A total of 88 cases of [torsades de pointes](#) were identified from the database over 15 years (median subject age, 74 years; range, 15 to 90 years; 70% female). [Sotalol](#) was implicated in 66%, [digoxin](#) in 11%, and [citalopram](#) in 10% of cases. In addition to the 9 cases in which [citalopram](#) was the single suspected agent, [citalopram](#) was also found to be a concomitant medication in 5 additional cases. Concomitant use of several medications was identified frequently, and patients were prescribed 6 or more medications in 51% of identified cases. In addition to medication-related risks, 85% of cases had 2 or more additional risk factors, including [heart disease](#) (most common; 90% of cases), age over 65 years, female gender, and hypokalemia [42].

2) Postmarketing

a) [Torsade de pointes](#) has been reported during postmarketing use [3].

3) Adult Case Report

a)] **Torsades de pointes** occurred in a 81-year-old man within 4 months **citalopram** use. The patient was admitted to the emergency room for dizziness following dialysis. All vital signs, physical examination, serum tests, and blood counts were within normal limits. In the emergency room the patient experienced an episode of **torsade de pointes**, ECG showed prolonged QT interval of 572 milliseconds (msec) and QTc interval of 695 msec. After admission to the floor, the patient experienced another episode. Magnesium and **isoproterenol** were administered. The patient had no prior history of abnormal QTc intervals. Upon discontinuing **citalopram**, several ECGs indicated normal QT intervals within 3 days [43].

3.3.2] Dermatologic Effects

3.3.2.A] **Citalopram Hydrobromide**

3.3.2.A.1] **Diaphoresis**

- a)] Incidence: 5% to 18% [40] [45] [49] [48]
- b)] Increased sweating has been reported in 11% of patients treated with **citalopram** doses of 10 to 80 mg/day (n=1063) and 9% of those treated with placebo (n=446) in placebo-controlled trials of up to 6 weeks in duration. There was a positive dose response (p less than 0.05) between **citalopram** dose and increased sweating according to Jonckheere's trend test in a fixed-dose study of depressed patients treated with either **citalopram** 20, 40, and 60 mg or placebo [40].
- c)] Increased perspiration has been reported in approximately 18% of over 700 depressed patients treated with **citalopram** in a meta-analysis [45].
- d)] Increased perspiration was also reported in 11.3% of patients treated with **citalopram** in a double-blind, placebo-controlled study (n=1083) [49] [48].

3.3.2.A.2] **Hyperpigmentation of skin**

- a)] A 50-year-old woman developed **hyperpigmentation** in sun-exposed areas of her skin during 8 months of taking **citalopram** 40 mg/day for depression. She had no previous history of reaction to sunlight. There was no itching, **excoriation**, or **xerosis**. A punch biopsy showed an atrophic epidermis and sun- damaged collagen throughout the dermis. Six months after discontinuation of **citalopram** and avoidance of the sun, the pigmentation had partially regressed [63].

3.3.2.A.3] **Pruritus**

- a)] Incidence: At least 1% [40]
- b)] **Pruritus** has been reported in at least 1% of patients treated with multiple **citalopram** doses of 10 to 80 mg/day during any phase of a trial within the premarketing database (n=4422); causality has not been established [40].

3.3.2.A.4] **Rash**

- a)] Incidence: At least 1% [40]
- b)] Rash has been reported in at least 1% of patients treated with multiple **citalopram** doses of 10 to 80 mg/day during any phase of a trial within the premarketing database (n=4422); causality has not been established [40].

3.3.3] Endocrine/Metabolic Effects

3.3.3.A] Citalopram Hydrobromide

3.3.3.A.1] Blood glucose normal

a) Glycemic control in patients with [diabetic neuropathy](#) was not altered by [citalopram](#) therapy in one placebo-controlled study [56].

3.3.3.A.2] Hyponatremia

a) [Hyponatremia](#) may occur following treatment with SSRIs and SNRIs, including [citalopram](#). Signs and symptoms of [hyponatremia](#) include headache, difficulty concentrating, [memory impairment](#), confusion, weakness, and unsteadiness. Signs and symptoms associated with more severe and/or acute cases have included hallucination, syncope, seizure, coma, respiratory arrest, and death. In many cases, [hyponatremia](#) appeared to result from syndrome of [inappropriate antidiuretic hormone secretion](#) (SIADH), and was reversible after [citalopram](#) discontinuation. Cases with serum sodium below 110 mmol/L have been reported. There may be an increased risk of [hyponatremia](#) in patients who are elderly, taking diuretics, or volume-depleted. Consider discontinuation of [citalopram](#) in the event of symptomatic [hyponatremia](#) [40].

b) Summary

1) [Hyponatremia](#) may occur following treatment with [citalopram](#) with SSRIs and SNRIs, including [citalopram](#) [40]. [Hyponatremia](#), including one case leading to prolonged coma, has been reported [57] [58]. In many cases, [hyponatremia](#) appeared to result from syndrome of [inappropriate antidiuretic hormone secretion](#) (SIADH), and was reversible after [citalopram](#) discontinuation. There may be an increased risk of [hyponatremia](#) in patients who are elderly, taking diuretics, or volume-depleted. Consider discontinuation of [citalopram](#) in the event of symptomatic [hyponatremia](#) [40].

c) A 78-year-old woman developed the syndrome of [inappropriate secretion of antidiuretic hormone](#) (SIADH) with resultant [hyponatremia](#) 4 to 6 days after starting treatment with [citalopram](#) 10 mg/day for depression. At hospitalization, on day 6 of treatment, she was lethargic and disoriented and had been vomiting. Her serum sodium concentration was 113 mmol/L. [Citalopram](#) treatment was discontinued, and she was treated with water restriction, infusion of 3% [sodium chloride](#) at a rate of 0.5 mL/min and subsequently with infusion of isotonic saline. The lethargy gradually improved, vomiting stopped, and she became oriented. She was released after 4 days, with a serum sodium concentration of 130 mmol/L [58].

d) Prolonged coma secondary to [hyponatremia](#) occurred in a 47-year-old woman with [multiple sclerosis](#) receiving [citalopram](#) for an adjustment disorder with depressive symptoms. The patient had started [citalopram](#) on a dose of 10 mg/day; the dose was increased to 20 mg/day after the first week. Four weeks after starting [citalopram](#), the patient was found unconscious in her apartment and transported to the hospital. Thirty hours prior, she had been seen outside and appeared healthy. It was estimated that she was comatose for approximately 24 hours before being admitted. Laboratory results showed low serum sodium levels of 108 mmol/L (normal: greater than 135 mmol/L), low serum osmolality of 246 mOsm/kg (normal: greater than 281 mOsm/kg), elevated [serum creatine phosphokinase](#) of 3228 units/L; (normal: less than 70 units/L), elevated serum myoglobin of 4626 nanograms (ng)/mL (normal: less than 90 ng/mL), and elevated C-reactive protein of 180 mg/L (upper limit: 5 mg/L). The latter findings were thought to be consistent with [rhabdomyolysis](#). Treatment consisted of saline infusions. On day 3, [endotracheal intubation](#) was removed; the patient seemed somnolent, confused, and disoriented. Serum sodium reached normal levels on day 4. She recovered and was discharged on day 19 [57].

3.3.3.A.3] Weight gain

- a) Incidence: At least 1% [40]
- b) Increased weight has been reported in at least 1% of patients treated with multiple [citalopram](#) doses of 10 to 80 mg/day during any phase of a trial within the premarketing database (n=4422); causality has not been established [40].

3.3.3.A.4] Weight loss

- a) Incidence: At least 1% [40]
- b) A weight loss of 0.5 kg has been reported in patients treated with [citalopram](#) compared to no change in those treated with placebo group in controlled trials. Decreased weight has been reported in at least 1% of patients treated with multiple [citalopram](#) doses of 10 to 80 mg/day during any phase of a trial within the premarketing database (n=4422); causality has not been established [40].

3.3.4] Gastrointestinal Effects

3.3.4.A] [Citalopram](#) Hydrobromide

3.3.4.A.1] Abdominal pain

- a) Incidence: 3% [40]
- b) Abdominal pain has been reported in 3% of patients treated with [citalopram](#) doses of 10 to 80 mg/day (n=1063) and 2% of those treated with placebo (n=446) in placebo-controlled trials of up to 6 weeks in duration [40].

3.3.4.A.2] Constipation

- a) Incidence: 13% [45]
- b) Constipation was reported in 13% of patients treated with [citalopram](#) in a meta-analysis of [citalopram](#) therapy [45].

3.3.4.A.3] Diarrhea

- a) Incidence: 8% [40]
- b) Diarrhea has been reported in 8% of patients treated with [citalopram](#) doses of 10 to 80 mg/day (n=1063) and 5% of those treated with placebo (n=446) in placebo-controlled trials of up to 6 weeks in duration [40].

3.3.4.A.4] [Gastrointestinal hemorrhage](#)

See Drug Consult reference: CONCOMITANT USE OF SSRIs AND NSAIDs - INCREASED RISK OF [GASTROINTESTINAL BLEEDING](#)

3.3.4.A.5] [Grinding teeth](#)

- a) Incidence: 0.1% to 1% [40]
- b) [Teeth grinding](#) has been reported in 0.1% to 1% of patients treated with multiple [citalopram](#) doses of 10 to 80 mg/day during any phase of a trial within the premarketing database (n=4422); causality has not been established [40].
- c) Nocturnal SSRI-associated [bruxism](#) occurred in two patients taking [citalopram](#). In one patient oral [citalopram](#) 20 mg/day was prescribed and the dose was increased to 40 mg/day six weeks later. Ten days after the dose increase, [nocturnal bruxism](#) resulted in removal of a molar. Oral [buspirone](#)

was prescribed (dosage not reported) and the [bruxism](#) ceased. A second patient was prescribed oral [citalopram](#) 40 mg/day and oral [buspirone](#) 10 mg twice daily for moderate depression and somatic symptoms. Four months later, the [buspirone](#) was discontinued and three weeks after discontinuation of [buspirone](#) therapy the patient reported [nocturnal bruxism](#). The [citalopram](#) was reduced to 20 mg/day and the [bruxism](#) stopped [59].

3.3.4.A.6] Indigestion

a) Incidence: 5% [40]

b) [Dyspepsia](#) has been reported in 5% of patients treated with [citalopram](#) doses of 10 to 80 mg/day (n=1063) and 4% of those treated with placebo (n=446) in placebo-controlled trials of up to 6 weeks in duration [40].

c) [Dyspepsia](#) has been reported less frequently following [citalopram](#) therapy [45]

3.3.4.A.7] Loss of appetite

a) Incidence: 4% [40]

b) Anorexia has been reported in 4% of patients treated with [citalopram](#) doses of 10 to 80 mg/day (n=1063) and 2% of those treated with placebo (n=446) in placebo-controlled trials of up to 6 weeks in duration [40].

3.3.4.A.8] Nausea

a) Incidence: 20% to 21% [40] [45]

b) Nausea has been reported in 21% of patients treated with [citalopram](#) doses of 10 to 80 mg/day (n=1063) and 14% of those treated with placebo (n=446) in placebo-controlled trials of up to 6 weeks in duration. Nausea was associated with discontinuation in 4% and 0% of those treated with [citalopram](#) and placebo, respectively [40].

c) Nausea was reported in 20% of patients treated with [citalopram](#) in a meta-analysis of [citalopram](#) therapy [45]

3.3.4.A.9] Summary

a) Gastrointestinal symptoms have tended to lessen with continued therapy [45] [49].

3.3.4.A.10] Vomiting

a) Incidence: 4% to 20% [40] [45]

b) Vomiting has been reported in 4% of patients treated with [citalopram](#) doses of 10 to 80 mg/day (n=1063) and 3% of those treated with placebo (n=446) in placebo-controlled trials of up to 6 weeks in duration. Vomiting was associated with discontinuation in 1% and 0% of those treated with [citalopram](#) and placebo, respectively [40].

c) Vomiting was reported in 20% of patients treated with [citalopram](#) in a meta-analysis of [citalopram](#) therapy [45]

3.3.4.A.11] Xerostomia

a) Incidence: 17% to 20% [40] [45]

b) Dry mouth has been reported in 20% of patients treated with [citalopram](#) doses of 10 to 80 mg/day (n=1063) and 14% of those treated with placebo (n=446) in placebo-controlled trials of up to 6 weeks in duration. Dry mouth was associated with discontinuation in 1% and less than 1% of those treated with [citalopram](#) and placebo, respectively [40].

c) Dry mouth was reported in 20% of patients treated with [citalopram](#) in a meta-analysis of [citalopram](#) therapy [45]

3.3.5] Hematologic Effects

3.3.5.A] [Citalopram](#) Hydrobromide

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

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

b) [Anemia](#) has been reported in 0.1% to 1% of patients treated with multiple [citalopram](#) doses of 10 to 80 mg/day during any phase of a trial within the premarketing database (n=4422); causality has not been established [40].

3.3.5.A.2] [Immune thrombocytopenia](#) (Severe)

a) A 32-year-old woman developed severe [immune thrombocytopenia](#) within 4 weeks after the initiation of [citalopram](#) 40 mg/day for the treatment of depression. The patient was receiving [mirtazapine](#) 45 mg/day for depression and was self-medicating with vitamin B12 and not taking other medications, herbal remedies or herbal food. After 3 months of treatment with [mirtazapine](#), the patient did not achieve a clinical response and was initiated on cross-titration to [citalopram](#). When the [citalopram](#) dose titration reached 40 mg/day, the [mirtazapine](#) was discontinued. Three weeks later, the patient noticed [petechiae](#) under the tongue and on the lower legs and after 6 days, the patient was hospitalized because of abnormal vaginal bleeding. [Blood chemistry](#) analysis revealed severe [thrombocytopenia](#) with a [platelet](#) count of 4000 per mcL and elevated rheumatoid factor of 34 international units/mL (normal value is less than 14 international units/mL). Bone marrow investigation showed an increased megakaryopoiesis (compatible with [immune thrombocytopenia](#)) without other alterations. The [citalopram](#) was discontinued and the patient received 2 [transfusions of platelet concentrates](#). Therapy with [prednisolone](#) 100 mg/day was initiated and after 5 days the [platelet](#) count had increased to 50,000/mcL and the bleeding resolved. Three days after being discharged from the hospital, the [platelet](#) count was 109,000/mcL and after 1 week, the [platelet](#) count was normalized at greater than 150,000/mcL. The patient was started on [venlafaxine](#) for depression and the [prednisolone](#) was slowly tapered and discontinued after 2 months. Over the following 10 months of [observation](#) the [platelet count](#) remained higher than 230,000/mcL [39].

3.3.5.A.3] [Leukocytosis](#)

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

b) [Leukocytosis](#) has been reported in 0.1% to 1% of patients treated with multiple [citalopram](#) doses of 10 to 80 mg/day during any phase of a trial within the premarketing database (n=4422); causality has not been established [40].

3.3.5.A.4] [Purpura](#)

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

b) [Purpura](#) has been reported in 0.1% to 1% of patients treated with multiple [citalopram](#) doses of 10 to 80 mg/day during any phase of a trial within the premarketing database (n=4422); causality has not been established [40].

3.3.6] Hepatic Effects

3.3.6.A] [Citalopram](#) Hydrobromide

3.3.6.A.1] Increased liver enzymes

a)] Elevations of serum transaminases have occurred in a few patients treated with oral [citalopram](#) [50] [61], although a causal relationship to the drug is doubtful. No significant alterations in liver enzymes were reported in a meta-analysis of clinical studies including over 1000 depressed patients [45].

3.3.7] Immunologic Effects

3.3.7.A] [Citalopram](#) Hydrobromide

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

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

b)] [Lymphadenopathy](#) has been reported in 0.1% to 1% of patients treated with multiple [citalopram](#) doses of 10 to 80 mg/day during any phase of a trial within the premarketing database (n=4422); causality has not been established [40].

3.3.8] Musculoskeletal Effects

3.3.8.A] [Citalopram](#) Hydrobromide

3.3.8.A.1] Arthralgia

a)] Incidence: 2% [40]

b)] Arthralgia has been reported in 2% of patients treated with [citalopram](#) doses of 10 to 80 mg/day (n=1063) and 1% of those treated with placebo (n=446) in placebo-controlled trials of up to 6 weeks in duration [40].

3.3.8.A.2] Fracture of bone

a)] In a case-control study including fracture cases (n=124,655) during the year 2000 and age- and gender-matched controls (n=373,962), there was an increased risk of any fracture in participants who were using an average standard daily dose of [citalopram](#) (adjusted odds ratio (OR), 1.38; 95% confidence interval (CI), 1.33 to 1.44) compared to those who were not exposed to [citalopram](#). [Citalopram](#) use was associated with an increased risk of hip fracture (adjusted OR, 1.98; 95% CI, 1.82 to 2.16), [forearm fracture](#) (adjusted OR, 1.61; 95% CI, 1.44 to 1.79), and [spine fracture](#) (adjusted OR, 1.6; CI, 1.31 to 1.95) [65].

b)] In a population-based, randomly selected, prospective cohort study adjusted for potential covariates, an increased risk of fragility fracture was reported at the 5-year follow-up in patients 50 years of age and older who used daily SSRIs (n=137; mean age of 65.1 years), including [citalopram](#), compared with those who did not use an SSRI (n=4871; mean age of 65.7 years). Daily SSRI use was associated with a significant 2.1-fold increased risk of fragility fracture (95% confidence interval (CI), 1.3 to 3.4). Daily dose of SSRI use was associated with a 1.5-fold increased risk of fragility fracture (95% CI, 1.1 to 2.1). Daily SSRI users who were recurrent (ie, treated with SSRIs at baseline and at 5-year follow-up) had a significant 2.1-fold increased risk of fragility fracture (95% CI, 1.1 to 4.0). Fractures were reported at the following sites: forearm (40%), ankle and foot (21%), hip (13%), rib (13%), femur (9%), and back (4%). None were reported at the skull, toes, or fingers [66].

3.3.8.A.3] Fracture of bone, Nonvertebral

a)] In a prospective, population-based, cohort study (n=7983) with a mean follow-up of 8.4 years, there 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 [64].

3.3.8.A.4] Myalgia

a) Incidence: 2% [40]

b) Myalgia has been reported in 2% of patients treated with citalopram doses of 10 to 80 mg/day (n=1063) and 1% of those treated with placebo (n=446) in placebo-controlled trials of up to 6 weeks in duration [40].

3.3.9] Neurologic Effects

3.3.9.A] Citalopram Hydrobromide

3.3.9.A.1] Cerebrovascular accident

a) Incidence: 0.1% to less than 1% [38]

b) Adult Clinical Trials

1) Depression (oral route): 0.1% to less than 1% [38]

3.3.9.A.2] Dizziness

a) Incidence: 14% [44] [45] [48] [49] [50]

b) General Information

1) Reason for treatment discontinuation in 2% of patients vs less than 1% with placebo [38]

c) Adult Clinical Trials

1) Depression (oral route): 14% in a meta-analysis [44] [45] [48] [49] [50]

3.3.9.A.3] Dystonia

a) Incidence: Less than 1% [55]

b) General Information

1) Onset occurred a mean of 9 days (range, 6 to 17) after initiation, at a median dose of 27 mg/day, and patients had a mean age of 29 years [55].

2) Biperiden 5 mg IM given in all cases in a retrospective review and resulted in full recovery after the first or second injection [55]

c) Adult Clinical Trials

1) Depressive and anxiety disorders (oral route): Acute dystonia, 9 of 1875 (0.5%) [55]

3.3.9.A.4] Headache

a) Incidence: 18% [44] [45] [48] [49] [50]

b) Adult Clinical Trials

1) Depression (oral route): 18% in a meta-analysis [44] [45] [48] [49] [50]

3.3.9.A.5] Insomnia

a) Incidence: 15% [38]

b) General Information

1) Dose related [38]

2) Discontinuation due to insomnia, 3% vs 1% with placebo [38]

c) Adult Clinical Trials

1) Depression (oral route): 15% vs 14% with placebo [38]

3.3.9.A.6] Restless legs syndrome**a) General Information**

1) Symptoms occurred early in treatment (median of 2.5 days; range, 1 to 23 days) in a study of various antidepressants [51].

b) Adult Clinical Trials

1) Depression (oral route): New or worsening symptoms of **restless leg syndrome** occurred in 9% of patients receiving antidepressant therapy with **citalopram**, escitalopram, **duloxetine**, **fluoxetine**, **paroxetine**, **sertraline**, or **venlafaxine** [51]

c) Adult Case Reports

1) A 48-year-old woman with a history of major depressive disorder developed **restless legs syndrome** (RLS) immediately after **paroxetine** initiation, which worsened during treatment with **citalopram**. After 3 weeks of use, **paroxetine** was replaced by **citalopram** 20 mg daily, which was titrated to 60 mg daily in 1 week. At that time, an unpleasant sensation in her legs during the night dramatically worsened with symptoms occurring during each period of inactivity, extending to the arms after 1 week. At a psychiatric emergency unit, she presented with motor restlessness, nocturnal worsening of symptoms, association between the desire to move the limbs and paresthesia or dysesthesia, and worsening of symptoms during rest and partial relief with activity; International Restless Leg Syndrome Study Group (IRLSSG) rating scale score was 30 (maximum score, 40). Within 3 days of **citalopram** discontinuation and initiation of **bupropion** 150 mg daily and **sertraline** 50 mg daily, RLS symptoms started to diminish, and were completely resolved after 3 weeks [52].

3.3.9.A.7] Sedated

a) Incidence: 15% [44] [45] [48] [49] [50]

b) Adult Clinical Trials

1) Depression (oral route): 15% in a meta-analysis [44] [45] [48] [49] [50]

3.3.9.A.8] Seizure

a) Incidence: 0.3% [38]

b) Prevention and Management

- 1)) Use caution in patients who have a history of seizure disorder [38].
- c)) Adult Clinical Trials

1)) Depression (oral route): 0.3% (rate of 1 patient per 98 years of exposure) vs 0.5% (1 patient per 50 years of exposure) with placebo [38]

3.3.9.A.9] Somnolence

- a)) Incidence: 18% [38]
- b)) General Information

1)) Dose related [38]

2)) Discontinuation due to somnolence, 2% vs 1% with placebo [38]

- c)) Adult Clinical Trials

1)) Depression (oral route): 18% vs 10% with placebo [38]

3.3.9.A.10] Tremor

- a)) Incidence: 8% to 16% [38] [45]
- b)) Adult Clinical Trials

1)) Depression (oral route): 8% vs 6% with placebo [38]

2)) Depression (oral route): 16% in a meta-analysis [44] [45] [48] [49] [50]

- c)) Adult Case Reports

1)) Tremor associated with [Parkinson's disease](#) was worsened in a woman who was treated for depression with [citalopram](#) 20 mg/day. Two days after starting [citalopram](#), the woman noticed markedly increased duration of tremor. Over 2 months, her symptoms worsened. Other possible causes of the exacerbation were ruled out. [Citalopram](#) was stopped, and within 1 month, her motor status scores and tremor score had clearly improved [54].

3.3.9.A.11] Yawning

- a)) Incidence: 2% [38]
- b)) General Information

1)) Dose related [38]

- c)) Adult Clinical Trials

1)) Depression (oral route): 2% vs less than 1% with placebo [53]

3.3.10] Ophthalmic Effects

3.3.10.A] [Citalopram Hydrobromide](#)

3.3.10.A.1] [Angle-closure glaucoma](#), Worsening

- a)) General Information

1)) Angle closure episodes may occur in patients with anatomically narrow angles without patent [iridectomy](#) [38]

b) Prevention and Management

- 1) Consider examination to determine susceptibility to angle-closure. Prophylactic procedures such as an [iridectomy](#) may be considered in susceptible individuals [38]

c) Adult Postmarketing

- 1) Reported in postmarketing surveillance [38]

3.3.10.A.2] [Glaucoma](#)

a) [Glaucoma](#) has been reported during postmarketing use of [citalopram](#); causality cannot be established [40].

b) A 34-year-old man developed acute [myopia](#) and acute [glaucoma](#) following treatment with [topiramate](#) for migraine with and without aura while taking [citalopram](#) (20 mg daily for 2 months) for anxious-depressive syndrome. He was prescribed [topiramate](#) 25 mg/day, with a dose increase of 25 mg/day every 15 days up to a dose of 100 mg/day. Within 7 days following the initiation of [topiramate](#), the patient experienced blurred vision, ocular pain, confirmed ocular pressure of 40 mmHg in both eyes, anterior chamber shallowing, [hyperaemia](#) of the sclera, and light [corneal edema](#). Severe acute [glaucoma](#) and [myopia](#) (right eye = -5,5 diopters, left eye = -5 diopters) were confirmed. Plasma [topiramate](#) concentration of 1.7 mcg/mL was below the therapeutic range of 2 to 25 mcg/mL. [Topiramate](#) was immediately discontinued and antiglaucoma therapy ([acetazolamide](#), [latanoprost](#), [timolol](#) and [pilocarpine](#)) was initiated. Within 2 days, the patient's ocular pressure had decreased to 14 mmHg in his right eye and 17 mmHg in his left eye. Four days later, his anterior chamber depth returned to normal, and ocular tone decreased to 10 mmHg in both eyes. Full resolution was achieved 8 days after discontinuation of [topiramate](#), during which the patient had a visus of 10/10 bilaterally, normalized fundus oculi and ocular pressure. Although the exact mechanism of this side effect is unknown, it has been hypothesized that SSRI can strengthen the uveal effusion of [topiramate](#), thereby increasing the risk of developing of [glaucoma](#). In this patient, both [topiramate](#) and [citalopram](#) may attribute to the increase in intraocular pressure and subsequently [glaucoma](#) [62].

3.3.10.A.3] [Myopia](#)

a) A 34-year-old man developed acute [myopia](#) and acute [glaucoma](#) following treatment with [topiramate](#) for migraine with and without aura while taking [citalopram](#) (20 mg daily for 2 months) for anxious-depressive syndrome. He was prescribed [topiramate](#) 25 mg/day, with a dose increase of 25 mg/day every 15 days up to a dose of 100 mg/day. Within 7 days following the initiation of [topiramate](#), the patient experienced blurred vision, ocular pain, confirmed ocular pressure of 40 mmHg in both eyes, anterior chamber shallowing, [hyperaemia](#) of the sclera, and light [corneal edema](#). Severe acute [glaucoma](#) and [myopia](#) (right eye = -5,5 diopters, left eye = -5 diopters) were confirmed. Plasma [topiramate](#) concentration of 1.7 mcg/mL was below the therapeutic range of 2 to 25 mcg/mL. [Topiramate](#) was immediately discontinued and antiglaucoma therapy ([acetazolamide](#), [latanoprost](#), [timolol](#) and [pilocarpine](#)) was initiated. Within 2 days, the patient's ocular pressure had decreased to 14 mmHg in his right eye and 17 mmHg in his left eye. Four days later, his anterior chamber depth returned to normal, and ocular tone decreased to 10 mmHg in both eyes. Full resolution was achieved 8 days after discontinuation of [topiramate](#), during which the patient had a visus of 10/10 bilaterally, normalized fundus oculi and ocular pressure. Although the exact mechanism of this side effect is unknown, it has been hypothesized that SSRI can strengthen the uveal effusion of [topiramate](#), thereby increasing the risk of developing of [glaucoma](#). In this patient, both [topiramate](#) and [citalopram](#) may attribute to the increase in intraocular pressure and subsequently [glaucoma](#) [62].

3.3.10.A.4] Problem of visual accommodation

a)] Disturbances of visual accommodation have been reported in approximately 9% of patients treated with oral [citalopram](#) for up to 8 weeks (n=746) in a meta-analysis of clinical studies; this adverse effect is attributed to anticholinergic effects [45].

3.3.12] Psychiatric Effects

3.3.12.A] [Citalopram](#) Hydrobromide

3.3.12.A.1] Agitation

a)] Incidence: 3% to 10% [40] [44] [45] [48] [49] [50]

b)] Agitation has been reported in 3% of patients treated with [citalopram](#) doses of 10 to 80 mg/day (n=1063) and 1% of those treated with placebo (n=446) in placebo-controlled trials of up to 6 weeks in duration. Agitation was associated with discontinuation in 1% and less than 1% of those treated with [citalopram](#) and placebo, respectively [40].

c)] Restlessness was reported in 10% of patients treated with [citalopram](#) in a meta-analysis of clinical studies including depressed patients (n=746) where adverse effects were corrected for symptoms observed at baseline [44] [45] [48] [49] [50].

3.3.12.A.2] Anxiety

a)] Incidence: 4% [40]

b)] Anxiety has been reported in 4% of patients treated with [citalopram](#) doses of 10 to 80 mg/day (n=1063) and 3% of those treated with placebo (n=446) in placebo-controlled trials of up to 6 weeks in duration [40].

c)] An agitation-anxiety syndrome (possibly [akathisia](#)) has been reported as a frequent adverse effect of [citalopram](#) therapy [60].

3.3.12.A.3] Depression, Exacerbation

a)] Clinical worsening of depression has been reported in patients receiving [citalopram](#) therapy, particularly during the initial few months of treatment and during dose adjustments. It may persist until significant remission occurs. All patients treated with antidepressants for any indication should be monitored for signs of clinical worsening [40].

3.3.12.A.4] Hallucinations

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

b)] Hallucinations have been reported in 0.1% to 1% of patients treated with multiple [citalopram](#) doses of 10 to 80 mg/day during any phase of a trial within the premarketing database (n=4422); causality has not been established [40].

c)] A 27-year-old man developed hallucinations and delusions while receiving [citalopram](#) for the treatment of anxiety and depression. The patient presented with combat-related depression and [posttraumatic stress disorder](#) (PTSD) that started after he returned from his second deployment to Iraq. He was started on [citalopram](#) 20 mg per day. He took no other medications or supplements and had no significant personal or family history of psychiatric problems prior to his deployment to Iraq. Shortly following [citalopram](#) initiation, the patient noticed cold tingling and numbness to the extremities and across his back and increased irritability, agitation, difficulty concentrating, suspiciousness, and paranoia, which escalated following his fourth [citalopram](#) dose. He reported visual hallucinations of figures passing by his room, and suspected they intended to harm him. He was

evaluated by the psychiatry consult in the emergency department. He reported feeling aggravated and did laugh at inappropriate times; however, he did not have signs or symptoms of mania. He did not appear anxious and the hallucinations he described were different in nature than the PTSD flashbacks he experienced prior to starting [citalopram](#). Medical and neurological test results (including brain MRI with contrast, urinalysis, [thyroid function test](#), complete metabolic panel, and CBC) were within normal limits. The patient was admitted for inpatient psychiatric treatment, where [citalopram](#) was discontinued. Within 48 hours his symptoms resolved. On day 4 he was discharged and experienced no further hallucinations or delusions. Based on the Naranjo probability assessment score, his symptoms indicated a probable adverse drug reaction [71].

3.3.12.A.5] Panic attack

a) Panic attacks developed in a 61-year-old woman following an increase in her [citalopram](#) dose. The woman complained of worsening anxiety symptoms on the fourth day following an increase in her [citalopram](#) dose from 20 (mg daily to 40 mg daily. On the fifth day after the dose increase she developed panic attacks which occurred over the next two days at a rate of approximately 5 attacks per day. The [citalopram](#) was discontinued and her symptoms of anxiety resolved within 24 hours. No recurrence of symptoms was observed [67].

3.3.12.A.6] Suicidal thoughts

a) Adults

1) In a pooled analyses of placebo-controlled trials in adults with [major depressive disorder](#) (MDD) or other psychiatric disorders including 295 short-term trials (median duration of 2 months) of 11 antidepressant drugs in greater than 77,000 patients, the risk of suicidality varied among the drugs studied. However, for almost all drugs studied, there was a tendency toward increasing suicidality in younger patients. The risk difference (drug versus placebo in the number of cases of suicidality per 1000 patients treated) was 14 additional cases in patients less than 18 years of age, 5 additional cases in patients 18 to 24 years, 1 fewer case in patients 25 to 64 years, and 6 fewer cases in patients 65 years and older. No suicides occurred in the pediatric trials. Suicides did occur in the adult trials; however, the number of suicides was insufficient to determine causality. The risk of suicidality during longer-term use (ie, beyond several months) in pediatric patients is not known. However, evidence exists from placebo-controlled, maintenance trials in adults with depression to substantiate a delay in the recurrence of depression with antidepressant use [40] [68].

2) 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 [citalopram](#) (n=45,522; 24,054 person-years), suicide occurred at an event rate of 0.91/1000 person-years (95% confidence interval (CI), 0.57 to 1.38) and suicide attempts occurred at a rate of 3.59/1000 person-years (95% CI, 2.86 to 4.42). Based on data among treatment-naïve patients alone (no antidepressant use in the past 3 years; n=43,698; 23,112 person-years), suicide occurred at a rate of 0.95/1000 person-years (95% CI, 0.6 to 1.44) and suicide attempts occurred at a rate of 3.59/1000 person-years (95% CI, 2.86 to 4.45). Following an extensive propensity score adjustment in comparison with [fluoxetine](#) hydrochloride, [citalopram](#) hydrobromide had an overall hazard ratio of 1 (95% CI, 0.63 to 1.57). Most events were reported within the first 6 months after start of therapy [69].

b) Pediatrics

1) A causal role for antidepressants in inducing suicidality has been established in pediatric patients. Anyone considering the use of antidepressants in a child or adolescent must balance this risk with the clinical need. In pooled analyses of 24 short-term, placebo-controlled trials of nine antidepressants (citalopram, fluoxetine, fluvoxamine, paroxetine, sertraline, bupropion, mirtazapine, nefazodone, and venlafaxine extended-release) including over 4400 pediatric patients with major depressive disorder (MDD), obsessive compulsive disorder (OCD), or other psychiatric disorders, a greater risk of suicidal behavior or ideation during the first few months of therapy was demonstrated in patients receiving antidepressants as compared with placebo (4% vs 2%). The risk of suicidality was most consistently observed in the trials that included patients with MDD, but there were signs of risk emerging from trials in other psychiatric indications, such as OCD and social anxiety disorder [40] [68].

c) Management

1) Adult and pediatric patients being treated with antidepressants for major depressive disorder (MDD) who experience symptoms of anxiety, agitation, panic attacks, insomnia, irritability, hostility (aggressiveness), impulsivity, akathisia (psychomotor restlessness), hypomania, or mania may be at risk of suicidal ideation and behavior (suicidality). This same concern applies to treating patients with other psychiatric and nonpsychiatric disorders. If these symptoms are observed, therapy should be reevaluated and it may be necessary to discontinue medications when symptoms are severe, sudden in onset, or were not part of the patient's initial symptoms. Patients and their caregivers should be provided with the Medication Guide that is available for this drug. Closely monitor patients especially during the initial few months of therapy or at times of dose changes [40] [70].

3.3.12.A.7] Suicide

a) Suicide has been reported in adult patients receiving citalopram therapy in clinical trials; however, the number of suicides was insufficient to determine causality [40].

b) 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 citalopram (n=45,522; 24,054 person-years), suicide occurred at an event rate of 0.91/1000 person-years (95% confidence interval (CI), 0.57 to 1.38) and suicide attempts occurred at a rate of 3.59/1000 person-years (95% CI, 2.86 to 4.42). Based on data among treatment-naïve patients alone (no antidepressant use in the past 3 years; n=43,698; 23,112 person-years), suicide occurred at a rate of 0.95/1000 person-years (95% CI, 0.6 to 1.44) and suicide attempts occurred at a rate of 3.59/1000 person-years (95% CI, 2.86 to 4.45). Following an extensive propensity score adjustment in comparison with fluoxetine hydrochloride, citalopram hydrobromide had an overall hazard ratio of 1 (95% CI, 0.63 to 1.57). Most events were reported within the first 6 months after start of therapy [69].

3.3.12.A.8] Summary

a) 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 citalopram or any other antidepressant in a child, adolescent, or young adult must balance this risk with the clinical need. 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. [Citalopram](#) is not approved for use in pediatric patients [40].

3.3.13] Renal Effects

3.3.13.A] [Citalopram Hydrobromide](#)

3.3.13.A.1] Dysuria

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

b) Dysuria has been reported in 0.1% to 1% of patients treated with multiple [citalopram](#) doses of 10 to 80 mg/day during any phase of a trial within the premarketing database (n=4422); causality has not been established [40]. Dysuria, related to anticholinergic effects, has been reported in some patients treated with [citalopram](#) [60] [61]

3.3.13.A.2] Polyuria

a) Incidence: At least 1% [40]

b) Polyuria has been reported in at least 1% of patients treated with multiple [citalopram](#) doses of 10 to 80 mg/day during any phase of a trial within the premarketing database (n=4422); causality has not been established [40].

3.3.14] Reproductive Effects

3.3.14.A] [Citalopram Hydrobromide](#)

3.3.14.A.1] [Amenorrhea](#)

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

b) [Amenorrhea](#) has been reported in 0.1% to 1% of patients treated with multiple [citalopram](#) doses of 10 to 80 mg/day during any phase of a trial within the premarketing database (n=4422); causality has not been established [40].

3.3.14.A.2] [Disorder of ejaculation](#)

a) Incidence: 6.1% [40]

b) [Ejaculation disorder](#), primarily ejaculatory delay, has been reported in 6.1% of men treated with [citalopram](#) doses of 10 to 80 mg/day (n=425) and 1% of men treated with placebo (n=194) in placebo-controlled trials of up to 6 weeks in duration [40].

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

a) Incidence: 3% [40]

b) [Dysmenorrhea](#) has been reported in 3% of women treated with [citalopram](#) doses of 10 to 80 mg/day (n=638) and less than 2% of women treated with placebo (n=252) in placebo-controlled trials of up to 6 weeks in duration [40].

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

a) Incidence: 2.8% [40]

b) Impotence has been reported in 2.8% of men treated with [citalopram](#) doses of 10 to 80 mg/day (n=425) and less than 1% of men treated with placebo (n=194) in placebo-controlled trials of up to 6 weeks in duration. There was a positive dose response (p less than 0.05) between [citalopram](#) dose

and impotence according to Jonckheere's trend test in a fixed-dose study of depressed patients treated with either [citalopram](#) 20, 40, and 60 mg or placebo [40].

3.3.14.A.5] [Orgasm incapacity](#)

a) Incidence: Women, 1.1% [40]

b) In depressed women treated with [citalopram](#) (N=252), the incidence of [anorgasmia](#) was 1.1% [40].

3.3.14.A.6] [Priapism](#)

a) A 58-year-old man with a history of [priapism](#) resulting from [trazodone](#) use developed [priapism](#) after an inadvertent [overdose of citalopram](#) (60 mg in addition to his usual daily dose of 40 mg). He was given [morphine](#) sulfate for pain and [cefazolin](#) for prevention of infection. The corpus cavernosa was then irrigated with [phenylephrine](#), resulting in partial detumescence. On day 3, he was given an intracavernous injection of [phenylephrine](#) 400 mcg, which resulted in further detumescence. On day 4 he required creation of a glandular corporal cavernosa [fistula](#) and another intracavernous injection of [phenylephrine](#) 400 mcg. He recovered fully over several more days with no evidence of [erectile dysfunction](#). [Paroxetine](#) was prescribed for his depression. The authors pointed out that the patient was also taking [tamsulosin](#) 0.4 mg/day for [benign prostatic hyperplasia](#), which may have contributed to the [priapism](#) [72].

3.3.14.A.7] [Reduced libido](#)

a) Incidence: Men, 3.8%; women, 1.3% [40]

b) Decreased libido has been reported in 3.8% of men treated with [citalopram](#) doses of 10 to 80 mg/day (n=425) and less than 1% of men treated with placebo (n=194) in placebo-controlled trials of up to 6 weeks in duration. In depressed women treated with [citalopram](#) (N=638), the incidence of decreased libido was 1.3% [40].

3.3.14.A.8] [Sexual dysfunction](#)

a) [Ejaculation disorder](#), decreased libido, and impotence have been reported in men during [citalopram](#) therapy. Decreased libido and [anorgasmia](#) has been reported in women [40]. Reduced libido and ejaculatory or other sexual dysfunction were observed in some depressed elderly patients during [citalopram](#) therapy in one study [44].

3.3.15] [Respiratory Effects](#)

3.3.15.A] [Citalopram Hydrobromide](#)

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

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

b) [Epistaxis](#) has been reported in 0.1% to 1% of patients treated with multiple [citalopram](#) doses of 10 to 80 mg/day during any phase of a trial within the premarketing database (n=4422); causality has not been established [40].

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

a) Incidence: 5% [40]

b) [Rhinitis](#) has been reported in 5% of patients treated with [citalopram](#) doses of 10 to 80 mg/day (n=1063) and 3% of those treated with placebo (n=446) in placebo-controlled trials of up to 6 weeks in duration [40].

3.3.15.A.3] Sinusitis

a) Incidence: 3% [40]

b) Sinusitis has been reported in 3% of patients treated with citalopram doses of 10 to 80 mg/day (n=1063) and less than 1% of those treated with placebo (n=446) in placebo-controlled trials of up to 6 weeks in duration [40].

3.3.15.A.4] Upper respiratory infection

a) Incidence: 5% [40]

b) Upper respiratory tract infection has been reported in 5% of patients treated with citalopram doses of 10 to 80 mg/day (n=1063) and 4% of those treated with placebo (n=446) in placebo-controlled trials of up to 6 weeks in duration [40].

3.3.16] Other**3.3.16.A] Citalopram Hydrobromide****3.3.16.A.1] Summary**

a) Fatigue, fever, serotonin syndrome, and withdrawal have been reported with citalopram therapy. Serotonin syndrome, including cases that are life-threatening or that resemble neuroleptic malignant syndrome, has been reported [40]. Two case reports described serotonin syndrome following citalopram use [73]. Patients should be monitored for symptoms of serotonin syndrome or NMS-like symptoms [40]. Severe dizziness was also described following a missed dose of citalopram [75] [74].

3.3.16.A.2] Drug withdrawal

a) A case report described severe dizziness in a 45-year-old woman 3 hours after she inadvertently missed her citalopram 40 mg/day dose that morning. The dizziness lasted a few hours. She did not associate the episode with missing the dose until 2 weeks later, when she had another episode at the same time of day and realized that she had again neglected to take her citalopram dose. She took the dose immediately, and the dizziness abated in less than an hour [75].

3.3.16.A.3] Fatigue

a) Incidence: 5% [40]

b) Fatigue has been reported in 5% of patients treated with citalopram doses of 10 to 80 mg/day (n=1063) and 3% of those treated with placebo (n=446) in placebo-controlled trials of up to 6 weeks in duration. There was a positive dose response (p less than 0.05) between citalopram dose and fatigue according to Jonckheere's trend test in a fixed-dose study of depressed patients treated with either citalopram 20, 40, and 60 mg or placebo [40].

3.3.16.A.4] Fever

a) Incidence: 2% [40]

b) Fever has been reported in 2% of patients treated with citalopram doses of 10 to 80 mg/day (n=1063) and less than 1% of those treated with placebo (n=446) in placebo-controlled trials of up to 6 weeks in duration [40].

3.3.16.A.5] Serotonin syndrome

a) **Serotonin syndrome**, including life-threatening cases, or **neuroleptic malignant syndrome (NMS)**-like reactions have been reported with the use of **citalopram** alone. Signs and symptoms of **serotonin syndrome** include mental status changes (eg, agitation, hallucination, coma), autonomic instability (eg, **tachycardia**, labile blood pressure, **hyperthermia**), neuromuscular aberrations (eg, hyperreflexia, incoordination) and/or gastrointestinal symptoms (eg, nausea, vomiting, diarrhea). Severe **serotonin syndrome** can resemble NMS with symptoms including **hyperthermia**, muscle rigidity, autonomic instability with possible rapid fluctuation of vital signs, and mental status changes. **Serotonin syndrome** occurs most commonly with the concomitant use of serotonergic drugs, including triptans, with drugs that impair metabolism of serotonin, including MAOIs, or with antipsychotics or other **dopamine** antagonists [40].

b) A 36-year-old woman developed **serotonin syndrome** on 4 separate occasions; 2 were attributable to **fluoxetine** treatment and 2 to **citalopram** treatment. **Fluoxetine** was first prescribed when she reported anxiety and insomnia precipitated by a stalker. She routinely took **guaifenesin/pseudoephedrine** for nasal allergies. Approximately 1 month after starting **fluoxetine** 20 mg/day, she collapsed. She had earlier had a few mixed drinks. She became flaccid in all extremities and unresponsive to verbal commands and painful stimuli. This was followed by **apnea**, requiring ventilation for 1 hour before recovery of spontaneous respiration. She recovered from coma in another hour and was immediately alert and could move all muscles normally. She had diffuse muscle aches afterward. A week later, she resumed **fluoxetine** treatment, while avoiding alcohol. About 2 weeks later, she was found unresponsive and became apneic, again requiring ventilation, this time for about 2 hours. No diagnostic tests showed any abnormalities. She was diagnosed with **serotonin syndrome**. She recovered completely the next day. Afterward, she had severe diffuse muscle pain, weakness, and tremors, which were alleviated by magnesium and vitamin B6 supplements over a 2-month period. Nearly 2 years later, after reporting trembling, a shaky feeling, easy fatigability, palpitations, sweating, exaggerated startle response, and insomnia, she was given **alprazolam** 0.25 mg if needed in the morning and **zaleplon** 10 mg if needed for sleep at night. **Citalopram** 10 mg/day was later added, with no change in the **alprazolam** and **zaleplon** dosages. Three days after starting **citalopram**, she had another attack of **serotonin syndrome**, which she anticipated when she developed tremulousness and palpitations. Her neurologic response was the same as it had been previously, except that she did not develop **apnea**. The coma lasted 3 hours. The psychiatrist chose not to discontinue **citalopram** but reduced the dose to 5 mg/day. Three days later, she had another episode. The coma lasted for 1.5 hours. **Citalopram** was discontinued and she had no recurrence of symptoms of **serotonin syndrome** [73].

c) A 45-year-old man experienced **serotonin syndrome** (**hypomania**, myoclonus, diaphoresis, hot-cold feeling, shivering, loosening of stools) when his dose of **citalopram** was increased from 10 to 20 mg/day, 5 days after starting this medication. He had been treated with **zolpidem** for a sleep disturbance during a first **depressive episode**. Eight days after starting treatment, **citalopram** was discontinued and all the mentioned symptoms disappeared within hours. After a 3-day washout, **citalopram** was reintroduced at 10 mg/day and symptoms recurred on the same day. After 3 days, **citalopram** was again stopped, and symptoms disappeared. On day 21, **sertraline** 25 mg/day was prescribed. The same symptoms appeared on day 24 and disappeared on day 26 when **sertraline** was discontinued. After another washout period, mianserin 15 mg/day, later increased to 30 mg/day, was well tolerated. The authors speculated that the risk of **serotonin syndrome** is associated with the class of serotonin reuptake inhibitors [74].

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)) There is limited data on the use of [citalopram](#) during human pregnancy at this time. In animal studies, decreased embryo/fetal growth and survival and increased incidence of fetal abnormalities (eg, cardiovascular and skeletal defects) were reported in the offsprings of animals treated with [citalopram](#) doses that were considerably greater than the maximum recommended human dose [53]. In humans, exposure during embryogenesis has not been associated with apparent major teratogenic risk, while third trimester exposure has been associated with an increased risk for need of neonatal intensive care [53] [386] [383] (eg, prolonged hospitalization, tube feeding, respiratory support), sometimes immediately after delivery. Symptoms have been consistent with either a direct toxic effect of the agent or a possible drug discontinuation syndrome (eg, constant crying; irritability; jitteriness or tremor; hyperreflexia; hypertonia or hypotonia; [hypoglycemia](#); vomiting; feeding difficulties; temperature instability; seizures; or respiratory distress, cyanosis, or [apnea](#)). In some cases, clinical findings were consistent with [serotonin syndrome](#) [53].

b)) Epidemiologic studies have shown an increased risk of [persistent pulmonary hypertension of the newborn](#) (PPHN) with prenatal exposure to [citalopram](#) and other SSRIs during pregnancy [53]. Another study of prospectively collected data suggests antenatal use of selective serotonin-reuptake inhibitor (SSRI) antidepressants is associated with QTc interval prolongation in exposed neonates [382]. One small study indicated no long-term effects on cognitive ability but did show evidence of an increased risk for social-behavioral abnormalities at 2 to 6 years of age in children exposed to SSRIs or SNRIs in utero who developed [neonatal abstinence syndrome](#) (NAS) at birth [385]. Until more information is available, use caution when considering the use of [citalopram](#) in pregnant women, particularly during the third trimester.

5)) Literature Reports

a)) Infants exposed to [citalopram](#) during pregnancy and the late third trimester showed increased risk of neonatal complications. Epidemiologic studies showed an increased risk of [persistent pulmonary hypertension of the newborn](#) (PPHN) with prenatal exposure to [citalopram](#) and other SSRIs during pregnancy, a condition associated with considerable neonatal morbidity and mortality. Prenatal exposure late in the third trimester has been linked to complications that required intensive care (eg, prolonged hospitalization, tube feeding, respiratory support), sometimes immediately after delivery. Symptoms have been consistent with either a direct toxic effect of the agent or a possible drug discontinuation syndrome (eg, constant crying; irritability; jitteriness or tremor; hyperreflexia; hypertonia or hypotonia; [hypoglycemia](#); vomiting; feeding difficulties;

temperature instability; seizures; or respiratory distress, cyanosis, or [apnea](#)). In some cases, clinical findings were consistent with [serotonin syndrome](#) [53].

b) A nested case-controlled study showed that [citalopram](#), [sertraline](#), [fluoxetine](#), [fluvoxamine](#), or combined use of 2 or more SSRIs during pregnancy did not correspond with a significantly increased risk of [spontaneous abortion](#). However, [paroxetine](#) or [venlafaxine](#) use alone did increase the [spontaneous abortion](#) risk. Data collected from the Quebec Pregnancy Registry between January 1998 and December 2003 on women who filled at least 1 antidepressant prescription during pregnancy and had a clinically detected [spontaneous abortion](#) by the twentieth week of gestation (n=284) showed an increased risk of [spontaneous abortion](#) (adjusted odds ratio (OR), 1.68; 95% confidence interval (CI), 1.38 to 2.06) when compared with randomly selected registry controls (4 matched controls per case) without antidepressant use. Tracked antidepressant categories included SSRIs, tricyclic antidepressants, serotonin-norepinephrine reuptake inhibitors, combined use of 2 or more antidepressant classes, or others. [Paroxetine](#) use (adjusted OR 1.75; 95% CI, 1.31 to 2.34) or [venlafaxine](#) use (adjusted OR 2.11; 95% CI, 1.34 to 3.3) alone were independently associated with a higher risk of [spontaneous abortion](#). The highest daily doses of [paroxetine](#) or [venlafaxine](#) during pregnancy were associated with the greatest [spontaneous abortion](#) risk; of the women taking [paroxetine](#) (n=84) or [venlafaxine](#) (n=33) who spontaneously aborted, an adjusted analysis showed 25.5% averaged daily doses of more than 25 mg of [paroxetine](#) and 50% averaged daily doses greater than 150 mg of [venlafaxine](#) [381].

c) 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 [382].

d) A population-based study of 1782 pregnant women exposed to SSRIs demonstrated no increased risk of adverse perinatal outcome; however, a higher incidence of neonatal intensive or special care unit was noted, 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 (range, 23 to 37 years). There were more than twice as many smokers and 6 times as many pregnancies induced by artificial reproductive techniques in the SSRI group compared with controls (p less than 0.001). Mean length of gestation and birth weight were lower (p less than 0.001) in the SSRI group. Malformations 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 554 women purchasing [citalopram](#) during the first trimester, 219 during the second trimester, 228 during the third, and 94 throughout pregnancy. Compared

with first trimester exposure, special or intensive care unit visits were more common for the infants exposed during the third trimester (11.2% vs 15.7%; $p=0.009$). This difference remained statistically significant even after adjusting for confounding variables (OR 1.6; 95% confidence interval (CI), 1.1 to 2.2) [383].

e) An increased risk for CNS serotonergic symptoms was observed during the first 4 days of life in infants whose mothers were taking SSRIs during the third trimester of pregnancy. In a controlled, prospective study, pregnant women received 20 to 40 mg/day of either [citalopram](#) ($n=10$), [fluoxetine](#) ($n=10$), or did not receive an SSRI ($n=20$). Exposure to SSRI therapy ranged from 7 to 41 weeks. Newborns in the SSRI group had lower Apgar scores at 15 minutes compared with the control group (8.8 vs 9.4; $p=0.02$). At 2 weeks, a higher heart rate was observed in the SSRI group compared with the control group (mean, 153 vs 141 beats per minute; $p=0.049$). Serotonergic symptom scores in the first 4 days after birth were significantly higher in the SSRI group compared with the control group (121 vs 30; $p=0.008$). Tremor, restlessness, and rigidity were the most prominent symptoms. Myoclonus was reported in one infant exposed to [fluoxetine](#). Significantly lower cord blood 5-hydroxyindoleacetic acid (5-HIAA) concentrations were seen in the SSRI group compared with the control group (mean, 63 mmol/L vs 77 mmol/L; $p=0.02$). Additionally, a significant inverse correlation was observed between the serotonergic symptom score and the umbilical vein 5-HIAA concentrations in the SSRI group compared with the control group ($p=0.007$). Although not statistically significant, mean umbilical cord serum prolactin concentrations were 29% lower in SSRI-exposed infants than in control infants at the time of birth [384].

f) 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; $p=0.068$) [385].

g) A prospective comparative study to evaluate the safety of [citalopram](#) use during pregnancy demonstrated no association with [citalopram](#) use during embryogenesis and apparent major [teratogenicity](#); however, exposure late in pregnancy was associated with a 4-fold increased risk for neonatal intensive care (relative risk 4.2; 95% confidence interval 1.71 to 10.26). Complications included [pneumothorax](#), fetal distress, decreased heart rate, heart rate variability, [meconium staining](#) and [meconium aspiration](#). Women ($n=396$) were chosen for enrollment from among pregnant women or those planning pregnancy, who contacted the Motherisk Program, a Teratogen Information Center in Toronto, Ontario, regarding the safety of [citalopram](#) and other medications in pregnancy. There were 132 women in each group. The exposed group included women who took [citalopram](#) during pregnancy. This group was compared with a disease-matched group (pregnant women with similar psychiatric diagnoses in pregnancy but treated with other SSRI antidepressants)

and a nonteratogen group (women not exposed to teratogens). The exposed group and the 2 comparator groups were matched for maternal age at time of conception and gestational stage of pregnancy. Of the exposed group, 125 took [citalopram](#) at least in the first trimester, with 71 continuing the drug throughout pregnancy. There were 114 live births, 14 [spontaneous abortions](#), 2 elective terminations and 2 stillbirths in this group. There was no statistical difference among the 3 groups in terms of fetal survival rates, mean birth weights or duration of pregnancy. Only one case of major malformation occurred among the 108 infants exposed to [citalopram](#) in the first trimester; an infant with umbilical and [scrotal hernia](#) requiring surgery. The rate of perinatal complications in infants exposed to [citalopram](#) in the third trimester did not differ statistically from the unexposed groups [386].

B) Breastfeeding

1) Micromedex Lactation Rating: Infant risk has been demonstrated.

a) Evidence and/or expert consensus has demonstrated harmful infant effects when used during breastfeeding. An alternative to this drug should be prescribed or patients should be advised to discontinue breastfeeding.

2) Clinical Management

a) [Citalopram](#) is excreted into human breast milk, and the drug has been found in low, but detectable amounts in the serum of nursing infants [387]. The American Academy of Pediatrics considers antidepressants to be drugs worthy of concern in the nursing infant, particularly when used for long periods of time [391]. If the use of [citalopram](#) in a nursing mother is necessary, the infant should be monitored for unusual sleepiness, changes in appetite, and weight loss. The infant's exposure to the drug can be limited by administering the lowest effective dose to the mother, and by replacing breastfeeding with formula feeds during the drug absorption phase (approximately 3 to 9 hours after drug intake) [389]. The long-term effects of exposure to selective serotonin reuptake inhibitors (SSRI's) via breast milk on the cognitive development of the infant have not been determined.

3) Literature Reports

a) A study describing 9 lactating women treated with [citalopram](#) and their 10 nursing infants found either low (n=6) or undetectable (n=4) levels of the drug in infant serum. The maximum detectable concentration was 4.8% of the corresponding maternal serum drug concentration. Additionally, one of the mothers was deficient in CYP2C19 (the major enzyme involved in the metabolism of [citalopram](#)) metabolizing capabilities. There was no evidence of adverse effects in the infants as reported by the mothers. The authors suggest that breastfeeding should generally not be discouraged in mothers treated with serotonin reuptake inhibitor antidepressants [387].

b) One study reported a milk/serum ratio of 1.16 to 1.88 [388]; a higher milk/serum ratio of 3 was reported in another study [389]. The first study estimated that the infant would ingest 4.3 mcg/kg/day with a relative dose of 0.7% to 5.9% of the weight-adjusted maternal dose. The manufacturer describes two infants with excessive somnolence, decreased appetite, and weight loss associated with consuming breast milk from mothers treated with [citalopram](#). One infant fully recovered once the mother stopped the medication; the second infant was reported to be doing well at 4 years of age [390].

4) Drug Levels in Breastmilk**a) Citalopram Hydrobromide****1) Parent Drug****a) Milk to Maternal Plasma Ratio****1) 1.8 to 3.0 [396]****2) Active Metabolites****a) demethylcitalopram [395]****3.5] Drug Interactions****3.5.1] Drug-Drug Combinations****3.5.1.A] Abciximab****1) Interaction Effect:** an increased risk of bleeding

2) Summary: The concomitant use of citalopram and an antiplatelet drug may increase the risk of bleeding. The release of serotonin by platelets is important for maintaining hemostasis. Case-controlled and cohort studies have shown that the combined use of selective serotonin reuptake inhibitors and antiplatelet agents has been associated with an increased risk of bleeding. Bleeding events reported have included epistaxis, ecchymosis, hematoma, petechiae, and life-threatening hemorrhages. Monitor patient for signs of increased bleeding when citalopram is administered concomitantly with an antiplatelet drug [40].

3) Severity: major**4) Onset:** unspecified**5) Substantiation:** probable

6) Clinical Management: When citalopram and an antiplatelet agent are given concurrently, monitor patient for signs of increased bleeding [40].

7) Probable Mechanism: unknown**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 SSRIs due to an increased risk of gastrointestinal bleeding [228] [229]. Bleeding events have included epistaxis, ecchymosis, hematoma, petechiae, and life-threatening hemorrhages [231] [53] [232] [233]. 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:** probable

6) Clinical Management: Use caution if NSAIDs and SSRIs are coadministered. Concomitant use of NSAIDs and SSRIs may cause an increased risk of bleeding [228] [229]. When an SSRI and an NSAID are given concurrently, monitor the patient for signs of increased bleeding.

7) Probable Mechanism: unknown

8) Literature Reports

a) SSRIs increase the risk of upper gastrointestinal (GI) bleeding, and this effect is potentiated by concurrent use of NSAIDs or low-dose [aspirin](#). Hospitalizations for [upper GI bleeding](#) were searched among 26,005 users of antidepressant medications and compared with the number of hospitalizations in those patients who did not receive prescriptions for antidepressants. The amount of [upper GI bleeding](#) episodes was 3.6 times more than expected (95% CI, 2.7 to 4.7). Combined use of an SSRI and NSAIDs or low-dose [aspirin](#) increased the risk to 12.2 (95% CI, 7.1 to 19.5) and 5.2 (95% CI, 3.2 to 8), respectively. The findings of this study demonstrate an increased risk of [upper GI bleeding](#) during the use of SSRIs. Combined use of SSRIs and NSAIDs or low-dose [aspirin](#) increased the risk even further [230].

b) The 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 [53].

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 SSRIs due to an increased risk of [gastrointestinal bleeding](#) [228] [229]. Bleeding events have included [epistaxis](#), ecchymosis, [hematoma](#), [petechiae](#), and life-threatening hemorrhages [231] [53] [232] [233]. 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: probable

6) Clinical Management: Use caution if NSAIDs and SSRIs are coadministered. Concomitant use of NSAIDs and SSRIs may cause an increased risk of bleeding [228] [229]. When an SSRI and an NSAID are given concurrently, monitor the patient for signs of increased bleeding.

7) Probable Mechanism: unknown

8) Literature Reports

a) SSRIs increase the risk of upper gastrointestinal (GI) bleeding, and this effect is potentiated by concurrent use of NSAIDs or low-dose [aspirin](#). Hospitalizations for [upper GI bleeding](#) were searched among 26,005 users of antidepressant medications and compared with the number of hospitalizations in those patients who did not receive prescriptions for antidepressants. The amount of [upper GI bleeding](#) episodes was 3.6 times more than expected (95% CI, 2.7 to 4.7). Combined use of an SSRI and NSAIDs or low-dose [aspirin](#) increased the risk to 12.2 (95% CI, 7.1 to 19.5) and 5.2 (95% CI, 3.2 to 8), respectively. The findings of this study demonstrate an increased risk of [upper GI bleeding](#) during the use of SSRIs. Combined use of SSRIs and NSAIDs or low-dose [aspirin](#) increased the risk even further [230].

b) The 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 [53].

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 [340] [341] [339]. 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](#) [341] [339].

3) Severity: major

4) Onset: unspecified

5) Substantiation: probable

6) Clinical Management: When [citalopram](#) and an anticoagulant are given concurrently, monitor patients for signs of increased bleeding. Patients who are taking [warfarin](#) should be monitored closely for altered anticoagulant effects, including increased bleeding, when [citalopram](#) therapy is initiated or discontinued [339].

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 [340].

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 [341].

c) The pharmacokinetics of [warfarin](#), a CYP3A4 substrate, were not affected by the administration of [citalopram](#) 40 mg/day for 21 days, while the prothrombin time was increased by 5%. The clinical significance of this is unknown [339].

3.5.1.E] [Alfuzosin](#)

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

2) Summary: [Citalopram](#) causes dose-dependent prolongation of the QTc interval [76] and [alfuzosin](#) has also been associated with QT interval prolongation [168]. The concomitant use of [alfuzosin](#) and [citalopram](#) is not recommended due to a potential for additive effects on QT interval prolongation and an increased risk of cardiac adverse events, including [ventricular arrhythmias](#) and/or [torsade de pointes](#). If

coadministration is required, monitor for ECG changes. Do not exceed [citalopram](#) doses of 40 mg/day and discontinue [citalopram](#) in patients who have persistent QTc measurements greater than 500 milliseconds [76].

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: The concomitant use of [alfuzosin](#) and [citalopram](#) is not recommended due to a potential for additive effects on QT interval prolongation and an increased risk of serious cardiovascular effects. If coadministration is required, monitor for ECG changes. Do not exceed [citalopram](#) doses of 40 mg/day and discontinue [citalopram](#) in patients who have persistent QTc measurements greater than 500 milliseconds [76].

7) Probable Mechanism: additive effects on QT interval prolongation

8) Literature Reports

a) In a postmarketing study that evaluated the effect of concomitant administration of [alfuzosin](#) with another QT interval-prolonging drug of similar effect size, the observed QT interval prolongation was greater than that seen with either drug alone, but was not more than additive. The corrected (Fridericia) QT interval (QTcF) increased by 5.9 milliseconds (upper bound of 95% confidence interval (CI), 9.4 milliseconds). The QTcF increase observed with [moxifloxacin](#) 400 mg (positive control) was 10.2 milliseconds (upper bound 95% CI, 13.8 milliseconds). The mean placebo-subtracted QTcF increase following administration of [alfuzosin](#) 10 mg alone was 1.9 milliseconds (upper bound 95% CI, 5.5 milliseconds) [168].

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 [292]. 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](#) [95].

3) Severity: major

4) Onset: delayed

5) Substantiation: theoretical

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

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

8) Literature Reports

a) Concomitant administration of [fluoxetine](#) and [almotriptan](#) is well tolerated and [fluoxetine](#) has only a modest effect on [almotriptan](#) maximum plasma concentration (Cmax). Other [almotriptan](#) pharmacokinetics are not significantly affected. A randomized, open-label, two-way crossover study involving 14 healthy volunteers has been conducted. Subjects received each of the following treatments with a minimum 3-week washout between periods: (1) three 20 mg [fluoxetine](#) capsules on day 1 to 8 and one dose [almotriptan](#) 12.5 mg on day 8, (2) one dose of [almotriptan](#) 12.5 mg

on day 8 with no treatment on days 1 through 7. Peak [almotriptan](#) concentrations were 18% higher following concomitant administration of [fluoxetine](#) than after [almotriptan](#) administration alone. This difference was statistically significant (p equal 0.023). Mean [almotriptan](#) area under the concentration-time curve (AUC) and oral clearance were borderline statistically different between treatment groups. Mean half-life was not statistically different between the treatment groups. During [fluoxetine](#) coadministration, 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 [291].

3.5.1.G] Amifampridine

- 1) Interaction Effect: increased risk of QT-interval prolongation
- 2) Summary: The concomitant use of amifampridine with drugs that cause QT-interval prolongation is contraindicated, as coadministration may increase the risk of [ventricular arrhythmias](#) [331].
- 3) Severity: contraindicated
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: The concomitant use of amifampridine with drugs that cause QT-interval prolongation is contraindicated, as coadministration may increase the risk of [ventricular arrhythmias](#) [331].
- 7) Probable Mechanism: additive QT-interval prolongation

3.5.1.H] Amiodarone

- 1) Interaction Effect: increased risk of QT interval prolongation
- 2) Summary: [Citalopram](#) causes dose-dependent prolongation of the QTc interval [76] and [amiodarone](#) has been associated with QT prolongation [307]. Although this interaction has not been evaluated, the concomitant use of [amiodarone](#) with [citalopram](#) is not recommended as coadministration may increase the risk of QT interval prolongation and [torsade de pointes](#) [76]. A case of life-threatening [torsade de pointes](#), precipitated by the concomitant use of [citalopram](#) and [amiodarone](#), was reported in an 83-year-old female [306]. If coadministration is required, do not exceed [citalopram](#) doses of 40 mg/day and monitor for ECG changes. Discontinue [citalopram](#) in patients who have persistent QTc measurements greater than 500 milliseconds [76].
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: probable
- 6) Clinical Management: The concomitant use of [amiodarone](#) with [citalopram](#) is not recommended as concurrent use of these agents may increase the risk of cardiac adverse events, including [torsade de pointes](#). If coadministration is required, do not exceed [citalopram](#) doses of 40 mg/day and monitor for ECG changes. Discontinue [citalopram](#) in patients who have persistent QTc measurements greater than 500 milliseconds [76].
- 7) Probable Mechanism: additive effects on the QT interval
- 8) Literature Reports

a) A case of life-threatening [torsade de pointes](#) (TdP), precipitated by the concomitant use of [citalopram](#) and [amiodarone](#), was reported in an 83-year-old female. The patient's medical history included [hypertension](#), [atrial fibrillation](#), and depression, and her medication profile consisted of [losartan](#) 50 mg, [amiodarone](#) 200 mg, [fludione](#), [lercanidipine](#) 10 mg, and [citalopram](#) 20 mg. Three weeks after starting [citalopram](#), the patient presented with complaints of dizziness and palpitations. Physical exam and laboratory values were significant only for a mitral systolic

regurgitation (1/6) and hypokalemia (3 mmol/L). A prolonged corrected QT interval of 526 milliseconds and profound T waves in the precordial leads were evident on the initial ECG and continuous monitoring revealed self-terminating TdP following ventricular ectopic beats. Further workup with echocardiography showed the patient had moderate concentric left ventricular (LV) hypertrophy with a normal LV ejection fraction of 70%. Amiodarone and citalopram were discontinued and the patient received treatment with administration of magnesium and potassium. After 3 days, TdP did not recur, the potassium level and QT interval normalized (corrected QT interval of 385 milliseconds), and the patient was discharged home with no further complications [306].

3.5.1.I] Amitriptyline

- 1) Interaction Effect: an increased risk of QT interval prolongation
- 2) Summary: Concomitant use of amitriptyline and citalopram is not recommended due to a potential for additive effects on QT interval prolongation and an increased risk of serious cardiovascular effects. If concomitant use is required, monitor for ECG changes. Do not exceed citalopram doses of 40 mg/day, and discontinue citalopram in patients who have persistent QTc measurements greater than 500 milliseconds [76]. Additionally, caution is advised when using amitriptyline, a CYP2D6 substrate, with a CYP2D6 inhibitor, such as citalopram, as lower doses of amitriptyline and/or citalopram may be required. It is desirable to monitor amitriptyline concentrations whenever a CYP2D6 inhibitor is used concurrently [78].
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Concomitant use of amitriptyline and citalopram is not recommended due to a potential for additive effects on QT interval prolongation and an increased risk of serious cardiovascular effects. If concomitant use is required, monitor for ECG changes. Do not exceed citalopram doses of 40 mg/day, and discontinue citalopram in patients who have persistent QTc measurements greater than 500 milliseconds [76]. Additionally, caution is advised when using amitriptyline, a CYP2D6 substrate, with a CYP2D6 inhibitor, such as citalopram. Consider monitoring amitriptyline concentrations and lower doses of amitriptyline and/or citalopram may be required [78].
- 7) Probable Mechanism: additive effects on QT interval prolongation

3.5.1.J] Amoxapine

- 1) Interaction Effect: an increased risk of QT interval prolongation
- 2) Summary: Concomitant use of amoxapine and citalopram is not recommended due to a potential for additive effects on QT interval prolongation and an increased risk of serious cardiovascular effects. If concomitant therapy is considered necessary, monitor for ECG changes. Do not exceed citalopram doses of 40 mg/day and discontinue citalopram in patients who have persistent QTc measurements greater than 500 milliseconds [76].
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Concomitant use of amoxapine and citalopram is not recommended due to a potential for additive effects on QT interval prolongation and an increased risk of serious cardiovascular effects. If concomitant therapy is considered necessary, monitor for ECG changes. Do not exceed citalopram doses of 40 mg/day and discontinue citalopram in patients who have persistent QTc measurements greater than 500 milliseconds [76].
- 7) Probable Mechanism: additive effects on QT interval prolongation

3.5.1.K] Amtolmetin Guacil

- 1) Interaction Effect: an increased risk of bleeding
- 2) Summary: Caution is recommended with the concomitant use of NSAIDs and SSRIs due to an increased risk of [gastrointestinal bleeding](#) [228] [229]. Bleeding events have included [epistaxis](#), ecchymosis, [hematoma](#), [petechiae](#), and life-threatening hemorrhages [231] [53] [232] [233]. 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: probable
- 6) Clinical Management: Use caution if NSAIDs and SSRIs are coadministered. Concomitant use of NSAIDs and SSRIs may cause an increased risk of bleeding [228] [229]. When an SSRI and an NSAID are given concurrently, monitor the patient for signs of increased bleeding.
- 7) Probable Mechanism: unknown
- 8) Literature Reports

a) SSRIs increase the risk of upper gastrointestinal (GI) bleeding, and this effect is potentiated by concurrent use of NSAIDs or low-dose [aspirin](#). Hospitalizations for [upper GI bleeding](#) were searched among 26,005 users of antidepressant medications and compared with the number of hospitalizations in those patients who did not receive prescriptions for antidepressants. The amount of [upper GI bleeding](#) episodes was 3.6 times more than expected (95% CI, 2.7 to 4.7). Combined use of an SSRI and NSAIDs or low-dose [aspirin](#) increased the risk to 12.2 (95% CI, 7.1 to 19.5) and 5.2 (95% CI, 3.2 to 8), respectively. The findings of this study demonstrate an increased risk of [upper GI bleeding](#) during the use of SSRIs. Combined use of SSRIs and NSAIDs or low-dose [aspirin](#) increased the risk even further [230].

b) The 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 [53].

3.5.1.L] Anagrelide

- 1) Interaction Effect: increased risk of QT prolongation; increased risk of bleeding
- 2) Summary: [Anagrelide](#) has been associated with QT interval prolongation. Coadministration with another drug known to prolong the QT interval, such as [citalopram](#), should be avoided because of risk for additive effects on the QT interval that can lead to serious cardiac adverse effects, including [torsade de pointes](#) [234] [38]. If coadministration is required, do not exceed [citalopram](#) doses of 40 mg/day, and [ECG monitoring](#) is recommended. Discontinue [citalopram](#) in patients who have persistent QTc measurements greater than 500 milliseconds [38]. Coadministration of [anagrelide](#) with [citalopram](#) may also increase the risk of bleeding. Monitor patients for bleeding if coadministration is required [234].
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: [Anagrelide](#) has been associated with QT interval prolongation. Coadministration with another drug known to prolong the QT interval, such as [citalopram](#), should be avoided because of risk for additive effects on the QT interval that can lead to serious cardiac adverse effects, including [torsade de pointes](#) [234] [38]. If coadministration is required, do not exceed [citalopram](#) doses of 40 mg/day, and [ECG monitoring](#) is recommended. Discontinue [citalopram](#) in patients who have persistent QTc measurements greater than 500 milliseconds [38]. Coadministration of [anagrelide](#) with

citalopram may also increase the risk of bleeding. Monitor patients for bleeding if coadministration is required [234].

7J) Probable Mechanism: additive effects on QT interval; additive effects on hemostasis

3.5.1.MJ Ancrod

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 [340] [341] [339]. 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 [341] [339].

3J) Severity: major

4J) Onset: unspecified

5J) Substantiation: probable

6J) Clinical Management: When citalopram and an anticoagulant are given concurrently, monitor patients for signs of increased bleeding. Patients who are taking warfarin should be monitored closely for altered anticoagulant effects, including increased bleeding, when citalopram therapy is initiated or discontinued [339].

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 [340].

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 [341].

c) The pharmacokinetics of [warfarin](#), a CYP3A4 substrate, were not affected by the administration of [citalopram](#) 40 mg/day for 21 days, while the prothrombin time was increased by 5%. The clinical significance of this is unknown [339].

3.5.1.N] [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 [340] [341] [339]. 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](#) [341] [339].

3) Severity: major

4) Onset: unspecified

5) Substantiation: probable

6) Clinical Management: When [citalopram](#) and an anticoagulant are given concurrently, monitor patients for signs of increased bleeding. Patients who are taking [warfarin](#) should be monitored closely for altered anticoagulant effects, including increased bleeding, when [citalopram](#) therapy is initiated or discontinued [339].

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 [340].

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 [341].

c) The pharmacokinetics of [warfarin](#), a CYP3A4 substrate, were not affected by the administration of [citalopram](#) 40 mg/day for 21 days, while the prothrombin time was increased by 5%. The clinical significance of this is unknown [339].

3.5.1.O] 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 [340] [341] [339]. 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](#) [341] [339].

3) Severity: major

4) Onset: unspecified

5) Substantiation: probable

6) Clinical Management: When [citalopram](#) and an anticoagulant are given concurrently, monitor patients for signs of increased bleeding. Patients who are taking [warfarin](#) should be monitored closely for altered anticoagulant effects, including increased bleeding, when [citalopram](#) therapy is initiated or discontinued [339].

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 [340].

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 [341].

- c) The pharmacokinetics of [warfarin](#), a CYP3A4 substrate, were not affected by the administration of [citalopram](#) 40 mg/day for 21 days, while the prothrombin time was increased by 5%. The clinical significance of this is unknown [339].

3.5.1.P] 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 [167]. 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 [167]. 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.Q] Apomorphine

- 1) Interaction Effect: an increased risk of QT interval prolongation
- 2) Summary: [Citalopram](#) causes dose-dependent prolongation of the QTc interval [76] and [apomorphine](#) has also been associated with QT prolongation [84]. Although this interaction has not been studied, the concomitant use of [apomorphine](#) and [citalopram](#) may increase the risk of QT interval prolongation and [torsade de pointes](#) and is, therefore, not recommended. If coadministration is required, do not exceed [citalopram](#) doses of 40 mg/day and monitor for ECG changes. Discontinue [citalopram](#) in patients who have persistent QTc measurements greater than 500 milliseconds. [Torsade de pointes](#) has been reported during postmarketing use of [citalopram](#) [76].
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Concomitant use of [citalopram](#) with other drugs that prolong the QT interval, such as [apomorphine](#) [84], is not recommended as concurrent use may increase the risk of cardiac adverse events, including [torsade de pointes](#). If coadministration is required, do not exceed [citalopram](#) doses of 40 mg/day and monitor for ECG changes. Discontinue [citalopram](#) in patients who have persistent QTc measurements greater than 500 milliseconds [76].
- 7) Probable Mechanism: additive effects on QT interval prolongation

3.5.1.R] 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 [340] [341] [339]. 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](#) [341] [339].

- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: probable
- 6) Clinical Management: When [citalopram](#) and an anticoagulant are given concurrently, monitor patients for signs of increased bleeding. Patients who are taking [warfarin](#) should be monitored closely for altered anticoagulant effects, including increased bleeding, when [citalopram](#) therapy is initiated or discontinued [339].
- 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 [340].

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 [341].

c) The pharmacokinetics of [warfarin](#), a CYP3A4 substrate, were not affected by the administration of [citalopram](#) 40 mg/day for 21 days, while the prothrombin time was increased by 5%. The clinical significance of this is unknown [339].

3.5.1.S] [Aripiprazole](#)

- 1) Interaction Effect: increased risk of [serotonin syndrome](#) (hypertension, hyperthermia, myoclonus, mental status changes); increased risk of QT-interval prolongation
- 2) Summary: [Citalopram](#) is a serotonergic antidepressant, [aripiprazole](#) is an antipsychotic with partial agonist activity at serotonin (1A) receptors, both are associated with QTc-interval prolongation [38] [192], and concurrent use should be avoided [38]. Although this combination has not been studied, a 64-year-old man receiving [citalopram](#) experienced serotonin toxicity after just one 5-mg dose of [aripiprazole](#) [191], and coadministration may increase risk for QT-interval prolongation. If concurrent use is required, monitor ECG, electrolytes, and for serotonergic effects, especially during initiation and around dose increases.

Drug discontinuation and supportive symptomatic treatment is recommended if [serotonin syndrome](#) develops [38].

3) Severity: major

4) Onset: unspecified

5) Substantiation: probable

6) Clinical Management: [Citalopram](#) is a serotonergic known to cause dose-dependent QT-interval prolongation, and coadministration with another QT-prolonging drug, such as [aripiprazole](#), should be avoided [38]. Additionally, [serotonin syndrome](#) has been reported with concurrent use [191]. If coadministration is required, monitor ECG, electrolytes, and for serotonergic effects, especially during initiation and around dose increases. Drug discontinuation and supportive symptomatic treatment is recommended if [serotonin syndrome](#) develops. 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) [38].

7) Probable Mechanism: additive serotonergic effects; additive effects on QT interval

8) Literature Reports

a) A case report described serotonin toxicity in 64-year-old man following the concomitant use of [citalopram](#) and [aripiprazole](#). The patient, who had [coronary heart disease](#) and [hypertension](#), presented to the emergency room (ER) with agitation, diaphoresis, tremors, and nausea more than 1 hour after taking his first dose of [aripiprazole](#) 5 mg in combination with [citalopram](#) 60 mg. Adherence with antihypertensives and a statin was reported, and [citalopram](#) dose had not changed in many years. While in the ER, the patient was somnolent but oriented and physical exam revealed blood pressure fluctuations, dilated pupils, diffuse fasciculations, upper-extremity postural tremors, cogwheel rigidity, diffuse hyperreflexia with clonus elicited at both knees and ankles, and appendicular ataxia that prevented the patient from standing independently. Laboratory and [brain imaging](#) studies were unremarkable, including CPK, [TSH](#), and urine toxicology. All symptoms and clinical findings resolved within 24 hours of stopping psychiatric medications and treatment with [cyproheptadine](#) and supportive care [191].

3.5.1.T] [Arsenic Trioxide](#)

1) Interaction Effect: increased risk of QT interval prolongation

2) Summary: Both [arsenic trioxide](#) and [citalopram](#) have been associated with QT prolongation [76] [360]. Although this interaction has not been evaluated, the coadministration of [arsenic trioxide](#) with [citalopram](#) is not recommended due to a potential for additive effects on QT interval prolongation and an increased risk of serious cardiovascular effects. If coadministration is required, monitor for ECG changes. Do not exceed [citalopram](#) doses of 40 mg/day, and discontinue [citalopram](#) in patients who have persistent QTc measurements greater than 500 milliseconds [76].

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Concomitant use of [arsenic trioxide](#) and [citalopram](#) is not recommended due to a potential for additive effects on QT interval prolongation and an increased risk of serious cardiovascular effects. However, if concomitant use is required, monitor for ECG changes. Do not exceed [citalopram](#) doses of 40 mg/day, and discontinue [citalopram](#) in patients who have persistent QTc measurements greater than 500 milliseconds [76].

7) Probable Mechanism: additive effects on the QT interval

3.5.1.U] [Artemether](#)

- 1) Interaction Effect: increased risk of QT-interval prolongation
- 2) Summary: Avoid concomitant use of artemether/lumefantrine and [citalopram](#) due to a potential for additive effects on QT-interval prolongation and an increased risk of serious cardiovascular effects, including [torsade de pointes](#). If concomitant use is required, monitor for ECG changes. Do not exceed [citalopram](#) doses of 40 mg/day, and discontinue [citalopram](#) in patients who have persistent QTc measurements greater than 500 milliseconds [76]. Additionally, caution is advised when administering drugs that prolong the QT interval after completing artemether/lumefantrine therapy, due to the long half-life of lumefantrine (3 to 6 days) [356].
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Avoid concomitant use of artemether/lumefantrine and [citalopram](#) due to a potential for additive effects on QT-interval prolongation and an increased risk of serious cardiovascular effects, including [torsade de pointes](#). If concomitant use is required, monitor for ECG changes. Do not exceed [citalopram](#) doses of 40 mg/day, and discontinue [citalopram](#) in patients who have persistent QTc measurements greater than 500 milliseconds [76]. Additionally, caution is advised when administering drugs that prolong the QT interval after completing artemether/lumefantrine therapy, due to the long half-life of lumefantrine (3 to 6 days) [356].
- 7) Probable Mechanism: additive effects on the QT interval

3.5.1.V] Asenapine

- 1) Interaction Effect: an increased risk of QT interval prolongation
- 2) Summary: Concomitant use of asenapine and [citalopram](#) is not recommended as both agents have been associated with QT prolongation [76] [361]. Although this interaction has not been evaluated, the concomitant use of asenapine with [citalopram](#) may increase the risk of QT interval prolongation and [torsade de pointes](#). If coadministration is required, monitor for ECG changes. Do not exceed [citalopram](#) doses of 40 mg/day and discontinue [citalopram](#) in patients who have persistent QTc measurements greater than 500 milliseconds [76].
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Avoid the coadministration of asenapine and [citalopram](#) as both agents are known to increase the QT interval and concurrent use may increase the risk of cardiac adverse events [76] [361], including [torsade de pointes](#). If coadministration is required, monitor for ECG changes. Do not exceed [citalopram](#) doses of 40 mg/day and discontinue [citalopram](#) in patients who have persistent QTc measurements greater than 500 milliseconds [76].
- 7) Probable Mechanism: additive effects on the QT interval

3.5.1.W] Aspirin

- 1) Interaction Effect: an increased risk of bleeding
- 2) Summary: Caution is recommended with the concomitant use of NSAIDs and SSRIs due to an increased risk of [gastrointestinal bleeding](#) [228] [229]. Bleeding events have included [epistaxis](#), ecchymosis, [hematoma](#), [petechiae](#), and life-threatening hemorrhages [231] [53] [232] [233]. 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: probable

6) Clinical Management: Use caution if NSAIDs and SSRIs are coadministered. Concomitant use of NSAIDs and SSRIs may cause an increased risk of bleeding [228] [229]. When an SSRI and an NSAID are given concurrently, monitor the patient for signs of increased bleeding.

7) Probable Mechanism: unknown

8) Literature Reports

a) SSRIs increase the risk of upper gastrointestinal (GI) bleeding, and this effect is potentiated by concurrent use of NSAIDs or low-dose [aspirin](#). Hospitalizations for [upper GI bleeding](#) were searched among 26,005 users of antidepressant medications and compared with the number of hospitalizations in those patients who did not receive prescriptions for antidepressants. The amount of [upper GI bleeding](#) episodes was 3.6 times more than expected (95% CI, 2.7 to 4.7). Combined use of an SSRI and NSAIDs or low-dose [aspirin](#) increased the risk to 12.2 (95% CI, 7.1 to 19.5) and 5.2 (95% CI, 3.2 to 8), respectively. The findings of this study demonstrate an increased risk of [upper GI bleeding](#) during the use of SSRIs. Combined use of SSRIs and NSAIDs or low-dose [aspirin](#) increased the risk even further [230].

b) The 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 [53].

3.5.1.X] [Astemizole](#)

1) Interaction Effect: increased risk of QT interval prolongation

2) Summary: Both [astemizole](#) and [citalopram](#) have been associated with QT prolongation. Although this interaction has not been studied, the concomitant use of [astemizole](#) and [citalopram](#) is generally not recommended due to a potential for additive effects on QT interval prolongation and an increased risk of serious cardiovascular effects. If coadministration is required, monitor for ECG changes. Do not exceed [citalopram](#) doses of 40 mg/day, and discontinue [citalopram](#) in patients who have persistent QTc measurements greater than 500 milliseconds [76].

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Concomitant use of [astemizole](#) and [citalopram](#) is generally not recommended due to a potential for additive effects on QT interval prolongation and an increased risk of serious cardiovascular effects, including [torsade de pointes](#). If coadministration is required, monitor for ECG changes. Do not exceed [citalopram](#) doses of 40 mg/day, and discontinue [citalopram](#) in patients who have persistent QTc measurements greater than 500 milliseconds [76].

7) Probable Mechanism: additive effects on the QT interval

3.5.1.Y] [Azithromycin](#)

1) Interaction Effect: increased risk of QT interval prolongation

2) Summary: Concomitant use of [azithromycin](#) and [citalopram](#) is generally not recommended due to a potential for additive effects on QT interval prolongation and an increased risk of serious cardiovascular effects. If coadministration is required, monitor for ECG changes. Do not exceed [citalopram](#) doses of 40 mg/day and discontinue [citalopram](#) in patients who have persistent QTc measurements greater than 500 milliseconds [76].

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6)) Clinical Management: Concomitant use of [azithromycin](#) and [citalopram](#) is generally not recommended due to a potential for additive effects on QT interval prolongation and an increased risk of serious cardiovascular effects. If concomitant therapy is considered necessary, monitor for ECG changes. Do not exceed [citalopram](#) doses of 40 mg/day and discontinue [citalopram](#) in patients who have persistent QTc measurements greater than 500 milliseconds [76].

7)) Probable Mechanism: additive effects on QT interval prolongation

3.5.1.Z] [Bedaquiline](#)

1)) Interaction Effect: increased risk of QT prolongation

2)) Summary: Bedaquiline is associated with QT-interval prolongation. Concomitant use of bedaquiline with other drugs that prolong the QT interval, including fluoroquinolones, macrolide antibacterial drugs, and the antimycobacterial drug, [clofazimine](#), may result in additive prolonging effects on the QT interval. Close monitoring of baseline and on-treatment ECGs are recommended when bedaquiline is coadministered with other QT-prolonging agents [139].

3)) Severity: major

4)) Onset: unspecified

5)) Substantiation: theoretical

6)) Clinical Management: Concomitant administration of bedaquiline and other QT-prolonging drugs may result in additive prolongation effects on the QT interval. Baseline and on-treatment ECGs should be monitored closely when bedaquiline is coadministered with other QT-prolonging agents, including fluoroquinolones, macrolide antibacterial drugs, and the antimycobacterial drug, [clofazimine](#) [139].

7)) Probable Mechanism: additive QT-interval prolongation

8)) Literature Reports

a)) The mean increase in QTc interval at week 24 was greater in patients who received concomitant bedaquiline and [clofazimine](#), compared with patients who received bedaquiline without [clofazimine](#) (mean change from reference, 31.9 msec vs 12.3 msec, respectively) in an open-label, noncomparative study in previously treated patients with multidrug-resistant pulmonary Mycobacterium [tuberculosis](#) [139].

3.5.1.AA] [Bepridil](#)

1)) Interaction Effect: increased risk of QT-interval prolongation

2)) Summary: The concomitant use of [bepridil](#) with drugs that cause QT-interval prolongation is contraindicated [251], as coadministration may increase the risk of [ventricular arrhythmias](#).

3)) Severity: contraindicated

4)) Onset: unspecified

5)) Substantiation: theoretical

6)) Clinical Management: The concomitant use of [bepridil](#) with drugs that cause QT-interval prolongation is contraindicated [251], as coadministration may increase the risk of [ventricular arrhythmias](#).

7)) Probable Mechanism: additive QT-interval prolongation

3.5.1.AB] [Bivalirudin](#)

1)) Interaction Effect: an increased risk of bleeding

2)) Summary: The release of serotonin by [platelets](#) is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs and anticoagulants has been associated with an increased risk of bleeding [340] [341] [339]. 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](#) [341] [339].

- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: probable
- 6) Clinical Management: When [citalopram](#) and an anticoagulant are given concurrently, monitor patients for signs of increased bleeding. Patients who are taking [warfarin](#) should be monitored closely for altered anticoagulant effects, including increased bleeding, when [citalopram](#) therapy is initiated or discontinued [339].
- 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 [340].

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 [341].

c) The pharmacokinetics of [warfarin](#), a CYP3A4 substrate, were not affected by the administration of [citalopram](#) 40 mg/day for 21 days, while the prothrombin time was increased by 5%. The clinical significance of this is unknown [339].

3.5.1.AC] [Bromfenac](#)

- 1) Interaction Effect: an increased risk of bleeding
- 2) Summary: Caution is recommended with the concomitant use of NSAIDs and SSRIs due to an increased risk of [gastrointestinal bleeding](#) [228] [229]. Bleeding events have included [epistaxis](#), ecchymosis, [hematoma](#), [petechiae](#), and life-threatening hemorrhages [231] [53] [232] [233]. 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: probable

6j) Clinical Management: Use caution if NSAIDs and SSRIs are coadministered. Concomitant use of NSAIDs and SSRIs may cause an increased risk of bleeding [228] [229]. When an SSRI and an NSAID are given concurrently, monitor the patient for signs of increased bleeding.

7j) Probable Mechanism: unknown

8j) Literature Reports

aj) SSRIs increase the risk of upper gastrointestinal (GI) bleeding, and this effect is potentiated by concurrent use of NSAIDs or low-dose [aspirin](#). Hospitalizations for [upper GI bleeding](#) were searched among 26,005 users of antidepressant medications and compared with the number of hospitalizations in those patients who did not receive prescriptions for antidepressants. The amount of [upper GI bleeding](#) episodes was 3.6 times more than expected (95% CI, 2.7 to 4.7). Combined use of an SSRI and NSAIDs or low-dose [aspirin](#) increased the risk to 12.2 (95% CI, 7.1 to 19.5) and 5.2 (95% CI, 3.2 to 8), respectively. The findings of this study demonstrate an increased risk of [upper GI bleeding](#) during the use of SSRIs. Combined use of SSRIs and NSAIDs or low-dose [aspirin](#) increased the risk even further [230].

bj) The 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 [53].

3.5.1.ADj Bufexamac

1j) Interaction Effect: an increased risk of bleeding

2j) Summary: Caution is recommended with the concomitant use of NSAIDs and SSRIs due to an increased risk of [gastrointestinal bleeding](#) [228] [229]. Bleeding events have included [epistaxis](#), ecchymosis, [hematoma](#), [petechiae](#), and life-threatening hemorrhages [231] [53] [232] [233]. 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: probable

6j) Clinical Management: Use caution if NSAIDs and SSRIs are coadministered. Concomitant use of NSAIDs and SSRIs may cause an increased risk of bleeding [228] [229]. When an SSRI and an NSAID are given concurrently, monitor the patient for signs of increased bleeding.

7j) Probable Mechanism: unknown

8j) Literature Reports

aj) SSRIs increase the risk of upper gastrointestinal (GI) bleeding, and this effect is potentiated by concurrent use of NSAIDs or low-dose [aspirin](#). Hospitalizations for [upper GI bleeding](#) were searched among 26,005 users of antidepressant medications and compared with the number of hospitalizations in those patients who did not receive prescriptions for antidepressants. The amount of [upper GI bleeding](#) episodes was 3.6 times more than expected (95% CI, 2.7 to 4.7). Combined use of an SSRI and NSAIDs or low-dose [aspirin](#) increased the risk to 12.2 (95% CI, 7.1 to 19.5) and 5.2 (95% CI, 3.2 to 8), respectively. The findings of this study demonstrate an increased risk of [upper GI bleeding](#) during the use of SSRIs. Combined use of SSRIs and NSAIDs or low-dose [aspirin](#) increased the risk even further [230].

bj) The 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 [53].

3.5.1.AE] 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 [227].
- 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 [227].
- 7) Probable Mechanism: unknown

3.5.1.AF] Buserelin

- 1) Interaction Effect: increased risk of QT-interval prolongation
- 2) Summary: Gonadotropin-releasing hormone (GnRH) agonists prolong the QT interval through their androgen-depriving action [261] [262] [263], while [citalopram](#) causes dose-dependent QT-interval prolongation that can lead to life-threatening [ventricular tachycardia](#) or [Torsade de Pointes](#). Avoid concomitant use of [citalopram](#) with GnRH agonists. If concurrent use is essential, [ECG monitoring](#) is recommended. Discontinue [citalopram](#) if persistent QTc measurements above 500 msec occur [38].
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Avoid concomitant use of [citalopram](#) with gonadotropin-releasing hormone (GnRH) agonists, a class of drug known to prolong the QT interval, as additive QT-interval prolongation may occur. If concurrent use is essential, [ECG monitoring](#) is recommended. Discontinue [citalopram](#) if persistent QTc measurements above 500 msec occur [38].
- 7) Probable Mechanism: additive effects on the QT interval

3.5.1.AG] Buspirone

- 1) Interaction Effect: increased risk of [serotonin syndrome](#) ([hypertension](#), [hyperthermia](#), myoclonus, mental status changes)
- 2) Summary: An isolated case has been reported of [serotonin syndrome](#) and [hyponatremia](#) after ingesting higher than prescribed doses of [citalopram](#) and [busPIRone](#). Notably, [citalopram](#) alone has been associated with post-marketing reports of [serotonin syndrome](#), [hyponatremia](#), and syndrome of inappropriate antidiuretic hormone (SIADH) [189]. [Serotonin syndrome](#) can result in death if it is not recognized and correctly treated [190].
- 3) Severity: moderate
- 4) Onset: delayed
- 5) Substantiation: theoretical
- 6) Clinical Management: Monitor patients receiving concurrent [busPIRone](#) and [citalopram](#) for signs and symptoms of [serotonin syndrome](#) ([hypertension](#), [hyperthermia](#), myoclonus, mental status changes). The risk of developing [serotonin syndrome](#) may increase as dose increases.
- 7) Probable Mechanism: serotonin reuptake inhibition
- 8) Literature Reports

a) A 69-year-old female with recurrent depressive episodes was treated with citalopram 40 mg daily for approximately 18 months. BusPIRone 10 mg daily was initiated, and the patient developed signs of serotonin syndrome in six weeks. She became disoriented, confused, hyperactive, agitated, and experienced auditory and visual hallucinations. She also could not stand or walk, and experienced involuntary tremors of her arms and legs. Upon admission to the hospital, her serum sodium level was 121 mmol/L. Following the discontinuation of citalopram and busPIRone, the neuromuscular and psychiatric symptoms gradually disappeared, and her serum sodium level increased to 137 mmol/L without specific treatment. It was discovered that the patient had been taking higher than prescribed doses of both citalopram and busPIRone in the few days before her symptoms appeared. Four days after the discontinuation of citalopram, her serum concentration was 155 nmol/L. Although the citalopram level was not measured upon admission, it was extrapolated to be more than 1200 nmol/L. By comparison, 33 patients receiving citalopram 40 mg daily had a mean steady state citalopram level of 256 nmol/L [188].

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 [86]. 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 [85].

3.5.1.AI] Carbamazepine

- 1) Interaction Effect: decreased exposure of CYP3A4 substrates
- 2) Summary: Concomitant use of carbamazepine (a potent CYP3A4 inducer) and a CYP3A4 substrate may result in decreased exposure of the CYP3A4 substrate. If used concomitantly, monitoring of the CYP3A4 substrate concentrations or dose adjustments may be needed [193] [194].
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical

6) Clinical Management: Concomitant use of [carbamazepine](#), a potent CYP3A4 inducer, and a CYP3A4 substrate may result in decreased exposure of the CYP3A4 substrate. If used concomitantly, monitoring of the CYP3A4 substrate concentrations or dose adjustments may be needed [193] [194].

7) Probable Mechanism: induction of CYP3A4-mediated metabolism by [carbamazepine](#)

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 SSRIs due to an increased risk of [gastrointestinal bleeding](#) [228] [229]. Bleeding events have included [epistaxis](#), ecchymosis, [hematoma](#), [petechiae](#), and life-threatening hemorrhages [231] [53] [232] [233]. 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: probable

6) Clinical Management: Use caution if NSAIDs and SSRIs are coadministered. Concomitant use of NSAIDs and SSRIs may cause an increased risk of bleeding [228] [229]. When an SSRI and an NSAID are given concurrently, monitor the patient for signs of increased bleeding.

7) Probable Mechanism: unknown

8) Literature Reports

a) SSRIs increase the risk of upper gastrointestinal (GI) bleeding, and this effect is potentiated by concurrent use of NSAIDs or low-dose [aspirin](#). Hospitalizations for [upper GI bleeding](#) were searched among 26,005 users of antidepressant medications and compared with the number of hospitalizations in those patients who did not receive prescriptions for antidepressants. The amount of [upper GI bleeding](#) episodes was 3.6 times more than expected (95% CI, 2.7 to 4.7). Combined use of an SSRI and NSAIDs or low-dose [aspirin](#) increased the risk to 12.2 (95% CI, 7.1 to 19.5) and 5.2 (95% CI, 3.2 to 8), respectively. The findings of this study demonstrate an increased risk of [upper GI bleeding](#) during the use of SSRIs. Combined use of SSRIs and NSAIDs or low-dose [aspirin](#) increased the risk even further [230].

b) The 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 [53].

3.5.1.AK] Ceritinib

1) Interaction Effect: increased exposure of CYP3A substrate

2) Summary: Avoid concomitant use of ceritinib and a CYP3A substrate as this may increase exposure to and adverse effects of the substrate. If concurrent use cannot be avoided, consider dose reductions of the CYP3A substrate [354].

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Avoid concomitant use of ceritinib and a CYP3A substrate as this may increase exposure to and adverse effects of the substrate. If concurrent use cannot be avoided, consider dose reductions of the CYP3A substrate [354].

7) Probable Mechanism: inhibition of CYP3A-mediated metabolism of drug by ceritinib

3.5.1.AL] Certoparin

- 1) Interaction Effect: an increased risk of bleeding
- 2) Summary: The release of serotonin by [platelets](#) is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs and anticoagulants has been associated with an increased risk of bleeding [340] [341] [339]. 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](#) [341] [339].
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: probable
- 6) Clinical Management: When [citalopram](#) and an anticoagulant are given concurrently, monitor patients for signs of increased bleeding. Patients who are taking [warfarin](#) should be monitored closely for altered anticoagulant effects, including increased bleeding, when [citalopram](#) therapy is initiated or discontinued [339].
- 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 [340].

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 [341].

c) The pharmacokinetics of [warfarin](#), a CYP3A4 substrate, were not affected by the administration of [citalopram](#) 40 mg/day for 21 days, while the prothrombin time was increased by 5%. The clinical significance of this is unknown [339].

3.5.1.AM] [Chloramphenicol](#)

- 1) Interaction Effect: increased [citalopram](#) exposure and risk of QT interval prolongation

2) Summary: In a [pharmacokinetic study](#) in patients who received [citalopram](#) 40 mg/day for 21 days, combined administration with [cimetidine](#) (a potent CYP2C19 inhibitor) 400 mg/day for 8 days resulted in an increase in [citalopram](#) AUC and Cmax of 43% and 39%, respectively. Although the interaction between [citalopram](#) (a CYP2C19 substrate) and [chloramphenicol](#) (another CYP2C19 inhibitor) has not been specifically studied, concomitant use may result in increased [citalopram](#) exposure and risk of QT prolongation. If coadministration of [chloramphenicol](#) with [citalopram](#) is required, do not exceed [citalopram](#) doses of 20 mg/day [76].

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: The concomitant use of [citalopram](#), a CYP2C19 substrate, and [chloramphenicol](#), CYP2C19 inhibitor, may result in increased [citalopram](#) exposure and risk of QT prolongation. If coadministration of [citalopram](#) with [chloramphenicol](#) is required, do not exceed [citalopram](#) doses of 20 mg/day [76].

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

3.5.1.AN] [Chloroquine](#)

1) Interaction Effect: increased risk of QT interval prolongation

2) Summary: [Citalopram](#) causes dose-dependent prolongation of the QTc interval and [chloroquine](#) has been associated with QT prolongation. Although this interaction has not been studied, the concomitant use of [chloroquine](#) and [citalopram](#) may increase the risk of QT interval prolongation and [torsade de pointes](#) and is, therefore, not recommended. If coadministration is required, monitor for ECG changes. Do not exceed [citalopram](#) doses of 40 mg/day and discontinue [citalopram](#) in patients who have persistent QTc measurements greater than 500 milliseconds [76].

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Concomitant use of [citalopram](#) with other drugs that prolong the QT interval, such as [chloroquine](#), is not recommended as concurrent use may increase the risk of cardiac adverse events, including [torsade de pointes](#). If coadministration is required, monitor for ECG changes. Do not exceed [citalopram](#) doses of 40 mg/day and discontinue [citalopram](#) in patients who have persistent QTc measurements greater than 500 milliseconds [76].

7) Probable Mechanism: additive effects on the QT interval

3.5.1.AO] [Chlorpromazine](#)

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

2) Summary: [Chlorpromazine](#) and [citalopram](#) have both been associated with QT interval prolongation [285] [76]. Concomitant use of [chlorpromazine](#) and [citalopram](#) is generally not recommended due to a potential for additive effects on QT interval prolongation and an increased risk of serious cardiovascular effects. If coadministration is required, monitor for ECG changes. Do not exceed [citalopram](#) doses of 40 mg/day and discontinue [citalopram](#) in patients who have persistent QTc measurements greater than 500 milliseconds [76].

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Concomitant use of [chlorpromazine](#) and [citalopram](#) is generally not recommended due to a potential for additive effects on QT interval prolongation and an increased risk of serious cardiovascular effects. If coadministration is required, monitor for ECG changes. Do not

exceed [citalopram](#) doses of 40 mg/day, and discontinue [citalopram](#) in patients who have persistent QTc measurements greater than 500 milliseconds [76].

7J) Probable Mechanism: additive effects on QT interval prolongation

3.5.1.AP] [Choline Salicylate](#)

1J) Interaction Effect: an increased risk of bleeding

2J) Summary: Caution is recommended with the concomitant use of NSAIDs and SSRIs due to an increased risk of [gastrointestinal bleeding](#) [228] [229]. Bleeding events have included [epistaxis](#), ecchymosis, [hematoma](#), [petechiae](#), and life-threatening hemorrhages [231] [53] [232] [233]. 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: probable

6J) Clinical Management: Use caution if NSAIDs and SSRIs are coadministered. Concomitant use of NSAIDs and SSRIs may cause an increased risk of bleeding [228] [229]. When an SSRI and an NSAID are given concurrently, monitor the patient for signs of increased bleeding.

7J) Probable Mechanism: unknown

8J) Literature Reports

aJ) SSRIs increase the risk of upper gastrointestinal (GI) bleeding, and this effect is potentiated by concurrent use of NSAIDs or low-dose [aspirin](#). Hospitalizations for [upper GI bleeding](#) were searched among 26,005 users of antidepressant medications and compared with the number of hospitalizations in those patients who did not receive prescriptions for antidepressants. The amount of [upper GI bleeding](#) episodes was 3.6 times more than expected (95% CI, 2.7 to 4.7). Combined use of an SSRI and NSAIDs or low-dose [aspirin](#) increased the risk to 12.2 (95% CI, 7.1 to 19.5) and 5.2 (95% CI, 3.2 to 8), respectively. The findings of this study demonstrate an increased risk of [upper GI bleeding](#) during the use of SSRIs. Combined use of SSRIs and NSAIDs or low-dose [aspirin](#) increased the risk even further [230].

bJ) The 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 [53].

3.5.1.AQ] [Cilostazol](#)

1J) Interaction Effect: an increased risk of bleeding

2J) Summary: The concomitant use of [citalopram](#) and an antiplatelet drug may increase the risk of bleeding. The release of serotonin by [platelets](#) is important for maintaining hemostasis. Case-controlled and cohort studies have shown that the combined use of selective serotonin reuptake inhibitors and antiplatelet agents has been associated with an increased risk of bleeding. Bleeding events reported have included [epistaxis](#), ecchymosis, [hematoma](#), [petechiae](#), and life-threatening hemorrhages. Monitor patient for signs of increased bleeding when [citalopram](#) is administered concomitantly with an antiplatelet drug [40].

3J) Severity: major

4J) Onset: unspecified

5J) Substantiation: probable

6J) Clinical Management: When [citalopram](#) and an antiplatelet agent are given concurrently, monitor patient for signs of increased bleeding [40].

7J) Probable Mechanism: unknown

3.5.1.AR] Cimetidine

- 1) Interaction Effect: increased [citalopram](#) exposure and risk of QT-interval prolongation
- 2) Summary: In a [pharmacokinetic study](#) in patients who received [citalopram](#) (a CYP2C19 substrate) 40 mg/day for 21 days, combined administration with [cimetidine](#) (a potent CYP2C19 inhibitor) 400 mg twice daily for 8 days resulted in an increase in [citalopram](#) AUC and Cmax of 43% and 39%, respectively. Due to the risk of QT-interval prolongation, if coadministration of [cimetidine](#) and [citalopram](#) is required, do not exceed [citalopram](#) doses of 20 mg/day [375].
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: probable
- 6) Clinical Management: The concomitant use of [citalopram](#), a CYP2C19 substrate, and [cimetidine](#), a potent CYP2C19 inhibitor, may result in increased [citalopram](#) exposure and risk of QT prolongation. If coadministration of [citalopram](#) with [cimetidine](#) is required, do not exceed [citalopram](#) doses of 20 mg/day [375].
- 7) Probable Mechanism: inhibition of CYP2C19-mediated [citalopram](#) metabolism by [cimetidine](#)

3.5.1.AS] Ciprofloxacin

- 1) Interaction Effect: increased risk of QT interval prolongation
- 2) Summary: [Citalopram](#) causes dose-dependent prolongation of the QTc interval. Concomitant use of [citalopram](#) and other QT prolonging drugs, such as [ciprofloxacin](#) [91], may increase the risk of QT interval prolongation and is, therefore, not recommended. If concurrent therapy is required, monitor for ECG changes. Do not exceed [citalopram](#) doses of 40 mg/day, and discontinue [citalopram](#) in patients who have persistent QTc measurements greater than 500 milliseconds [76].
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Coadministration of [ciprofloxacin](#) and [citalopram](#), both drugs that prolong the QT interval [3], may increase the potential for serious cardiovascular effects and is not recommended. If concomitant therapy is required, monitor for ECG changes. Do not exceed [citalopram](#) doses of 40 mg/day, and discontinue [citalopram](#) in patients who have persistent QTc measurements greater than 500 milliseconds [76].
- 7) Probable Mechanism: additive effects on the QT interval

3.5.1.AT] Cisapride

- 1) Interaction Effect: increased risk of QT-interval prolongation
- 2) Summary: The concomitant use of [cisapride](#) with drugs that cause QT-interval prolongation is contraindicated, as coadministration may increase the risk of QT prolongation and serious [ventricular arrhythmias](#) [266].
- 3) Severity: contraindicated
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: The concomitant use of [cisapride](#) with drugs that cause QT-interval prolongation is contraindicated, as coadministration may increase the risk of QT prolongation and serious [ventricular arrhythmias](#) [266].
- 7) Probable Mechanism: additive QT-interval prolongation

3.5.1.AU] Clarithromycin

- 1) Interaction Effect: increased risk of QT interval prolongation
- 2) Summary: Citalopram has caused dose-dependent prolongation of the QTc interval [76] and clarithromycin has been associated with QT prolongation [325]. Clarithromycin is a CYP3A4 inhibitor and has the potential to increase citalopram exposure. The concomitant use of citalopram with clarithromycin is not recommended as coadministration may increase the risk of QT interval prolongation and torsade de pointes. If coadministration is required, monitor for ECG changes. Do not exceed citalopram doses of 40 mg/day, and discontinue citalopram in patients who have persistent QTc measurements greater than 500 milliseconds [325].
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Concomitant use of citalopram and clarithromycin is generally not recommended due to a potential for additive effects on QT interval prolongation and an increased risk of serious cardiovascular effects. If coadministration is required, monitor for ECG changes. Do not exceed citalopram doses of 40 mg/day, and discontinue citalopram in patients who have persistent QTc measurements greater than 500 milliseconds [76].
- 7) Probable Mechanism: inhibition of citalopram CYP3A4-mediated metabolism; additive effects on QT interval prolongation

3.5.1.AV] Clomipramine

- 1) Interaction Effect: an increased risk of QT interval prolongation
- 2) Summary: Concomitant use of citalopram and clomipramine is generally not recommended due to a potential for additive effects on QT interval prolongation and an increased risk of serious cardiovascular effects. If concomitant use is required, do not exceed citalopram doses of 40 mg/day and monitor for ECG changes. Discontinue citalopram in patients who have persistent QTc measurements greater than 500 milliseconds [76]. Additionally, caution is advised when using clomipramine, a CYP2D6 substrate, with citalopram, a weak CYP2D6 inhibitor. It is advisable to monitor clomipramine concentrations whenever a CYP2D6 inhibitor is used concurrently. Lower doses of clomipramine or citalopram may be necessary [259].
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Concomitant use of citalopram and clomipramine is generally not recommended due to a potential for additive effects on QT interval prolongation and an increased risk of serious cardiovascular effects. If concomitant use is required, do not exceed citalopram doses of 40 mg/day and monitor for ECG changes. Discontinue citalopram in patients who have persistent QTc measurements greater than 500 milliseconds [76]. Additionally, caution is advised when using clomipramine, a CYP2D6 substrate, with citalopram, a weak CYP2D6 inhibitor. Consider monitoring clomipramine concentrations and use lower doses of clomipramine or citalopram, if necessary [259].
- 7) Probable Mechanism: additive effects on QT interval prolongation

3.5.1.AW] Clonixin

- 1) Interaction Effect: an increased risk of bleeding
- 2) Summary: Caution is recommended with the concomitant use of NSAIDs and SSRIs due to an increased risk of gastrointestinal bleeding [228] [229]. Bleeding events have included epistaxis, ecchymosis,

hematoma, petechiae, and life-threatening hemorrhages [231] [53] [232] [233]. 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: probable

6) Clinical Management: Use caution if NSAIDs and SSRIs are coadministered. Concomitant use of NSAIDs and SSRIs may cause an increased risk of bleeding [228] [229]. When an SSRI and an NSAID are given concurrently, monitor the patient for signs of increased bleeding.

7) Probable Mechanism: unknown

8) Literature Reports

a) SSRIs increase the risk of upper gastrointestinal (GI) bleeding, and this effect is potentiated by concurrent use of NSAIDs or low-dose aspirin. Hospitalizations for upper GI bleeding were searched among 26,005 users of antidepressant medications and compared with the number of hospitalizations in those patients who did not receive prescriptions for antidepressants. The amount of upper GI bleeding episodes was 3.6 times more than expected (95% CI, 2.7 to 4.7). Combined use of an SSRI and NSAIDs or low-dose aspirin increased the risk to 12.2 (95% CI, 7.1 to 19.5) and 5.2 (95% CI, 3.2 to 8), respectively. The findings of this study demonstrate an increased risk of upper GI bleeding during the use of SSRIs. Combined use of SSRIs and NSAIDs or low-dose aspirin increased the risk even further [230].

b) The 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 [53].

3.5.1.AX] Clopidogrel

1) Interaction Effect: an increased risk of bleeding

2) Summary: The concomitant use of citalopram and an antiplatelet drug may increase the risk of bleeding. The release of serotonin by platelets is important for maintaining hemostasis. Case-controlled and cohort studies have shown that the combined use of selective serotonin reuptake inhibitors and antiplatelet agents has been associated with an increased risk of bleeding. Bleeding events reported have included epistaxis, ecchymosis, hematoma, petechiae, and life-threatening hemorrhages. Monitor patient for signs of increased bleeding when citalopram is administered concomitantly with an antiplatelet drug [40].

3) Severity: major

4) Onset: unspecified

5) Substantiation: probable

6) Clinical Management: When citalopram and an antiplatelet agent are given concurrently, monitor patient for signs of increased bleeding [40].

7) Probable Mechanism: unknown

3.5.1.AY] Clorgyline

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

2) Summary: Concurrent administration or overlapping therapy with citalopram 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 [101] [102] [103]. Concomitant use is contraindicated [104].

- 3) Severity: contraindicated
- 4) Onset: rapid
- 5) Substantiation: established
- 6) Clinical Management: Concurrent use of [citalopram](#) and a MAO inhibitor is contraindicated. Wait at least two weeks after discontinuing a MAO inhibitor before initiating therapy with [citalopram](#). Wait two weeks after discontinuing [citalopram](#) before initiating therapy with a MAO inhibitor.
- 7) Probable Mechanism: serotonin reuptake inhibition
- 8) Literature Reports

a) Concomitant use of selective serotonin reuptake inhibitors and monoamine oxidase inhibitors can produce a toxic reaction known as [serotonin syndrome](#) [96]. [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 [97].

c) A drug interaction was reported in a 61-year old woman in which [sertraline](#) 100 mg twice daily was added to a regimen of [lithium](#), [phenelzine](#), [thioridazine](#), and [doxepin](#). Three hours after taking the first [sertraline](#) dose, the patient was found in a semicomatose state, with elevated body temperature, increased pulse, increased respiration rate, and a blood pressure of 140/110 mm Hg. After transportation to the hospital, the patient was misdiagnosed as having [neuroleptic malignant syndrome](#) (NMS) which was later changed to [serotonin syndrome](#) due to a reaction between [sertraline](#) and [phenelzine](#). The authors suggest that monoamine oxidase inhibitor (MAOI) therapy should be discontinued for at least two weeks before initiation of therapy with a selective serotonin reuptake inhibitor (SSRI) and that before starting a MAOI, SSRI therapy should be discontinued for at least five half-lives of the parent drug and any active metabolites [98].

d) Two case reports suggested a possible interaction between [fluoxetine](#) and [selegiline](#) [99]. 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.

e) Five fatal overdose cases were reported due to [serotonin syndrome](#). In three of the five cases, the drug combination that induced the fatal syndrome was moclobemide, a selective monoamine oxidase inhibitor, and [citalopram](#). Of the three patients, blood concentrations of moclobemide ranged from 5 times the therapeutic level to 50 times the therapeutic level, and [citalopram](#) concentrations ranged from normal therapeutic levels to 5 times the therapeutic level [100].

3.5.1.AZ| [Clozapine](#)

- 1) Interaction Effect: increased risk of QT prolongation

2) Summary: Clozapine is associated with QT-interval prolongation. Concomitant administration of clozapine with other drugs that prolong the QT interval may result in additive prolongation effects on the QT interval and increase the risk of serious cardiac events, including ventricular arrhythmias and torsade de pointes. If concomitant therapy is required, use caution and monitor the patient closely for QT-interval prolongation. Discontinue clozapine if the corrected QT interval exceeds 500 milliseconds. Cardiac evaluation and treatment discontinuation are warranted if the patient develops symptoms of torsade de pointes or other arrhythmias [184].

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Concomitant administration of clozapine and QT-prolonging drugs may result in additive prolongation effects on the QT interval. If concomitant therapy is required, use caution and monitor the patient closely for QT-interval prolongation. Discontinue clozapine if the corrected QT interval exceeds 500 milliseconds. Cardiac evaluation and treatment discontinuation are warranted if the patient develops symptoms of torsade de pointes or other arrhythmias [184].

7) Probable Mechanism: additive QT-interval prolongation

3.5.1.BA] Cobicistat

1) Interaction Effect: increased citalopram plasma concentrations

2) Summary: Caution is advised when using cobicistat, a potent CYP3A4 inhibitor, together with a CYP3A4 substrate such as citalopram, as this may result in elevated plasma concentrations of citalopram [241]. If concomitant use is required, initiate citalopram at the lowest dose possible and titrate dose carefully based on patient response [242] [241].

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Caution is advised when using cobicistat, a potent CYP3A4 inhibitor, together with a CYP3A4 substrate such as citalopram, as this may result in elevated plasma concentrations of citalopram [241]. If concomitant use is required, initiate citalopram at the lowest dose possible and titrate dose carefully based on patient response [242] [241].

7) Probable Mechanism: inhibition of CYP3A4-mediated metabolism of citalopram by cobicistat

3.5.1.BB] Crizotinib

1) Interaction Effect: increased risk of QT-interval prolongation

2) Summary: Coadministration of citalopram with crizotinib is not recommended [76]. Although this interaction has not been evaluated, concurrent use of citalopram with crizotinib may increase the risk for prolonged QT interval and other serious cardiac adverse events, including torsade de pointes. If coadministration is required, do not exceed citalopram doses of 40 mg/day [76] and monitor for ECG changes [183] [76] and electrolyte disturbances [183]; crizotinib dose reduction may also be warranted.

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Both citalopram and crizotinib are known to increase the QT interval and concurrent use of these agents may increase the risk of serious cardiac adverse events, including torsade de pointes [183] [76]. If concomitant use of citalopram with crizotinib is required, do not exceed citalopram doses of 40 mg/day [76] and monitor for ECG changes [183] [76] and electrolyte disturbances [183]; crizotinib dose reduction may also be warranted.

7) Probable Mechanism: additive effects on QT interval

3.5.1.BC] Cyclobenzaprine

- 1) Interaction Effect: increased risk of QT prolongation and [serotonin syndrome](#)
- 2) Summary: Coadministration of [citalopram](#) and other drugs that prolong the QT interval, such as [cyclobenzaprine](#), is not recommended due to the risk of QT-interval prolongation [53] and [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 [346] [347]. If coadministration of [citalopram](#) and [cyclobenzaprine](#) is necessary, also monitor patients for [cardiac arrhythmias](#) and QT prolongation [53].
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Coadministration of [citalopram](#) and other drugs that prolong the QT interval, such as [cyclobenzaprine](#), is not recommended due to the risk of QT-interval prolongation [53] and [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 [346] [347]. If coadministration of [citalopram](#) and [cyclobenzaprine](#) is necessary, monitor patients for [cardiac arrhythmias](#) and QT prolongation [53].
- 7) Probable Mechanism: additive QT prolonging and serotonergic effects

3.5.1.BD] Dabrafenib

- 1) Interaction Effect: decreased [citalopram](#) exposure; increased risk of QT-interval prolongation
- 2) Summary: Avoid coadministering [citalopram](#) with dabrafenib [76]. Dabrafenib is a moderate CYP3A4 inducer, [citalopram](#) is a CYP3A4 substrate, and both are known to prolong the QT interval [367] [76]. Although this interaction has not been evaluated, coadministration may result in decreased [citalopram](#) plasma concentrations and an increased risk of QT-interval prolongation. Alternate agents should be used whenever feasible. If concomitant use is required, monitor patients for loss of [citalopram](#) efficacy [366] and monitor for ECG changes. Do not exceed [citalopram](#) doses of 40 mg/day, and discontinue [citalopram](#) in patients who have persistent QTc measurements greater than 500 milliseconds [76].
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Coadministration of dabrafenib with [citalopram](#) is not recommended due to a potential for additive effects on QT interval prolongation and risk of serious cardiovascular effects [76]. Additionally, concurrent use may result in reduced [citalopram](#) exposure. If concomitant use is required, monitor patients for loss of [citalopram](#) efficacy [366] and monitor for ECG changes. Do not exceed [citalopram](#) doses of 40 mg/day, and discontinue [citalopram](#) in patients who have persistent QTc measurements greater than 500 milliseconds [76].
- 7) Probable Mechanism: induction of CYP3A4-mediated metabolism of [citalopram](#) by dabrafenib; additive effects on QT interval

3.5.1.BE] 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 [340] [341] [339]. 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](#) [341] [339].
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: probable
- 6) Clinical Management: When [citalopram](#) and an anticoagulant are given concurrently, monitor patients for signs of increased bleeding. Patients who are taking [warfarin](#) should be monitored closely for altered anticoagulant effects, including increased bleeding, when [citalopram](#) therapy is initiated or discontinued [339].
- 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 [340].

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 [341].

c) The pharmacokinetics of [warfarin](#), a CYP3A4 substrate, were not affected by the administration of [citalopram](#) 40 mg/day for 21 days, while the prothrombin time was increased by 5%. The clinical significance of this is unknown [339].

3.5.1.BF] [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 [340] [341] [339]. 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](#) [341] [339].

3) Severity: major

4) Onset: unspecified

5) Substantiation: probable

6) Clinical Management: When [citalopram](#) and an anticoagulant are given concurrently, monitor patients for signs of increased bleeding. Patients who are taking [warfarin](#) should be monitored closely for altered anticoagulant effects, including increased bleeding, when [citalopram](#) therapy is initiated or discontinued [339].

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 [340].

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 [341].

c) The pharmacokinetics of [warfarin](#), a CYP3A4 substrate, were not affected by the administration of [citalopram](#) 40 mg/day for 21 days, while the prothrombin time was increased by 5%. The clinical significance of this is unknown [339].

3.5.1.BG| [Darunavir](#)

1) Interaction Effect: SSRI effects unknown; increased tricyclic antidepressant exposure

2) Summary: Use caution with coadministration of [darunavir](#) with antidepressants (ie, SSRIs, tricyclic antidepressants, or [trazodone](#)). If coadministered, carefully titrate the antidepressant to the desired effect.

Use the lowest effective antidepressant dose and monitor antidepressant response with concurrent use [273].

3J) Severity: major

4J) Onset: unspecified

5J) Substantiation: theoretical

6J) Clinical Management: Use caution with coadministration of [darunavir](#) with antidepressants (ie, SSRIs, tricyclic antidepressants, or [trazodone](#)). If coadministered, carefully titrate the antidepressant to the desired effect. Use the lowest effective antidepressant dose and monitor antidepressant response with concurrent use [273].

7J) Probable Mechanism: unknown

3.5.1.BH] [Dasatinib](#)

1J) Interaction Effect: increased risk of QT interval prolongation

2J) Summary: Although the interaction has not been studied, both [citalopram](#) and [dasatinib](#) are known to cause QT interval prolongation [77]. Concomitant use of [dasatinib](#) and [citalopram](#) is generally not recommended due to a potential for additive effects on QT interval prolongation and an increased risk of serious cardiovascular effects. If coadministration is required, monitor for ECG changes. Do not exceed [citalopram](#) doses of 40 mg/day, and discontinue [citalopram](#) in patients who have persistent QTc measurements greater than 500 milliseconds [76].

3J) Severity: major

4J) Onset: unspecified

5J) Substantiation: theoretical

6J) Clinical Management: Concomitant use of [citalopram](#) and [dasatinib](#) is generally not recommended due to a potential for additive effects on QT interval prolongation and an increased risk of serious cardiovascular effects, including [torsade de pointes](#). If coadministration is required, monitor for ECG changes. Do not exceed [citalopram](#) doses of 40 mg/day, and discontinue [citalopram](#) in patients who have persistent QTc measurements greater than 500 milliseconds [76].

7J) Probable Mechanism: additive effects on the QT interval

3.5.1.BI] [Deferasirox](#)

1J) Interaction Effect: reduced plasma concentrations of CYP3A4 substrate

2J) Summary: Concomitant use of [deferiasirox](#), a CYP3A4 inducer, and drugs that are metabolized by CYP3A4 may lead to decreased CYP3A4 substrate concentrations. Concomitant use [midazolam](#), a CYP3A4 substrate, and [deferiasirox](#) resulted in decreases in the [midazolam](#) C_{max} and AUC by 23% and 17%, respectively, in healthy volunteers. In the clinical setting, this effect may be more pronounced. Therefore, caution should be used when [deferiasirox](#) is coadministered with other CYP3A4 substrates. If concomitant use is required, monitor patients for reduced effectiveness [284].

3J) Severity: moderate

4J) Onset: unspecified

5J) Substantiation: theoretical

6J) Clinical Management: Concomitant use of [deferiasirox](#) and a CYP3A4 substrate such as [escitalopram](#), [imatinib](#), and [tacrolimus](#), may result in decreased CYP3A4 substrate plasma concentrations. Therefore, caution is advised when [deferiasirox](#) and drugs metabolized by CYP3A4 are coadministered and monitoring of patients for reduced effectiveness is recommended [284].

7J) Probable Mechanism: induction of CYP3A4-mediated metabolism by [deferiasirox](#)

3.5.1.BJ] [Defibrotide](#)

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 [340] [341] [339]. 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](#) [341] [339].

3j) Severity: major

4j) Onset: unspecified

5j) Substantiation: probable

6j) Clinical Management: When [citalopram](#) and an anticoagulant are given concurrently, monitor patients for signs of increased bleeding. Patients who are taking [warfarin](#) should be monitored closely for altered anticoagulant effects, including increased bleeding, when [citalopram](#) therapy is initiated or discontinued [339].

7j) Probable Mechanism: unknown

8j) 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 [340].

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 [341].

c) The pharmacokinetics of [warfarin](#), a CYP3A4 substrate, were not affected by the administration of [citalopram](#) 40 mg/day for 21 days, while the prothrombin time was increased by 5%. The clinical significance of this is unknown [339].

3.5.1.BK] Degarelix

1j) Interaction Effect: increased risk of QT-interval prolongation

2j) Summary: Gonadotropin-releasing hormone (GnRH) agonists prolong the QT interval through their androgen-depriving action [261] [262] [263], while [citalopram](#) causes dose-dependent QT-interval

prolongation that can lead to life-threatening [ventricular tachycardia](#) or [Torsade de Pointes](#). Avoid concomitant use of [citalopram](#) with GnRH agonists. If concurrent use is essential, [ECG monitoring](#) is recommended. Discontinue [citalopram](#) if persistent QTc measurements above 500 msec occur [38].

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Avoid concomitant use of [citalopram](#) with gonadotropin-releasing hormone (GnRH) agonists, a class of drug known to prolong the QT interval, as additive QT-interval prolongation may occur. If concurrent use is essential, [ECG monitoring](#) is recommended. Discontinue [citalopram](#) if persistent QTc measurements above 500 msec occur [38].

7) Probable Mechanism: additive effects on the QT interval

3.5.1.BLJ 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](#) [152]. DHEA was also noted to cause mania in a patient with no previous personal or family history of [bipolar disorder](#) [153]. Elevated DHEA levels have been found in patients with mental disorders; DHEA suppression has led to improvement in psychotic symptoms [154]. DHEA possesses proserotonergic activity which may predispose patients to [manic episodes](#) [155]. DHEA is a precursor to androgenic steroids, which in high doses may precipitate mania [153]. 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](#) [151].

3.5.1.BMJ Delamanid

1) Interaction Effect: increased risk of QT-interval prolongation

2j) Summary: Delamanid is a QT-interval-prolonging drug. Treatment initiation is not recommended in patients on other QT-interval-prolonging agents due to increased risk of the additive QT-interval prolongation effect. If the concurrent use cannot be avoided, an ECG should be obtained baseline and frequently (eg, more than once a month) during the full course of delamanid therapy [203].

3j) Severity: major

4j) Onset: unspecified

5j) Substantiation: theoretical

6j) Clinical Management: Delamanid is a QT-interval-prolonging drug. Treatment initiation is not recommended in patients on other QT-interval-prolonging agents due to increased risk of the additive QT-interval prolongation effect. If the concurrent use cannot be avoided, an ECG should be obtained baseline and frequently (eg, more than once a month) during the full course of delamanid therapy [203].

7j) Probable Mechanism: additive QT- interval prolongation

3.5.1.BN] Dermatan Sulfate

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 [340] [341] [339]. 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 [341] [339].

3j) Severity: major

4j) Onset: unspecified

5j) Substantiation: probable

6j) Clinical Management: When citalopram and an anticoagulant are given concurrently, monitor patients for signs of increased bleeding. Patients who are taking warfarin should be monitored closely for altered anticoagulant effects, including increased bleeding, when citalopram therapy is initiated or discontinued [339].

7j) Probable Mechanism: unknown

8j) 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 [340].

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 [341].

c) The pharmacokinetics of [warfarin](#), a CYP3A4 substrate, were not affected by the administration of [citalopram](#) 40 mg/day for 21 days, while the prothrombin time was increased by 5%. The clinical significance of this is unknown [339].

3.5.1.BO] [Desipramine](#)

- 1) Interaction Effect: a possible increase in the plasma concentrations of [desipramine](#)
- 2) Summary: Coadministration of [citalopram](#) and [imipramine](#) has been shown to increase the concentration of [desipramine](#), the major metabolite of [imipramine](#), by approximately 50%. However, [citalopram](#) was successfully substituted for [paroxetine](#) in a case of tricyclic antidepressant toxicity during coadministration of [desipramine](#) and [paroxetine](#); [desipramine](#) levels decreased after [citalopram](#) was initiated and no clinically toxic events were observed [164] [165].
- 3) Severity: moderate
- 4) Onset: unspecified
- 5) Substantiation: probable
- 6) Clinical Management: Caution is indicated in the coadministration of tricyclic antidepressants and [citalopram](#). Consider tricyclic antidepressant concentration monitoring and/or dose adjustment when there is a change in therapy or dose of [citalopram](#). [Citalopram](#) may be preferred over [paroxetine](#) when a tricyclic antidepressant is coadministered.
- 7) Probable Mechanism: inhibition of [desipramine](#) metabolism
- 8) Literature Reports

a) A case report describes a 45-year-old white female with [major depressive disorder](#) and [dysthymia](#). This patient failed several trials of antidepressants from all available drug classes, as well as [electroconvulsive therapy](#). The patient's medications included [pindolol](#), [desipramine](#), [clonazepam](#), and [olanzapine](#). [Paroxetine](#) was initiated and titration to 40 mg/day occurred over 3 months. The patient developed light-headedness, ataxia, and increased confusion after the titration. [Desipramine](#) serum levels were 1810 ng/mL (therapeutic range 75-300 ng/mL). After decreasing the daily [desipramine](#) 200 mg, the serum [desipramine](#) level was still 1665 ng/mL. The reduction in side effects were evident when the [paroxetine](#) dose was decreased to 30 mg/day and [desipramine](#) dose was decreased to 150 mg/day. Despite the dosage reduction of both drugs the patient's serum [desipramine](#) level was 1153 ng/mL. [Paroxetine](#) was discontinued and [desipramine](#) dose was decreased to 100 mg/day in divided doses. [Citalopram](#) was initiated and titrated to 40 mg/day. Over the next two months the patient's [desipramine](#) level decreased to 195 ng/mL. Depressive symptoms also improved. [Desipramine](#) toxicity is presumed to be caused by hepatic cytochrome P450 2D6 (CYP2D6) isoenzyme blockade from [paroxetine](#). The author concludes that the switch to [citalopram](#) likely is responsible for diminished [desipramine](#) serum levels, although alternative explanations should not be discounted [163].

3.5.1.BP] [Desirudin](#)

- 1) 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 [340] [341] [339]. 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](#) [341] [339].

3j) Severity: major

4j) Onset: unspecified

5j) Substantiation: probable

6j) Clinical Management: When [citalopram](#) and an anticoagulant are given concurrently, monitor patients for signs of increased bleeding. Patients who are taking [warfarin](#) should be monitored closely for altered anticoagulant effects, including increased bleeding, when [citalopram](#) therapy is initiated or discontinued [339].

7j) Probable Mechanism: unknown

8j) 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 [340].

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 [341].

c) The pharmacokinetics of [warfarin](#), a CYP3A4 substrate, were not affected by the administration of [citalopram](#) 40 mg/day for 21 days, while the prothrombin time was increased by 5%. The clinical significance of this is unknown [339].

3.5.1.BQ] Deslorelin

1j) Interaction Effect: increased risk of QT-interval prolongation

2j) Summary: Gonadotropin-releasing hormone (GnRH) agonists prolong the QT interval through their androgen-depriving action [261] [262] [263], while [citalopram](#) causes dose-dependent QT-interval

prolongation that can lead to life-threatening [ventricular tachycardia](#) or [Torsade de Pointes](#). Avoid concomitant use of [citalopram](#) with GnRH agonists. If concurrent use is essential, [ECG monitoring](#) is recommended. Discontinue [citalopram](#) if persistent QTc measurements above 500 msec occur [38].

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Avoid concomitant use of [citalopram](#) with gonadotropin-releasing hormone (GnRH) agonists, a class of drug known to prolong the QT interval, as additive QT-interval prolongation may occur. If concurrent use is essential, [ECG monitoring](#) is recommended. Discontinue [citalopram](#) if persistent QTc measurements above 500 msec occur [38].

7) Probable Mechanism: additive effects on the QT interval

3.5.1.BR] 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 [126].

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 [126].

7) Probable Mechanism: additive serotonergic effect

3.5.1.BS] 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 [citalopram](#), has the potential to cause [serotonin syndrome](#) [112]. [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 [113]. Dexfenfluramine should not be used in combination with [citalopram](#) [114].

3) Severity: major

4) Onset: rapid

5) Substantiation: probable

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

7) Probable Mechanism: additive serotonergic effects

3.5.1.BT] Dexibuprofen

1) Interaction Effect: an increased risk of bleeding

2) Summary: Caution is recommended with the concomitant use of NSAIDs and SSRIs due to an increased risk of [gastrointestinal bleeding](#) [228] [229]. Bleeding events have included [epistaxis](#), ecchymosis, [hematoma](#), [petechiae](#), and life-threatening hemorrhages [231] [53] [232] [233]. 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: probable

6) Clinical Management: Use caution if NSAIDs and SSRIs are coadministered. Concomitant use of NSAIDs and SSRIs may cause an increased risk of bleeding [228] [229]. When an SSRI and an NSAID are given concurrently, monitor the patient for signs of increased bleeding.

7) Probable Mechanism: unknown

8) Literature Reports

a) SSRIs increase the risk of upper gastrointestinal (GI) bleeding, and this effect is potentiated by concurrent use of NSAIDs or low-dose [aspirin](#). Hospitalizations for [upper GI bleeding](#) were searched among 26,005 users of antidepressant medications and compared with the number of hospitalizations in those patients who did not receive prescriptions for antidepressants. The amount of [upper GI bleeding](#) episodes was 3.6 times more than expected (95% CI, 2.7 to 4.7). Combined use of an SSRI and NSAIDs or low-dose [aspirin](#) increased the risk to 12.2 (95% CI, 7.1 to 19.5) and 5.2 (95% CI, 3.2 to 8), respectively. The findings of this study demonstrate an increased risk of [upper GI bleeding](#) during the use of SSRIs. Combined use of SSRIs and NSAIDs or low-dose [aspirin](#) increased the risk even further [230].

b) The 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 [53].

3.5.1.BU] Dexketoprofen

1) Interaction Effect: an increased risk of bleeding

2) Summary: Caution is recommended with the concomitant use of NSAIDs and SSRIs due to an increased risk of [gastrointestinal bleeding](#) [228] [229]. Bleeding events have included [epistaxis](#), ecchymosis, [hematoma](#), [petechiae](#), and life-threatening hemorrhages [231] [53] [232] [233]. 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: probable

6) Clinical Management: Use caution if NSAIDs and SSRIs are coadministered. Concomitant use of NSAIDs and SSRIs may cause an increased risk of bleeding [228] [229]. When an SSRI and an NSAID are given concurrently, monitor the patient for signs of increased bleeding.

7) Probable Mechanism: unknown

8) Literature Reports

a)) SSRIs increase the risk of upper gastrointestinal (GI) bleeding, and this effect is potentiated by concurrent use of NSAIDs or low-dose [aspirin](#). Hospitalizations for [upper GI bleeding](#) were searched among 26,005 users of antidepressant medications and compared with the number of hospitalizations in those patients who did not receive prescriptions for antidepressants. The amount of [upper GI bleeding](#) episodes was 3.6 times more than expected (95% CI, 2.7 to 4.7). Combined use of an SSRI and NSAIDs or low-dose [aspirin](#) increased the risk to 12.2 (95% CI, 7.1 to 19.5) and 5.2 (95% CI, 3.2 to 8), respectively. The findings of this study demonstrate an increased risk of [upper GI bleeding](#) during the use of SSRIs. Combined use of SSRIs and NSAIDs or low-dose [aspirin](#) increased the risk even further [230].

b)) The 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 [53].

3.5.1.BV] [Dextroamphetamine](#)

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

2)) Summary: Concurrent use of [citalopram](#) and [dextroamphetamine](#) resulted in symptoms of [serotonin syndrome](#) in a 32-year-old male [185]. If [citalopram](#) and [dextroamphetamine](#) are used concomitantly, monitor closely for symptoms of [serotonin syndrome](#). [Serotonin syndrome](#) can be life-threatening. If [serotonin syndrome](#) develops, discontinue the offending agents and provide supportive care and other therapy as necessary [81].

3)) Severity: major

4)) Onset: delayed

5)) Substantiation: probable

6)) Clinical Management: A case of [serotonin syndrome](#) was reported with coadministration of [citalopram](#) and [dextroamphetamine](#) [185]. If [citalopram](#) and [dextroamphetamine](#) are used concomitantly, monitor closely for symptoms of [serotonin syndrome](#) such as 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 [81].

7)) Probable Mechanism: additive pharmacologic effects

8)) Literature Reports

a)) A 32-year-old male on [dextroamphetamine](#) experienced [serotonin syndrome](#) approximately 1 week after starting [citalopram](#). He was on [dextroamphetamine](#) 5 mg three times daily for [attention deficit hyperactivity disorder](#). He started 75 mg a day of [venlafaxine](#) for 1 week then the dose was increased to 150 mg daily. Approximately 2 weeks after starting [venlafaxine](#) he experienced marked agitation, anxiety, shivering, and tremor. On admission he was alert and oriented. He experienced diaphoresis, shivering, and fine motor tremor. His heart rate was 140 beats per minute, blood pressure was 142/93 mmHg, and temperature was 37.3 degrees Celsius. No [nystagmus](#) or ocular clonus was noted. Pupils were 3 mm diameter and reactive. He had generalized hypertonia, hyperreflexia, inducible ankle clonus, frequent myoclonic jerking, and unilateral-tonic spasm of his orbicularis oris muscle. No abnormality was shown on ECG, except [sinus tachycardia](#) with a baseline tremor. [Dextroamphetamine](#) and [venlafaxine](#) were discontinued and [cyproheptadine](#) (up to a total of 32 mg over 3 hours) was administered. Symptoms resolved and he was discharged the following morning. [Dextroamphetamine](#) was restarted 3 days later. Four days later [citalopram](#) was started. Approximately 1 week later, he experienced similar symptoms as he did with

dextroamphetamine and venlafaxine. Agitation, nausea, diarrhea, and teeth clenching were still present 3 days after citalopram was discontinued. Two doses of cyproheptadine were given and within 2 days he was asymptomatic [185].

3.5.1.BW] Dextromethorphan

1) Interaction Effect: increased dextromethorphan plasma concentrations and increased risk of serotonin syndrome

2) Summary: Citalopram is a weak inhibitor of CYP2D6 [250] and dextromethorphan is a CYP2D6 substrate. While not specifically studied with citalopram, 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 citalopram with dextromethorphan may increase the risk of serotonin syndrome, initial dose reductions of dextromethorphan may be warranted [249] 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 citalopram), 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 citalopram [249].

7) Probable Mechanism: inhibition of CYP2D6-mediated dextromethorphan metabolism by citalopram

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 Cmax (1.7- and 1.5-fold, respectively) and a decrease in dextromethorphan AUC and Cmax (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 Cmax (1.5- and 1.4-fold, respectively), a decrease in dextromethorphan AUC and Cmax (14% and 18%, respectively) an increase in quinidine AUC and Cmax (1.4- and 1.3-fold, respectively), and an increase in paroxetine AUC and Cmax (2.3- and 2-fold, respectively) [249].

3.5.1.BX] Diclofenac

1) Interaction Effect: an increased risk of bleeding

2) Summary: Caution is recommended with the concomitant use of NSAIDs and SSRIs due to an increased risk of gastrointestinal bleeding [228] [229]. Bleeding events have included epistaxis, ecchymosis, hematoma, petechiae, and life-threatening hemorrhages [231] [53] [232] [233]. 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: probable

6) Clinical Management: Use caution if NSAIDs and SSRIs are coadministered. Concomitant use of NSAIDs and SSRIs may cause an increased risk of bleeding [228] [229]. When an SSRI and an NSAID are given concurrently, monitor the patient for signs of increased bleeding.

7) Probable Mechanism: unknown

8) Literature Reports

a) SSRIs increase the risk of upper gastrointestinal (GI) bleeding, and this effect is potentiated by concurrent use of NSAIDs or low-dose [aspirin](#). Hospitalizations for [upper GI bleeding](#) were searched among 26,005 users of antidepressant medications and compared with the number of hospitalizations in those patients who did not receive prescriptions for antidepressants. The amount of [upper GI bleeding](#) episodes was 3.6 times more than expected (95% CI, 2.7 to 4.7). Combined use of an SSRI and NSAIDs or low-dose [aspirin](#) increased the risk to 12.2 (95% CI, 7.1 to 19.5) and 5.2 (95% CI, 3.2 to 8), respectively. The findings of this study demonstrate an increased risk of [upper GI bleeding](#) during the use of SSRIs. Combined use of SSRIs and NSAIDs or low-dose [aspirin](#) increased the risk even further [230].

b) The 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 [53].

3.5.1.BY] 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 [340] [341] [339]. 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](#) [341] [339].

3) Severity: major

4) Onset: unspecified

5) Substantiation: probable

6) Clinical Management: When [citalopram](#) and an anticoagulant are given concurrently, monitor patients for signs of increased bleeding. Patients who are taking [warfarin](#) should be monitored closely for altered anticoagulant effects, including increased bleeding, when [citalopram](#) therapy is initiated or discontinued [339].

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 [340].

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 [341].

c) The pharmacokinetics of [warfarin](#), a CYP3A4 substrate, were not affected by the administration of [citalopram](#) 40 mg/day for 21 days, while the prothrombin time was increased by 5%. The clinical significance of this is unknown [339].

3.5.1.BZ] [Diflunisal](#)

1) Interaction Effect: an increased risk of bleeding

2) Summary: Caution is recommended with the concomitant use of NSAIDs and SSRIs due to an increased risk of [gastrointestinal bleeding](#) [228] [229]. Bleeding events have included [epistaxis](#), ecchymosis, [hematoma](#), [petechiae](#), and life-threatening hemorrhages [231] [53] [232] [233]. 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: probable

6) Clinical Management: Use caution if NSAIDs and SSRIs are coadministered. Concomitant use of NSAIDs and SSRIs may cause an increased risk of bleeding [228] [229]. When an SSRI and an NSAID are given concurrently, monitor the patient for signs of increased bleeding.

7) Probable Mechanism: unknown

8) Literature Reports

a) SSRIs increase the risk of upper gastrointestinal (GI) bleeding, and this effect is potentiated by concurrent use of NSAIDs or low-dose [aspirin](#). Hospitalizations for [upper GI bleeding](#) were searched among 26,005 users of antidepressant medications and compared with the number of hospitalizations in those patients who did not receive prescriptions for antidepressants. The amount of [upper GI bleeding](#) episodes was 3.6 times more than expected (95% CI, 2.7 to 4.7). Combined use of an SSRI and NSAIDs or low-dose [aspirin](#) increased the risk to 12.2 (95% CI, 7.1 to 19.5) and 5.2 (95% CI, 3.2 to 8), respectively. The findings of this study demonstrate an increased risk of [upper GI bleeding](#) during the use of SSRIs. Combined use of SSRIs and NSAIDs or low-dose [aspirin](#) increased the risk even further [230].

b) The 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 [53].

3.5.1.CA] [Dipyridamole](#)

1) Interaction Effect: an increased risk of bleeding

2) Summary: The concomitant use of [citalopram](#) and an antiplatelet drug may increase the risk of bleeding. The release of serotonin by [platelets](#) is important for maintaining hemostasis. Case-controlled and cohort studies have shown that the combined use of selective serotonin reuptake inhibitors and antiplatelet

agents has been associated with an increased risk of bleeding. Bleeding events reported have included [epistaxis](#), ecchymosis, [hematoma](#), [petechiae](#), and life-threatening hemorrhages. Monitor patient for signs of increased bleeding when [citalopram](#) is administered concomitantly with an antiplatelet drug [40].

3) Severity: major

4) Onset: unspecified

5) Substantiation: probable

6) Clinical Management: When [citalopram](#) and an antiplatelet agent are given concurrently, monitor patient for signs of increased bleeding [40].

7) Probable Mechanism: unknown

3.5.1.CB] Dipyrrone

1) Interaction Effect: an increased risk of bleeding

2) Summary: Caution is recommended with the concomitant use of NSAIDs and SSRIs due to an increased risk of [gastrointestinal bleeding](#) [228] [229]. Bleeding events have included [epistaxis](#), ecchymosis, [hematoma](#), [petechiae](#), and life-threatening hemorrhages [231] [53] [232] [233]. 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: probable

6) Clinical Management: Use caution if NSAIDs and SSRIs are coadministered. Concomitant use of NSAIDs and SSRIs may cause an increased risk of bleeding [228] [229]. When an SSRI and an NSAID are given concurrently, monitor the patient for signs of increased bleeding.

7) Probable Mechanism: unknown

8) Literature Reports

a) SSRIs increase the risk of upper gastrointestinal (GI) bleeding, and this effect is potentiated by concurrent use of NSAIDs or low-dose [aspirin](#). Hospitalizations for [upper GI bleeding](#) were searched among 26,005 users of antidepressant medications and compared with the number of hospitalizations in those patients who did not receive prescriptions for antidepressants. The amount of [upper GI bleeding](#) episodes was 3.6 times more than expected (95% CI, 2.7 to 4.7). Combined use of an SSRI and NSAIDs or low-dose [aspirin](#) increased the risk to 12.2 (95% CI, 7.1 to 19.5) and 5.2 (95% CI, 3.2 to 8), respectively. The findings of this study demonstrate an increased risk of [upper GI bleeding](#) during the use of SSRIs. Combined use of SSRIs and NSAIDs or low-dose [aspirin](#) increased the risk even further [230].

b) The 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 [53].

3.5.1.CC] Disopyramide

1) Interaction Effect: increased risk of QT interval prolongation

2) Summary: [Citalopram](#) has been associated with dose-dependent prolongation of the QTc interval and postmarketing cases of [torsade de pointes](#) [76] and [disopyramide](#) has been associated with QT prolongation [298]. Although this interaction has not been studied, the concomitant use of [citalopram](#) and [disopyramide](#) may increase the risk of QT interval prolongation and [torsade de pointes](#) and is, therefore, not recommended. If coadministration is required, monitor for ECG changes. Do not exceed [citalopram](#) doses of 40 mg/day and discontinue [citalopram](#) in patients who have persistent QTc measurements greater than 500 milliseconds [76].

3) Severity: major

- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Concomitant use of [citalopram](#) with other drugs that prolong the QT interval, such as [disopyramide](#) [298], is not recommended as concurrent use may increase the risk of cardiac adverse events, including [torsade de pointes](#). If coadministration is required, monitor for ECG changes. Do not exceed [citalopram](#) doses of 40 mg/day and discontinue [citalopram](#) in patients who have persistent QTc measurements greater than 500 milliseconds [76].
- 7) Probable Mechanism: additive effects on the QT interval

3.5.1.CD] [Dofetilide](#)

- 1) Interaction Effect: increased risk of QT interval prolongation
- 2) Summary: [Citalopram](#) causes dose-dependent prolongation of the QTc interval [76] and [dofetilide](#) has been associated with QT prolongation [311]. Although this interaction has not been evaluated, the concomitant use of [citalopram](#) with [dofetilide](#) is not recommended due to a risk of additive QT interval prolongation and [torsade de pointes](#). If coadministration is required, do not exceed [citalopram](#) doses of 40 mg/day and monitor for ECG changes. Discontinue [citalopram](#) in patients who have persistent QTc measurements greater than 500 milliseconds [76].
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Coadministration of [dofetilide](#) with [citalopram](#) is not recommended due to the potential for cardiac adverse events [311], including [torsade de pointes](#). If coadministration is required, do not exceed [citalopram](#) doses of 40 mg/day and monitor for ECG changes. Discontinue [citalopram](#) in patients who have persistent QTc measurements greater than 500 milliseconds [76].
- 7) Probable Mechanism: additive effects on the QT interval

3.5.1.CE] [Dolasetron](#)

- 1) Interaction Effect: increased risk of [serotonin syndrome](#) and QT-interval prolongation
- 2) Summary: Concomitant use of [dolasetron](#) with a drug that is a serotonergic agent with QT-interval prolonging effects may increase the risks of [serotonin syndrome](#) or QT-interval prolongation. [Serotonin syndrome](#) has been reported with the concurrent use of 5-hydroxytryptamine-3 antagonists and serotonergic drugs, primarily in infusion centers or in post-anesthesia care units. Inform patients of this increased risk and monitor for the emergence of [serotonin syndrome](#). If symptoms of [serotonin syndrome](#) occur, discontinue [dolasetron](#) and institute supportive therapy. Because [dolasetron](#) is known to prolong the QT-interval, administration with other QT-interval prolonging agents may result in additive effects, and should be undertaken with caution [87] [88].
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Concomitant use of [dolasetron](#) with a drug that is a serotonergic agent with QT-interval prolonging effects may increase the risks of [serotonin syndrome](#) or QT-interval prolongation. Inform patients of the increased risk of [serotonin syndrome](#) and monitor for the emergence of [serotonin syndrome](#). If symptoms of [serotonin syndrome](#) occur, discontinue [dolasetron](#) and institute supportive therapy. Because [dolasetron](#) is known to prolong the QT-interval, coadministration with other QT-interval prolonging agents may result in additive effects, and should be undertaken with caution [87] [88].
- 7) Probable Mechanism: unknown; additive QT-interval prolongation

3.5.1.CF] [Domperidone](#)

- 1) Interaction Effect: an increased risk of QT interval prolongation
- 2) Summary: Coadministration of [citalopram](#), a QT prolonging drug [76], and domperidone, a drug that has been associated with an increased risk of sudden cardiac death, is not recommended. In case control studies, an increased risk of sudden cardiac death was observed with the use of oral domperidone, particularly at doses greater than 30 mg/day and in patients older than 60 years of age [355]. If coadministration is required, monitor for ECG changes. Do not exceed [citalopram](#) doses of 40 mg/day and discontinue [citalopram](#) in patients who have persistent QTc measurements greater than 500 milliseconds [76]. Domperidone should be initiated at the lowest possible dose and titrated with caution. Discontinue domperidone if the patient experiences dizziness, palpitations, syncope, or seizure [355].
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Coadministration of [citalopram](#) and domperidone is not recommended due to a potential for additive effects on QT interval prolongation and an increased risk of serious cardiovascular effects. If coadministration is required, monitor for ECG changes. Do not exceed [citalopram](#) doses of 40 mg/day and discontinue [citalopram](#) in patients who have persistent QTc measurements greater than 500 milliseconds [76]. Domperidone should be initiated at the lowest possible dose and titrated with caution, particularly for domperidone doses greater than 30 mg/day and in patients older than 60 years. Discontinue domperidone if the patient experiences dizziness, palpitations, syncope, or seizure [355].
- 7) Probable Mechanism: additive effects on QT interval prolongation

3.5.1.CG| [Donepezil](#)

- 1) Interaction Effect: lower seizure threshold
- 2) Summary: Seizure threshold lowering effects have been associated with [donepezil](#) [83]. Use extreme caution when prescribing [donepezil](#) with drugs that lower seizure threshold (eg, antipsychotics, antidepressants, [theophylline](#), systemic corticosteroids). Begin treatment with a low initial dose and increase dose gradually.
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Seizure threshold lowering effects have been associated with [donepezil](#) [83]. Use extreme caution when prescribing [donepezil](#) with drugs that lower seizure threshold (eg, antipsychotics, antidepressants, [theophylline](#), systemic corticosteroids). Begin treatment with a low initial dose and increase dose gradually.
- 7) Probable Mechanism: unknown

3.5.1.CH| [Dronedaron](#)

- 1) Interaction Effect: increased risk of QT-interval prolongation
- 2) Summary: The concomitant use of dronedarone with drugs that cause QT-interval prolongation is contraindicated, as coadministration may increase the risk of QT prolongation and serious [ventricular arrhythmias](#) [201].
- 3) Severity: contraindicated
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: The concomitant use of dronedarone with drugs that cause QT-interval prolongation is contraindicated, as coadministration may increase the risk of QT prolongation and serious [ventricular arrhythmias](#) [201].
- 7) Probable Mechanism: additive QT-interval prolongation

3.5.1.CI] 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 [124].
- 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 [124].
- 7) Probable Mechanism: additive cardiac effects

3.5.1.CJ] Duloxetine

- 1) Interaction Effect: an increased risk of [serotonin syndrome](#)
- 2) Summary: [Duloxetine](#) is a selective serotonin and [norepinephrine](#) reuptake inhibitor. The concomitant use of [duloxetine](#) with [citalopram](#), a selective serotonin reuptake inhibitor, is not recommended due to the potential for [serotonin syndrome](#) [186].
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: The concomitant use of [citalopram](#) and [duloxetine](#) is not recommended due to the potential for development of [serotonin syndrome](#) [186].
- 7) Probable Mechanism: potentiation of serotonergic activity in the CNS by [duloxetine](#) and [citalopram](#)

3.5.1.CK] Efavirenz

- 1) Interaction Effect: increased [citalopram](#) exposure and increased risk for QT-interval prolongation
- 2) Summary: [Citalopram](#) is associated with dose-dependent increase in the QT interval. In a [pharmacokinetic study](#) in patients who received [citalopram](#) (a CYP2C19 substrate) 40 mg/day for 21 days, combined with [cimetidine](#) (a potent CYP2C19 inhibitor) 400 mg/day for 8 days resulted in an increase in [citalopram](#) AUC and Cmax of 43% and 39%, respectively. Although the interaction between [citalopram](#) and [efavirenz](#) (another CYP2C19 inhibitor) has not been specifically studied, concomitant use may increase [citalopram](#) exposure and increase the risk of QT interval prolongation. If concomitant use of [citalopram](#) and [efavirenz](#) is required, do not exceed [citalopram](#) doses of 20 mg/day [53] and consider [ECG monitoring](#) if clinically indicated.
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Concomitant administration of [citalopram](#) (a CYP2C19 substrate) and [efavirenz](#) (a CYP2C19 inhibitor) may lead to increased [citalopram](#) exposure and an increased risk of QT interval prolongation. If concomitant use of [citalopram](#) and [efavirenz](#) is required, do not exceed [citalopram](#) doses of 20 mg/day [53] and consider [ECG monitoring](#) if clinically indicated.
- 7) Probable Mechanism: inhibition of CYP2C19-mediated [citalopram](#) metabolism by [efavirenz](#)

3.5.1.CL] 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 [379].
- 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 [379].
- 7) Probable Mechanism: additive serotonergic effects

3.5.1.CM] 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 [340] [341] [339]. 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](#) [341] [339].
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: probable
- 6) Clinical Management: When [citalopram](#) and an anticoagulant are given concurrently, monitor patients for signs of increased bleeding. Patients who are taking [warfarin](#) should be monitored closely for altered anticoagulant effects, including increased bleeding, when [citalopram](#) therapy is initiated or discontinued [339].
- 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 [340].

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 [341].

c)) The pharmacokinetics of [warfarin](#), a CYP3A4 substrate, were not affected by the administration of [citalopram](#) 40 mg/day for 21 days, while the prothrombin time was increased by 5%. The clinical significance of this is unknown [339].

3.5.1.CN] [Eptifibatide](#)

1)) Interaction Effect: an increased risk of bleeding

2)) Summary: The concomitant use of [citalopram](#) and an antiplatelet drug may increase the risk of bleeding. The release of serotonin by [platelets](#) is important for maintaining hemostasis. Case-controlled and cohort studies have shown that the combined use of selective serotonin reuptake inhibitors and antiplatelet agents has been associated with an increased risk of bleeding. Bleeding events reported have included [epistaxis](#), ecchymosis, [hematoma](#), [petechiae](#), and life-threatening hemorrhages. Monitor patient for signs of increased bleeding when [citalopram](#) is administered concomitantly with an antiplatelet drug [40].

3)) Severity: major

4)) Onset: unspecified

5)) Substantiation: probable

6)) Clinical Management: When [citalopram](#) and an antiplatelet agent are given concurrently, monitor patient for signs of increased bleeding [40].

7)) Probable Mechanism: unknown

3.5.1.CO] [Erythromycin](#)

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

2)) Summary: [Citalopram](#) has caused dose-dependent prolongation of the QTc interval [76] and [erythromycin](#) has been associated with QT prolongation [300]. [Erythromycin](#) is a CYP3A4 inhibitor and has the potential to increase [citalopram](#) exposure. The concomitant use of [citalopram](#) with [erythromycin](#) is not recommended as coadministration may increase the risk of QT interval prolongation and [torsade de pointes](#). If coadministration is required, monitor for ECG changes. Do not exceed [citalopram](#) doses of 40 mg/day and discontinue [citalopram](#) in patients who have persistent QTc measurements greater than 500 milliseconds [76].

3)) Severity: major

4)) Onset: unspecified

5)) Substantiation: theoretical

6)) Clinical Management: The concomitant use of [citalopram](#) and [erythromycin](#) is not recommended due to an increased risk of cardiac adverse events, including [torsade de pointes](#). If coadministration is required, monitor for ECG changes. Do not exceed [citalopram](#) doses of 40 mg/day and discontinue [citalopram](#) in patients who have persistent QTc measurements greater than 500 milliseconds [76].

7J) Probable Mechanism: inhibition of [citalopram](#) CYP3A4-mediated metabolism; additive effects on the QT interval prolongation

3.5.1.CP| Escitalopram

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

2J) 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 [140].

3J) Severity: major

4J) Onset: unspecified

5J) Substantiation: theoretical

6J) 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 [140].

7J) Probable Mechanism: additive serotonergic effect

3.5.1.CQ| Eslicarbazepine Acetate

1J) Interaction Effect: decreased exposure of CYP3A4 substrate or increased exposure of CYP2C19 substrate

2J) Summary: Concurrent administration of eslicarbazepine acetate (a CYP3A4 inducer and a CYP2C19 inhibitor) with a CYP3A4 or a CYP2C19 substrate may decrease the exposure of the CYP3A4 substrate or increase the exposure of the CYP2C19 substrate [376]. If concomitantly administering, use caution and monitor the patient closely.

3J) Severity: major

4J) Onset: unspecified

5J) Substantiation: theoretical

6J) Clinical Management: Concurrent administration of eslicarbazepine acetate (a CYP3A4 inducer and a CYP2C19 inhibitor) with a CYP3A4 or a CYP2C19 substrate may decrease the exposure of the CYP3A4 substrate or increase the exposure of the CYP2C19 substrate [376]. If concomitantly administering, use caution and monitor the patient closely.

7J) Probable Mechanism: induction of CYP3A4-mediated metabolism; inhibition of CYP2C19-mediated metabolism by eslicarbazepine acetate

3.5.1.CR| [Esomeprazole](#)

1J) Interaction Effect: increased [citalopram](#) exposure and increased risk of QT interval prolongation

2J) Summary: [Citalopram](#) is associated with dose-dependent increase in the QT interval. In a [pharmacokinetic study](#) in patients who received [citalopram](#) 40 mg/day for 21 days, combined administration with [cimetidine](#) (a potent CYP2C19 inhibitor) 400 mg/day for 8 days resulted in an increase in [citalopram](#) AUC and C_{max} of 43% and 39%, respectively. Although the interaction between [citalopram](#) (a CYP2C19 substrate) and [esomeprazole](#) (another CYP2C19 inhibitor) has not been specifically studied, concomitant use may increase [citalopram](#) exposure and the risk of QT interval prolongation. If

concomitant administration of [citalopram](#) and [esomeprazole](#) is required, do not exceed [citalopram](#) doses of 20 mg/day [76].

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Concomitant administration of [citalopram](#) (a CYP2C19 substrate) and [esomeprazole](#), a potent CYP2C19 inhibitor, may lead to increased [citalopram](#) exposure and risk of QT interval prolongation. If concomitant use of [citalopram](#) and [esomeprazole](#) is required, do not exceed [citalopram](#) doses of 20 mg/day [76].

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

3.5.1.CS] [Etodolac](#)

1) Interaction Effect: an increased risk of bleeding

2) Summary: Caution is recommended with the concomitant use of NSAIDs and SSRIs due to an increased risk of [gastrointestinal bleeding](#) [228] [229]. Bleeding events have included [epistaxis](#), ecchymosis, [hematoma](#), [petechiae](#), and life-threatening hemorrhages [231] [53] [232] [233]. 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: probable

6) Clinical Management: Use caution if NSAIDs and SSRIs are coadministered. Concomitant use of NSAIDs and SSRIs may cause an increased risk of bleeding [228] [229]. When an SSRI and an NSAID are given concurrently, monitor the patient for signs of increased bleeding.

7) Probable Mechanism: unknown

8) Literature Reports

a) SSRIs increase the risk of upper gastrointestinal (GI) bleeding, and this effect is potentiated by concurrent use of NSAIDs or low-dose [aspirin](#). Hospitalizations for [upper GI bleeding](#) were searched among 26,005 users of antidepressant medications and compared with the number of hospitalizations in those patients who did not receive prescriptions for antidepressants. The amount of [upper GI bleeding](#) episodes was 3.6 times more than expected (95% CI, 2.7 to 4.7). Combined use of an SSRI and NSAIDs or low-dose [aspirin](#) increased the risk to 12.2 (95% CI, 7.1 to 19.5) and 5.2 (95% CI, 3.2 to 8), respectively. The findings of this study demonstrate an increased risk of [upper GI bleeding](#) during the use of SSRIs. Combined use of SSRIs and NSAIDs or low-dose [aspirin](#) increased the risk even further [230].

b) The 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 [53].

3.5.1.CT] [Etofenamate](#)

1) Interaction Effect: an increased risk of bleeding

2) Summary: Caution is recommended with the concomitant use of NSAIDs and SSRIs due to an increased risk of [gastrointestinal bleeding](#) [228] [229]. Bleeding events have included [epistaxis](#), ecchymosis, [hematoma](#), [petechiae](#), and life-threatening hemorrhages [231] [53] [232] [233]. 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: probable

6j) Clinical Management: Use caution if NSAIDs and SSRIs are coadministered. Concomitant use of NSAIDs and SSRIs may cause an increased risk of bleeding [228] [229]. When an SSRI and an NSAID are given concurrently, monitor the patient for signs of increased bleeding.

7j) Probable Mechanism: unknown

8j) Literature Reports

aj) SSRIs increase the risk of upper gastrointestinal (GI) bleeding, and this effect is potentiated by concurrent use of NSAIDs or low-dose [aspirin](#). Hospitalizations for [upper GI bleeding](#) were searched among 26,005 users of antidepressant medications and compared with the number of hospitalizations in those patients who did not receive prescriptions for antidepressants. The amount of [upper GI bleeding](#) episodes was 3.6 times more than expected (95% CI, 2.7 to 4.7). Combined use of an SSRI and NSAIDs or low-dose [aspirin](#) increased the risk to 12.2 (95% CI, 7.1 to 19.5) and 5.2 (95% CI, 3.2 to 8), respectively. The findings of this study demonstrate an increased risk of [upper GI bleeding](#) during the use of SSRIs. Combined use of SSRIs and NSAIDs or low-dose [aspirin](#) increased the risk even further [230].

bj) The 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 [53].

3.5.1.CU] Etoricoxib

1j) Interaction Effect: an increased risk of bleeding

2j) Summary: Caution is recommended with the concomitant use of NSAIDs and SSRIs due to an increased risk of [gastrointestinal bleeding](#) [228] [229]. Bleeding events have included [epistaxis](#), ecchymosis, [hematoma](#), [petechiae](#), and life-threatening hemorrhages [231] [53] [232] [233]. 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: probable

6j) Clinical Management: Use caution if NSAIDs and SSRIs are coadministered. Concomitant use of NSAIDs and SSRIs may cause an increased risk of bleeding [228] [229]. When an SSRI and an NSAID are given concurrently, monitor the patient for signs of increased bleeding.

7j) Probable Mechanism: unknown

8j) Literature Reports

aj) SSRIs increase the risk of upper gastrointestinal (GI) bleeding, and this effect is potentiated by concurrent use of NSAIDs or low-dose [aspirin](#). Hospitalizations for [upper GI bleeding](#) were searched among 26,005 users of antidepressant medications and compared with the number of hospitalizations in those patients who did not receive prescriptions for antidepressants. The amount of [upper GI bleeding](#) episodes was 3.6 times more than expected (95% CI, 2.7 to 4.7). Combined use of an SSRI and NSAIDs or low-dose [aspirin](#) increased the risk to 12.2 (95% CI, 7.1 to 19.5) and 5.2 (95% CI, 3.2 to 8), respectively. The findings of this study demonstrate an increased risk of [upper GI bleeding](#) during the use of SSRIs. Combined use of SSRIs and NSAIDs or low-dose [aspirin](#) increased the risk even further [230].

bj) The 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 [53].

3.5.1.CV] Felbamate

- 1) Interaction Effect: increased [citalopram](#) exposure and risk of QT interval prolongation
- 2) Summary: In a [pharmacokinetic study](#) in patients who received [citalopram](#) 40 mg/day for 21 days, combined administration with [cimetidine](#) (a potent CYP2C19 inhibitor) 400 mg/day for 8 days resulted in an increase in [citalopram](#) AUC and Cmax of 43% and 39%, respectively. Although the interaction between [citalopram](#) (a CYP2C19 substrate) and [felbamate](#) (another CYP2C19 inhibitor) has not been specifically studied, concomitant use may result in increased [citalopram](#) exposure and an increased risk of QT prolongation. If coadministration of [citalopram](#) with [felbamate](#) is required, do not exceed [citalopram](#) doses of 20 mg/day [76].
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: The concomitant use of [citalopram](#) with [felbamate](#) may result in increased [citalopram](#) exposure and risk of QT prolongation. If coadministration of [citalopram](#) with [felbamate](#) is required, do not exceed [citalopram](#) doses of 20 mg/day [76].
- 7) Probable Mechanism: inhibition of CYP2C19-mediated [citalopram](#) metabolism by [felbamate](#)

3.5.1.CW] Felbinac

- 1) Interaction Effect: an increased risk of bleeding
- 2) Summary: Caution is recommended with the concomitant use of NSAIDs and SSRIs due to an increased risk of [gastrointestinal bleeding](#) [228] [229]. Bleeding events have included [epistaxis](#), ecchymosis, [hematoma](#), [petechiae](#), and life-threatening hemorrhages [231] [53] [232] [233]. 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: probable
- 6) Clinical Management: Use caution if NSAIDs and SSRIs are coadministered. Concomitant use of NSAIDs and SSRIs may cause an increased risk of bleeding [228] [229]. When an SSRI and an NSAID are given concurrently, monitor the patient for signs of increased bleeding.
- 7) Probable Mechanism: unknown
- 8) Literature Reports

a) SSRIs increase the risk of upper gastrointestinal (GI) bleeding, and this effect is potentiated by concurrent use of NSAIDs or low-dose [aspirin](#). Hospitalizations for [upper GI bleeding](#) were searched among 26,005 users of antidepressant medications and compared with the number of hospitalizations in those patients who did not receive prescriptions for antidepressants. The amount of [upper GI bleeding](#) episodes was 3.6 times more than expected (95% CI, 2.7 to 4.7). Combined use of an SSRI and NSAIDs or low-dose [aspirin](#) increased the risk to 12.2 (95% CI, 7.1 to 19.5) and 5.2 (95% CI, 3.2 to 8), respectively. The findings of this study demonstrate an increased risk of [upper GI bleeding](#) during the use of SSRIs. Combined use of SSRIs and NSAIDs or low-dose [aspirin](#) increased the risk even further [230].

b) The 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 [53].

3.5.1.CX] 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 [citalopram](#), has the potential to cause [serotonin syndrome](#) [110]. [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 [111]. Until more data are available, [fenfluramine](#) should not be used in combination with [citalopram](#).
- 3) Severity: major
- 4) Onset: rapid
- 5) Substantiation: probable
- 6) Clinical Management: Concurrent use of [fenfluramine](#) and [citalopram](#) 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 [citalopram](#) or other serotonin specific reuptake inhibitors.
- 7) Probable Mechanism: additive serotonergic effects

3.5.1.CY] [Fenoprofen](#)

- 1) Interaction Effect: an increased risk of bleeding
- 2) Summary: Caution is recommended with the concomitant use of NSAIDs and SSRIs due to an increased risk of [gastrointestinal bleeding](#) [228] [229]. Bleeding events have included [epistaxis](#), ecchymosis, [hematoma](#), [petechiae](#), and life-threatening hemorrhages [231] [53] [232] [233]. 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: probable
- 6) Clinical Management: Use caution if NSAIDs and SSRIs are coadministered. Concomitant use of NSAIDs and SSRIs may cause an increased risk of bleeding [228] [229]. When an SSRI and an NSAID are given concurrently, monitor the patient for signs of increased bleeding.
- 7) Probable Mechanism: unknown
- 8) Literature Reports

a) SSRIs increase the risk of upper gastrointestinal (GI) bleeding, and this effect is potentiated by concurrent use of NSAIDs or low-dose [aspirin](#). Hospitalizations for [upper GI bleeding](#) were searched among 26,005 users of antidepressant medications and compared with the number of hospitalizations in those patients who did not receive prescriptions for antidepressants. The amount of [upper GI bleeding](#) episodes was 3.6 times more than expected (95% CI, 2.7 to 4.7). Combined use of an SSRI and NSAIDs or low-dose [aspirin](#) increased the risk to 12.2 (95% CI, 7.1 to 19.5) and 5.2 (95% CI, 3.2 to 8), respectively. The findings of this study demonstrate an increased risk of [upper GI bleeding](#) during the use of SSRIs. Combined use of SSRIs and NSAIDs or low-dose [aspirin](#) increased the risk even further [230].

b) The 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 [53].

3.5.1.CZ] [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, such as **citalopram** [53] [161]. . In 2 case reports, use of **fentanyl** with other serotonergic agents has resulted in symptoms consistent with **serotonin syndrome** [161] [160]. Monitor patients for signs and symptoms of **serotonin syndrome**, such as mental status changes, autonomic instability, neuromuscular abnormalities, and gastrointestinal symptoms, especially during treatment initiation and with dosage increases. If **serotonin syndrome** occurs, discontinue all serotonergic agents and provide supportive care [53]. Consider replacing **fentanyl** with a non-serotonergic opioids, such as **morphine**, when coadministering with **citalopram** if serotonergic symptoms occur.

3) Severity: major

4) Onset: unspecified

5) Substantiation: probable

6) Clinical Management: Coadministration of **fentanyl** with an SSRI, such as **citalopram**, may result in **serotonin syndrome** [53] [160]. . Monitor patients for signs and symptoms of **serotonin syndrome**, such as mental status changes (eg, agitation, hallucinations, **delirium**, and coma), autonomic instability (eg, **tachycardia**, labile blood pressure, dizziness, diaphoresis, flushing, **hyperthermia**), neuromuscular symptoms (eg, tremor, rigidity, myoclonus, hyperreflexia, incoordination), seizures and/or gastrointestinal symptoms (e., nausea, vomiting, diarrhea), especially during treatment initiation and with dosage increases. If **serotonin syndrome** occurs, discontinue all serotonergic agents and provide supportive care [53]. Consider replacing **fentanyl** with non-serotonergic opioids, such as **morphine**, during coadministration with **citalopram** if serotonergic symptoms occur.

7) Probable Mechanism: additive serotonergic effects

8) Literature Reports

a) A case report describes opioid associated **serotonin syndrome** in a 58-year-old man with a history of chronic back pain. The patient was stable while receiving treatment for pain and depression. His medication regimen included transdermal **fentanyl** 75 mcg/hr patches , **oxycodone** 5 mg/**acetaminophen** 325 mg twice daily, **celecoxib** 200 mg twice daily, **citalopram** 40 mg once daily, and **mirtazapine** 50 mg at night. The patient was also receiving **doxazosin** 4 mg daily and **zolpidem** 12.5 mg as needed for insomnia. The patient reported inadequate pain control and treatment with **fentanyl** was altered to replacing the patch every 2 days from every 3 days. Approximately 1 week after the **fentanyl** dose increase, the patient reported anxiety, tremulousness, fever, and sweating. **Clonidine** 0.2 mg every 4 hours was instituted without improvement in symptoms. The patient continued to have persistent symptoms and the following day was given **haloperidol** and **lorazepam** to treat anxiety and agitation. The patient discontinued his **fentanyl** patch and presented to the emergency room with opiate withdrawal 2 days later. The patient was then diagnosed with **serotonin syndrome** despite discontinuing his **fentanyl** patch for 30 hours. Treatment with **haloperidol**, **fentanyl**, **oxycodone/acetaminophen**, **citalopram**, and **mirtazapine** were immediately discontinued with a complete resolution of symptoms by the following day. The patient was prescribed **morphine** sulfate to replace **fentanyl** therapy, and was restarted on **citalopram** and **mirtazapine** with no recurrence of serotonergic symptoms on follow-up [161].

b) A 65-year-old woman treated with **citalopram** for depression experienced **serotonin syndrome** following initiation of **fentanyl** patch. She was recently diagnosed with myelodysplastic/myeloproliferative disease and her regular medication regimen included **rabeprazole**, **tolterodine**, **hydrocodone**, and over-the-counter NSAIDS. She was hospitalized upon presentation of abdominal pain and worsening back pain, and a spontaneous retroperitoneal hemorrhage was discovered. While hospitalized, her worsening back pain was treated with **fentanyl** transdermal patch (25 mcg/hr). Within 24 hours of **fentanyl** initiation, she progressively developed increasing confusion, agitation, combativeness, tremors in the upper extremities,

myoclonic jerks, hyperreflexia, and unsteady gait; consistent with [serotonin syndrome](#). [Tachycardia](#) was also observed (110 to 120 beats per minute). A [CT scan](#) and laboratory values did not reveal any abnormalities. [Fentanyl](#) was discontinued, and all of her symptoms resolved within 24 to 36 hours. Her symptoms did not recur with initiation of [oxycodone](#) for the treatment of the back pain. The association of this [serotonin syndrome](#) with the coadministration of [fentanyl](#) and [citalopram](#) in this case was deemed probable based on the Naranjo adverse event probability scale [160].

3.5.1.DA] Fepradinol

- 1) Interaction Effect: an increased risk of bleeding
- 2) Summary: Caution is recommended with the concomitant use of NSAIDs and SSRIs due to an increased risk of [gastrointestinal bleeding](#) [228] [229]. Bleeding events have included [epistaxis](#), ecchymosis, [hematoma](#), [petechiae](#), and life-threatening hemorrhages [231] [53] [232] [233]. 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: probable
- 6) Clinical Management: Use caution if NSAIDs and SSRIs are coadministered. Concomitant use of NSAIDs and SSRIs may cause an increased risk of bleeding [228] [229]. When an SSRI and an NSAID are given concurrently, monitor the patient for signs of increased bleeding.
- 7) Probable Mechanism: unknown
- 8) Literature Reports

a) SSRIs increase the risk of upper gastrointestinal (GI) bleeding, and this effect is potentiated by concurrent use of NSAIDs or low-dose [aspirin](#). Hospitalizations for [upper GI bleeding](#) were searched among 26,005 users of antidepressant medications and compared with the number of hospitalizations in those patients who did not receive prescriptions for antidepressants. The amount of [upper GI bleeding](#) episodes was 3.6 times more than expected (95% CI, 2.7 to 4.7). Combined use of an SSRI and NSAIDs or low-dose [aspirin](#) increased the risk to 12.2 (95% CI, 7.1 to 19.5) and 5.2 (95% CI, 3.2 to 8), respectively. The findings of this study demonstrate an increased risk of [upper GI bleeding](#) during the use of SSRIs. Combined use of SSRIs and NSAIDs or low-dose [aspirin](#) increased the risk even further [230].

b) The 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 [53].

3.5.1.DB] Feprazone

- 1) Interaction Effect: an increased risk of bleeding
- 2) Summary: Caution is recommended with the concomitant use of NSAIDs and SSRIs due to an increased risk of [gastrointestinal bleeding](#) [228] [229]. Bleeding events have included [epistaxis](#), ecchymosis, [hematoma](#), [petechiae](#), and life-threatening hemorrhages [231] [53] [232] [233]. 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: probable
- 6) Clinical Management: Use caution if NSAIDs and SSRIs are coadministered. Concomitant use of NSAIDs and SSRIs may cause an increased risk of bleeding [228] [229]. When an SSRI and an NSAID are given concurrently, monitor the patient for signs of increased bleeding.

7J) Probable Mechanism: unknown

8J) Literature Reports

aJ) SSRIs increase the risk of upper gastrointestinal (GI) bleeding, and this effect is potentiated by concurrent use of NSAIDs or low-dose [aspirin](#). Hospitalizations for [upper GI bleeding](#) were searched among 26,005 users of antidepressant medications and compared with the number of hospitalizations in those patients who did not receive prescriptions for antidepressants. The amount of [upper GI bleeding](#) episodes was 3.6 times more than expected (95% CI, 2.7 to 4.7). Combined use of an SSRI and NSAIDs or low-dose [aspirin](#) increased the risk to 12.2 (95% CI, 7.1 to 19.5) and 5.2 (95% CI, 3.2 to 8), respectively. The findings of this study demonstrate an increased risk of [upper GI bleeding](#) during the use of SSRIs. Combined use of SSRIs and NSAIDs or low-dose [aspirin](#) increased the risk even further [230].

bJ) The 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 [53].

3.5.1.DC] Fingolimod

1J) Interaction Effect: increased risk of [torsade de pointe](#)

2J) Summary: Both [citalopram](#) and fingolimod have been associated with an increased risk of QT interval prolongation and [torsade de pointes](#) [125] [76]. Drugs that prolong the QT interval, such as [citalopram](#), may increase the risk of [torsade de pointes](#) in patients with bradycardia. Since initiating fingolimod therapy may decrease heart rate and prolong QT interval, observe patients who are receiving [citalopram](#) with [continuous ECG monitoring](#) overnight in a medical facility when initiating fingolimod therapy [125].

3J) Severity: major

4J) Onset: unspecified

5J) Substantiation: theoretical

6J) Clinical Management: Concomitant use of [citalopram](#) and fingolimod should be avoided, due to an increased risk of QT interval prolongation and [torsade de pointes](#) [125] [76]. If coadministration is necessary, observe patients who are receiving [citalopram](#) with [continuous ECG monitoring](#) overnight in a medical facility when initiating fingolimod therapy [125].

7J) Probable Mechanism: additive QT interval prolongation

3.5.1.DD] [Flecainide](#)

1J) Interaction Effect: an increased risk of QT interval prolongation

2J) Summary: [Citalopram](#) causes dose-dependent prolongation of the QTc interval [76] and [flecainide](#) has been associated with QT prolongation [357]. Although this interaction has not been evaluated, the concomitant use of [citalopram](#) with [flecainide](#) is not recommended due to an increased risk of QT interval prolongation and [torsade de pointes](#). If coadministration is required, monitor for ECG changes. Do not exceed [citalopram](#) doses of 40 mg/day and discontinue [citalopram](#) in patients who have persistent QTc measurements greater than 500 milliseconds [76].

3J) Severity: major

4J) Onset: unspecified

5J) Substantiation: theoretical

6J) Clinical Management: The concomitant use of [citalopram](#) and [flecainide](#) is not recommended as both agents are known to increase the QT interval and concurrent use may increase the risk of cardiac adverse events, including [torsade de pointes](#). If coadministration is required, monitor for ECG changes. Do not exceed [citalopram](#) doses of 40 mg/day and discontinue [citalopram](#) in patients who have persistent QTc measurements greater than 500 milliseconds [76].

7J) Probable Mechanism: additive effects on the QT interval prolongation

3.5.1.DE] Floctafenine

1J) Interaction Effect: an increased risk of bleeding

2J) Summary: Caution is recommended with the concomitant use of NSAIDs and SSRIs due to an increased risk of [gastrointestinal bleeding](#) [228] [229]. Bleeding events have included [epistaxis](#), ecchymosis, [hematoma](#), [petechiae](#), and life-threatening hemorrhages [231] [53] [232] [233]. 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: probable

6J) Clinical Management: Use caution if NSAIDs and SSRIs are coadministered. Concomitant use of NSAIDs and SSRIs may cause an increased risk of bleeding [228] [229]. When an SSRI and an NSAID are given concurrently, monitor the patient for signs of increased bleeding.

7J) Probable Mechanism: unknown

8J) Literature Reports

aJ) SSRIs increase the risk of upper gastrointestinal (GI) bleeding, and this effect is potentiated by concurrent use of NSAIDs or low-dose [aspirin](#). Hospitalizations for [upper GI bleeding](#) were searched among 26,005 users of antidepressant medications and compared with the number of hospitalizations in those patients who did not receive prescriptions for antidepressants. The amount of [upper GI bleeding](#) episodes was 3.6 times more than expected (95% CI, 2.7 to 4.7). Combined use of an SSRI and NSAIDs or low-dose [aspirin](#) increased the risk to 12.2 (95% CI, 7.1 to 19.5) and 5.2 (95% CI, 3.2 to 8), respectively. The findings of this study demonstrate an increased risk of [upper GI bleeding](#) during the use of SSRIs. Combined use of SSRIs and NSAIDs or low-dose [aspirin](#) increased the risk even further [230].

bJ) The 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 [53].

3.5.1.DF] Fluconazole

1J) Interaction Effect: increased risk of QT interval prolongation and [serotonin syndrome](#)

2J) Summary: Concomitant use of drugs known to prolong the QT interval and that are metabolized by CYP3A4, such as [citalopram](#) [76] with [fluconazole](#) is contraindicated due to a potential for additive effects on QT interval prolongation and an increased risk of serious cardiac adverse events [312]. Additionally, 2 case reports describe the development of serotonin toxicity in female oncology patients undergoing concomitant administration of [citalopram](#) and [fluconazole](#) [313]. As [fluconazole](#) inhibits the CYP3A4-mediated [312] metabolism of [citalopram](#), patients receiving this combination may experience increased [citalopram](#) adverse events, including signs and symptoms of serotonin toxicity.

3J) Severity: contraindicated

4J) Onset: delayed

5J) Substantiation: probable

6J) Clinical Management: Concurrent use of drugs known to prolong the QT interval and that are metabolized by CYP3A4, such as [citalopram](#) [76], with [fluconazole](#) is contraindicated due to a potential for additive effects on QT interval prolongation and an increased risk of serious cardiac adverse events. Additionally, as [fluconazole](#) inhibits the CYP3A4-mediated [312] metabolism of [citalopram](#), increased [citalopram](#) adverse effects, including signs and symptoms of [serotonin syndrome](#), may result from coadministration.

- 7j) Probable Mechanism: additive effects on the QT interval; inhibition of CYP2C19-mediated and CYP3A4-mediated [citalopram](#) metabolism by [fluconazole](#)
- 8j) Literature Reports

a) A 46-year-old female developed signs and symptoms of [serotonin syndrome](#) several weeks after addition of [citalopram](#) 20 mg daily for depression while undergoing treatment of Philadelphia-positive [acute lymphocytic leukemia](#) prior to an allogeneic stem-cell transplant. Her medications included [fluconazole](#) 200 mg daily, [dapson](#) 100 mg daily, [acyclovir](#) 800 mg twice daily, [esomeprazole](#) 20 mg daily, [dexamethasone](#) 2.5 mg daily, [zolpidem](#) controlled release 12.5 mg nightly as needed, and [losartan/hydrochlorothiazide](#) 50 mg/12.5 mg daily. The patient presented after 2 weeks of worsening confusion, which was diagnosed as steroid vs methotrexate-induced [delirium](#) and treated with [olanzapine](#) 2.5 mg daily and a steroid taper. Eight days later, the patient presented again with worsening confusion and nonconvulsive seizures, and a clinical examination revealed severe perseveration, altered reflexes, impaired memory (short- and long-term), dull affect, and a Memorial [Delirium](#) Assessment Scale (MDAS) score of 9/30. After conditions such as [central nervous system leukemia](#) and [viral encephalitis](#) were ruled out, the patient was diagnosed with serotonin toxicity. [Citalopram](#) treatment was discontinued, and [phenytoin](#) 300 mg daily plus [olanzapine](#) 2.5 mg daily were initiated. Overall improvement was noted after 24 hours, with a substantial reduction in MDAS score to 2/30 after 2 days and improvement in depression, affect, and walking after 3 days. After 10 days, all psychiatric parameters were normal with no evidence of depression. A postulated mechanism for this interaction included inhibition of CYP2C19- and 3A4-mediated [citalopram](#) metabolism by [fluconazole](#) (a strong CYP2C19 inhibitor and moderate CYP3A4 inhibitor) leading to elevated [citalopram](#) concentrations [313].

b) A 73-year-old female developed signs and symptoms of serotonin toxicity during treatment of mild chronic depression with [citalopram](#) 40 mg daily and while undergoing treatment for [Burkitt's-like lymphoma](#) diagnosed 3 months prior. Her medications included [fluconazole](#) 100 mg daily, [clonazepam](#) 0.5 mg twice daily, [levofloxacin](#) 500 mg daily, [metoprolol](#) XL 100 mg daily, [acyclovir](#) 200 mg twice daily, [vancomycin](#) 1 gram twice daily, [amlodipine](#) 10 mg daily, [valsartan](#) 160 mg daily, and [pantoprazole](#) 40 mg daily. Two days after initiation of a routine cycle of [lymphoma](#) treatment, the patient developed fever and signs of [delirium](#), including somnolence and disorientation, which were attributed to ifosfamide treatment and did not improve with addition of methylene blue 50 mg every 8 hours and [olanzapine](#) 2.5 mg/hour. A clinical examination revealed [psychomotor impairment](#), disorientation with respect to time and place, absence of spontaneous speech, perplexed affect, dull thought process, and a Memorial [Delirium](#) Assessment Scale (MDAS) score of 13/30. The condition worsened over another 3 weeks, and the MDAS score increased to 18/30. After reevaluation, the patient was diagnosed with serotonin toxicity, which was attributed to inhibition of CYP2C19-mediated [citalopram](#) metabolism by [fluconazole](#) (a strong CYP2C19 inhibitor) leading to elevated [citalopram](#) concentrations and adverse events. Within 72 hours of discontinuing [citalopram](#) and increasing [olanzapine](#) to 7.5 mg daily, substantial improvement in [delirium](#) signs and symptoms as well as mood, affect, thought process, and MDAS score (10/30) were noted, and the patient was discharged after 1 week [313].

3.5.1.DG| Flufenamic Acid

- 1j) Interaction Effect: an increased risk of bleeding
- 2j) Summary: Caution is recommended with the concomitant use of NSAIDs and SSRIs due to an increased risk of [gastrointestinal bleeding](#) [228] [229]. Bleeding events have included [epistaxis](#), ecchymosis, [hematoma](#), [petechiae](#), and life-threatening hemorrhages [231] [53] [232] [233]. 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: probable
- 6) Clinical Management: Use caution if NSAIDs and SSRIs are coadministered. Concomitant use of NSAIDs and SSRIs may cause an increased risk of bleeding [228] [229]. When an SSRI and an NSAID are given concurrently, monitor the patient for signs of increased bleeding.
- 7) Probable Mechanism: unknown
- 8) Literature Reports

a) SSRIs increase the risk of upper gastrointestinal (GI) bleeding, and this effect is potentiated by concurrent use of NSAIDs or low-dose aspirin. Hospitalizations for upper GI bleeding were searched among 26,005 users of antidepressant medications and compared with the number of hospitalizations in those patients who did not receive prescriptions for antidepressants. The amount of upper GI bleeding episodes was 3.6 times more than expected (95% CI, 2.7 to 4.7). Combined use of an SSRI and NSAIDs or low-dose aspirin increased the risk to 12.2 (95% CI, 7.1 to 19.5) and 5.2 (95% CI, 3.2 to 8), respectively. The findings of this study demonstrate an increased risk of upper GI bleeding during the use of SSRIs. Combined use of SSRIs and NSAIDs or low-dose aspirin increased the risk even further [230].

b) The 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 [53].

3.5.1.DH] Fluoxetine

1) Interaction Effect: increased citalopram exposure and increased risk of QT interval prolongation and serotonin syndrome

2) Summary: Fluoxetine is an SSRI and a moderate CYP2C19 inhibitor associated with QT prolongation (and ventricular arrhythmias including torsade de pointes) [374], and citalopram is an SSRI and a CYP2C19 substrate associated with dose-dependent QT prolongation. In a pharmacokinetic study, patients who received citalopram 40 mg/day for 21 days coadministered with cimetidine (a potent CYP2C19 inhibitor) 400 mg/day for 8 days experienced an increase in citalopram AUC and Cmax of 43% and 39%, respectively [76]. Although the interaction between citalopram and fluoxetine has not been studied specifically, concomitant use may result in increased citalopram exposure, an increased risk of QT prolongation, and additive serotonergic effects. If coadministration of citalopram with fluoxetine is required, do not exceed citalopram 20 mg/day, and additionally monitor 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 citalopram and fluoxetine and initiate supportive care [76].

- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: The concomitant use of citalopram with fluoxetine may result in increased citalopram exposure and risk of QT prolongation. If coadministration of citalopram with fluoxetine is required, do not exceed citalopram doses of 20 mg/day. Additionally, concurrent use of citalopram with fluoxetine 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 [fluoxetine](#) and initiate supportive care [76].

7) Probable Mechanism: inhibition of CYP2C19-mediated [citalopram](#) metabolism of [fluoxetine](#); additive effects on QT interval prolongation; additive serotonergic effects

3.5.1.DI] [Flurbiprofen](#)

1) Interaction Effect: an increased risk of bleeding

2) Summary: Caution is recommended with the concomitant use of NSAIDs and SSRIs due to an increased risk of [gastrointestinal bleeding](#) [228] [229]. Bleeding events have included [epistaxis](#), ecchymosis, [hematoma](#), [petechiae](#), and life-threatening hemorrhages [231] [53] [232] [233]. 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: probable

6) Clinical Management: Use caution if NSAIDs and SSRIs are coadministered. Concomitant use of NSAIDs and SSRIs may cause an increased risk of bleeding [228] [229]. When an SSRI and an NSAID are given concurrently, monitor the patient for signs of increased bleeding.

7) Probable Mechanism: unknown

8) Literature Reports

a) SSRIs increase the risk of upper gastrointestinal (GI) bleeding, and this effect is potentiated by concurrent use of NSAIDs or low-dose [aspirin](#). Hospitalizations for [upper GI bleeding](#) were searched among 26,005 users of antidepressant medications and compared with the number of hospitalizations in those patients who did not receive prescriptions for antidepressants. The amount of [upper GI bleeding](#) episodes was 3.6 times more than expected (95% CI, 2.7 to 4.7). Combined use of an SSRI and NSAIDs or low-dose [aspirin](#) increased the risk to 12.2 (95% CI, 7.1 to 19.5) and 5.2 (95% CI, 3.2 to 8), respectively. The findings of this study demonstrate an increased risk of [upper GI bleeding](#) during the use of SSRIs. Combined use of SSRIs and NSAIDs or low-dose [aspirin](#) increased the risk even further [230].

b) The 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 [53].

3.5.1.DJ] [Fluvoxamine](#)

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 [370] 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 Cmax of 43% and 39%, respectively [76]. 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 [76].

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 [76].
- 7) Probable Mechanism: inhibition of CYP2C19-mediated [citalopram](#) metabolism by [fluvoxamine](#); additive serotonergic effects

3.5.1.DK] [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 [340] [341] [339]. 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](#) [341] [339].
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: probable
- 6) Clinical Management: When [citalopram](#) and an anticoagulant are given concurrently, monitor patients for signs of increased bleeding. Patients who are taking [warfarin](#) should be monitored closely for altered anticoagulant effects, including increased bleeding, when [citalopram](#) therapy is initiated or discontinued [339].
- 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 [340].

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 [341].

c) The pharmacokinetics of [warfarin](#), a CYP3A4 substrate, were not affected by the administration of [citalopram](#) 40 mg/day for 21 days, while the prothrombin time was increased by 5%. The clinical significance of this is unknown [339].

3.5.1.DL] [Formoterol](#)

1) Interaction Effect: increased risk of [ventricular arrhythmias](#)

2) Summary: [Formoterol](#) may prolong the QT interval, therefore concomitant use with other drugs that prolong the QT interval should be approached with caution due to additive effects on the QT interval and the potential for increased risk of [ventricular arrhythmias](#) [368]. Monitoring for QT interval prolongation may be warranted if [formoterol](#) and QT prolonging drugs are used concurrently.

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Use extreme caution with concomitant administration of [formoterol](#) and QT prolonging drugs as this may result in additive effects on the QT interval and may increase the risk of [ventricular arrhythmias](#) [368]. If coadministration is required, QT interval monitoring may be warranted.

7) Probable Mechanism: additive effects on QT interval

3.5.1.DM] [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) [377]. Because [frovatriptan](#) is a 5HT 1B/1D agonist, a similar interaction between SSRIs and [frovatriptan](#) may occur [378]. 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](#) [95].

3) Severity: major

4) Onset: delayed

5) Substantiation: probable

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

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

3.5.1.DN| Furazolidone

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

2J) Summary: Concomitant use of [citalopram](#) and an MAOI is contraindicated. Concurrent administration or overlapping therapy with [citalopram](#) 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, and tremor. A minimum of 14 days should elapse after discontinuing an MAOI intended to treat psychiatric disorders before initiating therapy with [citalopram](#), and a minimum of 14 days should elapse after discontinuing [citalopram](#) before initiating therapy with an MAOI intended to treat psychiatric disorders [53].

3J) Severity: contraindicated

4J) Onset: unspecified

5J) Substantiation: theoretical

6J) Clinical Management: Concurrent use of [citalopram](#) and an MAOI is contraindicated. Wait at least 14 days after discontinuing an MAOI intended to treat psychiatric disorders before initiating [citalopram](#). Wait at least 14 days after discontinuing [citalopram](#) before initiating therapy with an MAOI intended to treat psychiatric disorders [53].

7J) Probable Mechanism: additive serotonergic effect

3.5.1.DO| Gatifloxacin

1J) Interaction Effect: an increased risk of QT interval prolongation

2J) Summary: As [citalopram](#) causes dose-dependent prolongation of the QTc interval [76] and [gatifloxacin](#) has been associated with QT prolongation [326], the coadministration of these 2 agents is not recommended due to an increased risk of QT interval prolongation and [torsade de pointes](#). If coadministration is required, monitor for ECG changes. Do not exceed [citalopram](#) doses of 40 mg/day and discontinue [citalopram](#) in patients who have persistent QTc measurements greater than 500 milliseconds [76].

3J) Severity: major

4J) Onset: unspecified

5J) Substantiation: theoretical

6J) Clinical Management: The concomitant use of [citalopram](#) with [gatifloxacin](#) is not recommended as both agents are known to increase the QT interval and concurrent use may increase the risk of cardiac adverse events, including [torsade de pointes](#). If coadministration is required, monitor for ECG changes. Do not exceed [citalopram](#) doses of 40 mg/day and discontinue [citalopram](#) in patients who have persistent QTc measurements greater than 500 milliseconds [76].

7J) Probable Mechanism: additive effects on the QT interval

3.5.1.DP| Gemifloxacin

1J) Interaction Effect: an increased risk of QT interval prolongation

2J) Summary: [Citalopram](#) causes dose-dependent prolongation of the QTc interval [76]. Concomitant use of [citalopram](#) with other QT prolonging drugs, such as [gemifloxacin](#) [205], may increase the risk of QT interval prolongation and is not recommended. If concurrent therapy is required, do not exceed [citalopram](#) doses of 40 mg/day and monitor for ECG changes. Discontinue [citalopram](#) in patients who have persistent QTc measurements greater than 500 milliseconds [76].

3J) Severity: major

4J) Onset: unspecified

5J) Substantiation: theoretical

6) Clinical Management: Coadministration of [citalopram](#) with other QT-prolonging drugs, such as gemifloxacin [205], may increase the potential for serious cardiovascular effects and is not recommended. If concomitant therapy is required, do not exceed [citalopram](#) doses of 40 mg/day and monitor for ECG changes. Discontinue [citalopram](#) in patients who have persistent QTc measurements greater than 500 milliseconds [76].

7) Probable Mechanism: additive effects on the QT interval

3.5.1.DQJ Ginkgo

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

2) Summary: The addition of Ginkgo biloba and/or St. John's Wort to therapy with [buspirone](#) and [fluoxetine](#) may have precipitated a hypomanic episode in a case report [142]. 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 [143] [144], and has demonstrated serotonergic activity in animals [145] 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 [146]. Ginkgo biloba extract inhibited MAO-A/MAO-B in the rat brain in vitro [143] [144] and MAO-B in human [platelets](#) in vitro [144]. No significant MAO inhibition was found in mice following oral consumption [147].

3) Severity: moderate

4) Onset: delayed

5) Substantiation: probable

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

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

8) Literature Reports

a) A 42-year-old female experienced symptoms consistent with a mixed hypomanic episode following concomitant use of [fluoxetine](#), [buspirone](#), Ginkgo biloba, and St. John's Wort. The symptoms resolved following discontinuation of Ginkgo and St. John's Wort. The patient was being treated for depression following a mild [traumatic brain injury](#) with [fluoxetine](#) 20 milligrams (mg) twice daily and [buspirone](#) 15 mg twice daily. Several weeks prior to presentation, [buspirone](#) was increased to 20 mg twice daily for persistent anxiety and the patient began taking Ginkgo biloba, [melatonin](#), and St. John's Wort in unspecified doses. [Melatonin](#) was considered unlikely to have contributed to her symptoms. Ginkgo and St. John's Wort were considered possible contributors since they may potentiate antidepressants, and considering the temporal relationship between the use of the herbs and onset of symptoms and discontinuation of the herbs and resolution of symptoms. However, the [brain injury](#) was considered a possible contributor [141].

3.5.1.DRJ Gonadorelin

1) Interaction Effect: increased risk of QT-interval prolongation

2) Summary: Gonadotropin-releasing hormone (GnRH) agonists prolong the QT interval through their androgen-depriving action [261] [262] [263], while [citalopram](#) causes dose-dependent QT-interval prolongation that can lead to life-threatening [ventricular tachycardia](#) or [Torsade de Pointes](#). Avoid concomitant use of [citalopram](#) with GnRH agonists. If concurrent use is essential, [ECG monitoring](#) is recommended. Discontinue [citalopram](#) if persistent QTc measurements above 500 msec occur [38].

3) Severity: major

- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Avoid concomitant use of [citalopram](#) with gonadotropin-releasing hormone (GnRH) agonists, a class of drug known to prolong the QT interval, as additive QT-interval prolongation may occur. If concurrent use is essential, [ECG monitoring](#) is recommended. Discontinue [citalopram](#) if persistent QTc measurements above 500 msec occur [38].
- 7) Probable Mechanism: additive effects on the QT interval

3.5.1.DS] [Goserelin](#)

- 1) Interaction Effect: increased risk of QT-interval prolongation
- 2) Summary: Gonadotropin-releasing hormone (GnRH) agonists prolong the QT interval through their androgen-depriving action [261] [262] [263], while [citalopram](#) causes dose-dependent QT-interval prolongation that can lead to life-threatening [ventricular tachycardia](#) or [Torsade de Pointes](#). Avoid concomitant use of [citalopram](#) with GnRH agonists. If concurrent use is essential, [ECG monitoring](#) is recommended. Discontinue [citalopram](#) if persistent QTc measurements above 500 msec occur [38].
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Avoid concomitant use of [citalopram](#) with gonadotropin-releasing hormone (GnRH) agonists, a class of drug known to prolong the QT interval, as additive QT-interval prolongation may occur. If concurrent use is essential, [ECG monitoring](#) is recommended. Discontinue [citalopram](#) if persistent QTc measurements above 500 msec occur [38].
- 7) Probable Mechanism: additive effects on the QT interval

3.5.1.DT] [Granisetron](#)

- 1) Interaction Effect: increased risk of [serotonin syndrome](#) and QT-interval prolongation
- 2) Summary: Concomitant use of [granisetron](#) with a drug that is a serotonergic and QT-interval prolonging drug may increase the risk of [serotonin syndrome](#) [281] and the risk of QT-interval prolongation [282]. [Serotonin syndrome](#) has been reported with the cocurrent use of 5-hydroxytryptamine-3 antagonists and serotonergic drugs, primarily in infusion centers or in post-anesthesia care units. Inform patients of this increased risk. Monitor for the emergence of [serotonin syndrome](#) and discontinue treatment with [granisetron](#) and institute supportive therapy if symptoms of [serotonin syndrome](#) occur [281]. Coadministration with other drugs that prolong the QT-interval may result in additive effects on the QT-interval, therefore use with caution [282].
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Concomitant use of [granisetron](#) with a drug that is a serotonergic and QT-interval prolonging drug may increase the risk of [serotonin syndrome](#) [281] and the risk of QT-interval prolongation [282]. Inform patients of the increased risk of [serotonin syndrome](#). Monitor for the emergence of [serotonin syndrome](#) and discontinue treatment with [granisetron](#) and institute supportive therapy if symptoms of [serotonin syndrome](#) occur [281]. Coadministration with other drugs that prolong the QT-interval may result in additive effects on the QT-interval, therefore use with caution [282].
- 7) Probable Mechanism: unknown; additive QT-interval prolongation

3.5.1.DU] [Halofantrine](#)

- 1) Interaction Effect: increased risk of QT interval prolongation

2) Summary: [Citalopram](#) causes dose-dependent prolongation of the QTc interval [76] and [halofantrine](#) is also known to increase the QT interval. Concurrent use of these agents is not recommended due to an increased risk of cardiac adverse events, including rare reports of serious ventricular [dysrhythmias](#) sometimes associated with death. If administration of [halofantrine](#) is required in a patient receiving [citalopram](#), obtain a baseline ECG to ensure QTc interval is within normal limits, and monitor cardiac rhythm during and for 8 to 12 hours after completion of [halofantrine](#) therapy [330]. Additionally, do not exceed [citalopram](#) doses of 40 mg/day, and discontinue [citalopram](#) in patients who have persistent QTc measurements greater than 500 milliseconds [76].

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: The concomitant use of [citalopram](#) with [halofantrine](#) is not recommended due to an increased risk of cardiac adverse events, including serious ventricular [dysrhythmias](#) [76]. If administration of [halofantrine](#) is required in a patient receiving [citalopram](#), obtain a baseline ECG to ensure QTc interval is within normal limits, and monitor cardiac rhythm during and for 8 to 12 hours after completion of [halofantrine](#) therapy [330]. Additionally, do not exceed [citalopram](#) doses of 40 mg/day, and discontinue [citalopram](#) in patients who have persistent QTc measurements greater than 500 milliseconds [76].

7) Probable Mechanism: additive effects on the QT interval

3.5.1.DV] [Haloperidol](#)

1) Interaction Effect: increased risk of QT interval prolongation

2) Summary: [Citalopram](#) causes dose-dependent prolongation of the QTc interval [76] and [haloperidol](#) is known to prolong the QT interval [321]. Although this interaction has not been evaluated, the concomitant use of [citalopram](#) with [haloperidol](#) is not recommended as coadministration may increase the risk of QT interval prolongation and [torsade de pointes](#). If coadministration is required, do not exceed [citalopram](#) doses of 40 mg/day and monitor for ECG changes. Discontinue [citalopram](#) in patients who have persistent QTc measurements greater than 500 milliseconds [76].

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: The concomitant use of [citalopram](#) with [haloperidol](#) is not recommended, as both agents are known to increase the QT interval and concurrent use may increase the risk of cardiac adverse events, including [torsade de pointes](#). If coadministration is required, do not exceed [citalopram](#) doses of 40 mg/day and monitor for ECG changes. Discontinue [citalopram](#) in patients who have persistent QTc measurements greater than 500 milliseconds [76].

7) Probable Mechanism: additive effects on the QT interval

3.5.1.DW] [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 [340] [341] [339]. 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](#) [341] [339].

3) Severity: major

4) Onset: unspecified

5) Substantiation: probable

6j) Clinical Management: When [citalopram](#) and an anticoagulant are given concurrently, monitor patients for signs of increased bleeding. Patients who are taking [warfarin](#) should be monitored closely for altered anticoagulant effects, including increased bleeding, when [citalopram](#) therapy is initiated or discontinued [339].

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 [340].

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 [341].

cj) The pharmacokinetics of [warfarin](#), a CYP3A4 substrate, were not affected by the administration of [citalopram](#) 40 mg/day for 21 days, while the prothrombin time was increased by 5%. The clinical significance of this is unknown [339].

3.5.1.DX] [Histrelin](#)

1j) Interaction Effect: increased risk of QT-interval prolongation

2j) Summary: Gonadotropin-releasing hormone (GnRH) agonists prolong the QT interval through their androgen-depriving action [261] [262] [263], while [citalopram](#) causes dose-dependent QT-interval prolongation that can lead to life-threatening [ventricular tachycardia](#) or [Torsade de Pointes](#). Avoid concomitant use of [citalopram](#) with GnRH agonists. If concurrent use is essential, [ECG monitoring](#) is recommended. Discontinue [citalopram](#) if persistent QTc measurements above 500 msec occur [38].

3j) Severity: major

4j) Onset: unspecified

5j) Substantiation: theoretical

6j) Clinical Management: Avoid concomitant use of [citalopram](#) with gonadotropin-releasing hormone (GnRH) agonists, a class of drug known to prolong the QT interval, as additive QT-interval prolongation

may occur. If concurrent use is essential, [ECG monitoring](#) is recommended. Discontinue [citalopram](#) if persistent QTc measurements above 500 msec occur [38].

7J) Probable Mechanism: additive effects on the QT interval

3.5.1.DYJ [Hydroxychloroquine](#)

1J) Interaction Effect: increased risk of QT-interval prolongation

2J) Summary: [Hydroxychloroquine](#) has been associated with QT interval prolongation [314] [315], [ventricular premature contractions](#), and [torsade de pointes](#) [315]. Therefore, use caution with coadministration of [hydroxychloroquine](#) and other QT interval-prolonging drugs, as life-threatening additive effects on the QT interval, including [torsades de pointes](#), may occur. Consider close [ECG monitoring](#) at baseline and during concurrent therapy with QT-interval prolonging drugs.

3J) Severity: major

4J) Onset: unspecified

5J) Substantiation: probable

6J) Clinical Management: [Hydroxychloroquine](#) has been associated with QT interval prolongation [314] [315]. Therefore, use caution with coadministration of [hydroxychloroquine](#) and other QT interval-prolonging drugs, as life-threatening additive effects on the QT interval, including [torsades de pointes](#), may occur. Consider close [ECG monitoring](#) at baseline and during concurrent therapy with QT-interval prolonging drugs.

7J) Probable Mechanism: additive QT interval effects

8J) Literature Reports

aJ) Hydroxychloroquine-associated QT interval prolongation was reported in a 41-year-old woman with [congestive heart failure](#) with [systolic left ventricular dysfunction](#). Her comorbidities included [hypertension](#), [systemic lupus erythematosus](#), and [stage 5 chronic kidney disease](#). One week after reinitiation of [hydroxychloroquine](#) therapy, a significant prolongation of the QT interval (QTc 614 msec) was observed during a routine ECG. Following treatment discontinuation of [hydroxychloroquine](#), serial ECGs demonstrated a shortening of the QTc interval. The patient's QTc was 473 msec at a follow up 1 year after discharge [314].

bJ) QT prolongation and refractory [ventricular arrhythmia](#) were reported with chronic [hydroxychloroquine](#) use in a 67-year-old woman with [systemic lupus erythematosus](#). The patient had been receiving [prednisolone](#), [theophylline](#), and [hydroxychloroquine](#) 200 mg/day for 1 year. The patient had a medical history of [cirrhosis](#), [hepatitis B](#) virus related [hepatoma](#) with portal vein [thrombosis](#), and [asthma](#). The patient experienced a sudden episode of unconsciousness and generalized rigidity while at home. Although the patient regained consciousness within minutes and had no complaints of chest pain, palpitation, limb weakness, incontinence, or confusion, the episode recurred several times. Upon admission the ECG showed multiple [ventricular premature contractions](#), [torsade de pointes](#), and prolongation of the QT interval. Treatment with [hydroxychloroquine](#) was discontinued. Following medical management, [ventricular arrhythmia](#) subsided after 4 days and the QT interval shortened [315].

3.5.1.DZJ [Hydroxytryptophan](#)

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

2J) 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 [76].

- 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 [76].
- 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 [82].

3.5.1.EA] [Ibuprofen](#)

- 1) Interaction Effect: an increased risk of bleeding
- 2) Summary: Caution is recommended with the concomitant use of NSAIDs and SSRIs due to an increased risk of [gastrointestinal bleeding](#) [228] [229]. Bleeding events have included [epistaxis](#), ecchymosis, [hematoma](#), [petechiae](#), and life-threatening hemorrhages [231] [53] [232] [233]. 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: probable
- 6) Clinical Management: Use caution if NSAIDs and SSRIs are coadministered. Concomitant use of NSAIDs and SSRIs may cause an increased risk of bleeding [228] [229]. When an SSRI and an NSAID are given concurrently, monitor the patient for signs of increased bleeding.
- 7) Probable Mechanism: unknown
- 8) Literature Reports

a) SSRIs increase the risk of upper gastrointestinal (GI) bleeding, and this effect is potentiated by concurrent use of NSAIDs or low-dose [aspirin](#). Hospitalizations for [upper GI bleeding](#) were searched among 26,005 users of antidepressant medications and compared with the number of hospitalizations in those patients who did not receive prescriptions for antidepressants. The amount of [upper GI bleeding](#) episodes was 3.6 times more than expected (95% CI, 2.7 to 4.7). Combined use of an SSRI and NSAIDs or low-dose [aspirin](#) increased the risk to 12.2 (95% CI, 7.1 to 19.5) and 5.2 (95% CI, 3.2 to 8), respectively. The findings of this study demonstrate an increased risk of [upper GI bleeding](#) during the use of SSRIs. Combined use of SSRIs and NSAIDs or low-dose [aspirin](#) increased the risk even further [230].

b) The 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 [53].

3.5.1.EB] [Ibuprofen](#) Lysine

- 1) Interaction Effect: an increased risk of bleeding
- 2) Summary: Caution is recommended with the concomitant use of NSAIDs and SSRIs due to an increased risk of [gastrointestinal bleeding](#) [228] [229]. Bleeding events have included [epistaxis](#), ecchymosis,

hematoma, petechiae, and life-threatening hemorrhages [231] [53] [232] [233]. 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: probable

6) Clinical Management: Use caution if NSAIDs and SSRIs are coadministered. Concomitant use of NSAIDs and SSRIs may cause an increased risk of bleeding [228] [229]. When an SSRI and an NSAID are given concurrently, monitor the patient for signs of increased bleeding.

7) Probable Mechanism: unknown

8) Literature Reports

a) SSRIs increase the risk of upper gastrointestinal (GI) bleeding, and this effect is potentiated by concurrent use of NSAIDs or low-dose aspirin. Hospitalizations for upper GI bleeding were searched among 26,005 users of antidepressant medications and compared with the number of hospitalizations in those patients who did not receive prescriptions for antidepressants. The amount of upper GI bleeding episodes was 3.6 times more than expected (95% CI, 2.7 to 4.7). Combined use of an SSRI and NSAIDs or low-dose aspirin increased the risk to 12.2 (95% CI, 7.1 to 19.5) and 5.2 (95% CI, 3.2 to 8), respectively. The findings of this study demonstrate an increased risk of upper GI bleeding during the use of SSRIs. Combined use of SSRIs and NSAIDs or low-dose aspirin increased the risk even further [230].

b) The 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 [53].

3.5.1.EC] Ibutilide

1) Interaction Effect: increased risk of QT interval prolongation

2) Summary: Although the interaction has not been studied, both citalopram and ibutilide are known to cause QT interval prolongation [309] [76]. Concomitant use of ibutilide and citalopram is generally not recommended due to a potential for additive effects on QT interval prolongation and an increased risk of serious cardiovascular effects. If coadministration of citalopram and ibutilide is required, monitor for ECG changes. Do not exceed citalopram doses of 40 mg/day, and discontinue citalopram in patients who have persistent QTc measurements greater than 500 milliseconds [76].

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Concomitant use of citalopram and ibutilide is generally not recommended due to a potential for additive effects on QT interval prolongation and an increased risk of serious cardiovascular effects [309] [76]. If coadministration is required, monitor for ECG changes. Do not exceed citalopram doses of 40 mg/day, and discontinue citalopram in patients who have persistent QTc measurements greater than 500 milliseconds [76].

7) Probable Mechanism: additive effects on the QT interval

3.5.1.ED] Idelalisib

1) Interaction Effect: increased exposure of CYP3A substrate

2) Summary: Avoid coadministration of idelalisib (a strong CYP3A inhibitor) and a CYP3A substrate as this may increase exposure of the CYP3A substrate and increase the risk of adverse effects. During a drug interaction study, coadministration of idelalisib and midazolam (CYP3A substrate) resulted in a 5.4-fold increase in midazolam AUC and a 2.4 fold increase in midazolam Cmax [138].

- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Coadministration of idelalisib (a strong CYP3A inhibitor) and a CYP3A substrate should be avoided, as this may increase exposure of the CYP3A substrate and increase the risk of adverse effects [138].
- 7) Probable Mechanism: inhibition of CYP3A-mediated metabolism by idelalisib
- 8) Literature Reports

a) During a drug interaction study, administration of idelalisib 150 mg for 15 doses followed by a single dose of [midazolam](#) 5 mg (a CYP3A substrate) in healthy volunteers, resulted in a 5.4-fold increase in [midazolam](#) AUC and a 2.4 fold increase in [midazolam](#) Cmax [138].

3.5.1.EE] Iloperidone

- 1) Interaction Effect: an increased risk of QT interval prolongation
- 2) Summary: [Citalopram](#) causes dose-dependent prolongation of the QTc interval [76] and iloperidone has been associated with QT interval prolongation [327]. Concurrent use of these agents is not recommended [76] due to an increased risk of QT-interval prolongation, [torsade de pointes](#), and/or sudden death [327]. If coadministration is required, monitor for ECG changes. Do not exceed [citalopram](#) doses of 40 mg/day. Discontinue [citalopram](#) and/or iloperidone in patients who have persistent QTc measurements greater than 500 milliseconds [76] [327].
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: The concomitant use of [citalopram](#) with iloperidone is not recommended [76] as both agents are known to increase the QT interval resulting in an increased risk of QT interval prolongation, [torsade de pointes](#), and/or sudden death [327]. If coadministration is required, monitor for ECG changes [76]. Do not exceed [citalopram](#) doses of 40 mg/day. Discontinue [citalopram](#) and/or iloperidone in patients who have persistent QTc measurements greater than 500 milliseconds [76] [327].
- 7) Probable Mechanism: additive effects on the QT interval prolongation

3.5.1.EF] Imipramine

- 1) Interaction Effect: an increase in the bioavailability and half-life of [desipramine](#), the major metabolite of [imipramine](#)
- 2) Summary: [Imipramine](#) pharmacokinetics were not influenced by [citalopram](#) when the two were coadministered [245] [246]. However, [citalopram](#) may increase exposure to [desipramine](#), the major metabolite of [imipramine](#). Clinical events have not been reported and, in an isolated report, [citalopram](#) was successfully substituted for [paroxetine](#) in a patient who had experienced elevated tricyclic antidepressant levels during [paroxetine](#) treatment. Citalopram is an inhibitor of cytochrome P450 2D6 enzymes, and [imipramine](#), a tertiary amine, is converted to a secondary amine ([desipramine](#)) by N-demethylation. The secondary amine then undergoes hydroxylation, a process which is controlled by the oxidative enzymes of the CYP2D6 system [247].
- 3) Severity: moderate
- 4) Onset: rapid
- 5) Substantiation: probable
- 6) Clinical Management: Caution is indicated in the coadministration of tricyclic antidepressants and [citalopram](#). Consider monitoring tricyclic antidepressant concentration and/or dose adjustment when there is a change in therapy or dose of [citalopram](#). However, [citalopram](#) may be preferred over [paroxetine](#) when tricyclic antidepressants are coadministered.

7) Probable Mechanism: inhibition of [desipramine](#) metabolism, the major metabolite of [imipramine](#)

8) Literature Reports

a) Eight healthy male volunteers completed three phases of an interaction study to determine the effects of coadministered [imipramine](#) and [citalopram](#). All subjects were extensive metabolizers of sparteine, indicating normal cytochrome P450 2D6 enzyme activity. Each subject received [citalopram](#) 40 mg alone as a single daily dose for 10 days, [imipramine](#) 100 mg as a single oral dose, and a single oral dose of [imipramine](#) 100 mg coadministered on day 7 of [citalopram](#) therapy. At least two weeks separated each treatment phase. Results showed that the concurrent administration of [citalopram](#) and [imipramine](#) resulted in a 50% increase in the [desipramine](#) area under the concentration-time curve (AUC) and a similar decrease in the 2-hydroxy-desipramine AUC. Also, the [desipramine](#) half-life was approximately seven hours longer when administered with [citalopram](#) (27 hours vs. 20 hours). The AUC and half-life of [imipramine](#) were not affected by [citalopram](#) administration. These results showed that [citalopram](#) is an inhibitor of cytochrome P450 2D6 hepatic enzymes, since most tricyclic antidepressants rely on this system for metabolism [243].

b) A case report describes a 45-year-old white female with [major depressive disorder](#) and [dysthymia](#). This patient failed several trials of antidepressants from all available drug classes, as well as [electroconvulsive therapy](#). The patient's medications included [pindolol](#), [desipramine](#), [clonazepam](#), and [olanzapine](#). [Paroxetine](#) was initiated and titration to 40 mg/day occurred over 3 months. The patient developed light-headedness, ataxia, and increased confusion after the titration. [Desipramine](#) serum levels were 1810 ng/mL (therapeutic range 75-300 ng/mL). After decreasing the daily [desipramine](#) 200 mg, the serum [desipramine](#) level was still 1665 ng/mL. The reduction in side effects were evident when the [paroxetine](#) dose was decreased to 30 mg/day and [desipramine](#) dose was decreased to 150 mg/day. Despite the dosage reduction of both drugs the patient's serum [desipramine](#) level was 1153 ng/mL. [Paroxetine](#) was discontinued and [desipramine](#) dose was decreased to 100 mg/day in divided doses. [Citalopram](#) was initiated and titrated to 40 mg/day. Over the next two months the patient's [desipramine](#) level decreased to 195 ng/mL. Depressive symptoms also improved. [Desipramine](#) toxicity is presumed to be caused by hepatic cytochrome P450 2D6 (CYP2D6) isoenzyme blockade from [paroxetine](#). The author concludes that the switch to [citalopram](#) likely is responsible for diminished [desipramine](#) serum levels, although alternative explanations should not be discounted [244].

3.5.1.EG] [Indomethacin](#)

1) Interaction Effect: an increased risk of bleeding

2) Summary: Caution is recommended with the concomitant use of NSAIDs and SSRIs due to an increased risk of [gastrointestinal bleeding](#) [228] [229]. Bleeding events have included [epistaxis](#), ecchymosis, [hematoma](#), [petechiae](#), and life-threatening hemorrhages [231] [53] [232] [233]. 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: probable

6) Clinical Management: Use caution if NSAIDs and SSRIs are coadministered. Concomitant use of NSAIDs and SSRIs may cause an increased risk of bleeding [228] [229]. When an SSRI and an NSAID are given concurrently, monitor the patient for signs of increased bleeding.

7) Probable Mechanism: unknown

8) Literature Reports

a)) SSRIs increase the risk of upper gastrointestinal (GI) bleeding, and this effect is potentiated by concurrent use of NSAIDs or low-dose [aspirin](#). Hospitalizations for [upper GI bleeding](#) were searched among 26,005 users of antidepressant medications and compared with the number of hospitalizations in those patients who did not receive prescriptions for antidepressants. The amount of [upper GI bleeding](#) episodes was 3.6 times more than expected (95% CI, 2.7 to 4.7). Combined use of an SSRI and NSAIDs or low-dose [aspirin](#) increased the risk to 12.2 (95% CI, 7.1 to 19.5) and 5.2 (95% CI, 3.2 to 8), respectively. The findings of this study demonstrate an increased risk of [upper GI bleeding](#) during the use of SSRIs. Combined use of SSRIs and NSAIDs or low-dose [aspirin](#) increased the risk even further [230].

b)) The 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 [53].

3.5.1.EHJ [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 [290].

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 [290].

7)) Probable Mechanism: inhibition of [norepinephrine](#) transporter function by antidepressants

3.5.1.EI [Ioflupane I 123](#)

1)) Interaction Effect: interference with ioflupane I 123 imaging

2)) Summary: The ioflupane component of ioflupane I 123 binds to the [dopamine](#) transporter allowing for striatal [dopamine](#) transport visualization using [single photon emission computed tomography \(SPECT\) brain imaging](#). Because [citalopram](#) may increase or decrease ioflupane I 123 binding to the [dopamine](#) transporter, there is the potential for interference with ioflupane I 123 imaging. It is unknown whether discontinuing [citalopram](#) prior to ioflupane I 123 administration may minimize this interference [109]. The potential for imaging interference should be considered when administering ioflupane I 123 to patients who are already receiving [citalopram](#).

3)) Severity: moderate

4)) Onset: unspecified

5)) Substantiation: theoretical

6)) Clinical Management: Concomitant use of [citalopram](#) and ioflupane I 123 may result in interference with ioflupane I 123 imaging. It is unknown whether discontinuing [citalopram](#) prior to ioflupane I 123

administration may minimize the interference [109]. Consider the potential for imaging interference when administering ioflupane I 123 to patients who are already receiving [citalopram](#).

7J) Probable Mechanism: unknown

3.5.1.EJ] Iproniazid

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

2J) Summary: Concomitant use of [citalopram](#) and an MAOI is contraindicated. Concurrent administration or overlapping therapy with [citalopram](#) 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, and tremor. A minimum of 14 days should elapse after discontinuing an MAOI intended to treat psychiatric disorders before initiating therapy with [citalopram](#), and a minimum of 14 days should elapse after discontinuing [citalopram](#) before initiating therapy with an MAOI intended to treat psychiatric disorders [53].

3J) Severity: contraindicated

4J) Onset: unspecified

5J) Substantiation: theoretical

6J) Clinical Management: Concurrent use of [citalopram](#) and an MAOI is contraindicated. Wait at least 14 days after discontinuing an MAOI intended to treat psychiatric disorders before initiating [citalopram](#). Wait at least 14 days after discontinuing [citalopram](#) before initiating therapy with an MAOI intended to treat psychiatric disorders [53].

7J) Probable Mechanism: additive serotonergic effect

3.5.1.EK] Irinotecan

1J) Interaction Effect: an increased risk of [myopathy](#) or [rhabdomyolysis](#)

2J) Summary: [Rhabdomyolysis](#) has occurred in a patient after concomitant use of [irinotecan](#), a camptothelin which acts primarily as a topoisomerase I inhibitor, and [citalopram](#), a selective serotonin reuptake inhibitor (SSRI) [280].

3J) Severity: moderate

4J) Onset: delayed

5J) Substantiation: probable

6J) Clinical Management: If concurrent therapy is required, monitor the patient for signs and symptoms of [myopathy](#) or [rhabdomyolysis](#) (muscle pain, tenderness or weakness). Monitor [creatinine kinase](#) (CK) levels and discontinue use if CK levels show marked increase, or if [myopathy](#) or [rhabdomyolysis](#) is diagnosed or suspected.

7J) Probable Mechanism: inhibition of cytochrome P4503A4-mediated metabolism of [citalopram](#) by [irinotecan](#)

8J) Literature Reports

aJ) [Citalopram](#) interacted with [irinotecan](#) to produce [rhabdomyolysis](#) in a 74-year-old white male. He presented with 2-month history of fatigue, weight loss, and decreased appetite and was diagnosed with [adenocarcinoma](#). Three days before admission, he was treated with [irinotecan](#) in the outpatient clinic. On the day of admission, he presented to the emergency department complaining of weakness and pain. His medical history was significant for [coronary artery disease](#), [dyslipidemia](#), and [chronic obstructive lung disease](#). He was taking [enalapril](#), [alprazolam](#), [simvastatin](#), [citalopram](#), [nitroglycerin](#) and [aspirin](#) (no dosages were specified). Physical examination on admission was remarkable for generalized weakness and absence of focal neurologic signs. He had diffuse muscle tenderness. At admission his [creatinine kinase](#) (CK) level was 7400 units/liter (U/L) (49-397 U/L). All medications were discontinued following a diagnosis of

rhabdomyolysis. The CK decreased to 5542 U/L. The patient became depressed and **citalopram** 20 mg one time only was administered. The CK subsequently increased to 13529 U/L, and myoglobin was 27579 ng/mL. After **citalopram** was discontinued the CK and myoglobin decreased again during the next 5 days. The patient eventually regained his strength and was able to ambulate without pain upon discontinuation of **citalopram** [279].

3.5.1.EL] **Isocarboxazid**

- 1) Interaction Effect: an increased risk of **serotonin syndrome** (**hypertension**, **tachycardia**, **hyperthermia**, **myoclonus**, **mental status changes**)
- 2) Summary: Concomitant use of **citalopram** and an MAOI is contraindicated. Concurrent administration or overlapping therapy with **citalopram** 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, and tremor. A minimum of 14 days should elapse after discontinuing an MAOI intended to treat psychiatric disorders before initiating therapy with **citalopram**, and a minimum of 14 days should elapse after discontinuing **citalopram** before initiating therapy with an MAOI intended to treat psychiatric disorders [53].
- 3) Severity: contraindicated
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Concurrent use of **citalopram** and an MAOI is contraindicated. Wait at least 14 days after discontinuing an MAOI intended to treat psychiatric disorders before initiating **citalopram**. Wait at least 14 days after discontinuing **citalopram** before initiating therapy with an MAOI intended to treat psychiatric disorders [53].
- 7) Probable Mechanism: additive serotonergic effect

3.5.1.EM] **Itraconazole**

- 1) Interaction Effect: increased **citalopram** exposure and risk of QT interval prolongation
- 2) Summary: **Itraconazole** is a potent inhibitor of CYP3A4 and may result in increased **citalopram** exposure and risk of QT prolongation [76]. If administration of **itraconazole** with a drug that is metabolized by CYP3A4 (such as **citalopram**) is necessary, monitor plasma concentrations of **citalopram** if possible, and consider **citalopram** dosage adjustments [260].
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: The concomitant use of **citalopram**, a CYP3A4 substrate, and **itraconazole**, a potent CYP3A4 inhibitor, may result in increased **citalopram** exposure and risk of QT prolongation [76]. If administration of **itraconazole** with a drug that is metabolized by CYP3A4 (such as **citalopram**) is necessary, monitor plasma concentrations of **citalopram** if possible, and consider **citalopram** dosage adjustments [260].
- 7) Probable Mechanism: inhibition of CYP3A4-mediated **citalopram** metabolism by **itraconazole**

3.5.1.EN] **Ivabradine**

- 1) Interaction Effect: increased risk of QT prolongation
- 2) Summary: Ivabradine is associated with QT-interval prolongation. Concomitant administration of ivabradine with other drugs that prolong the QT interval, including antiarrhythmic medications, may have additive prolonging effects on the QT interval and should be avoided. If concomitant use is required, close cardiac monitoring is necessary [318] [319]. Consider a baseline ECG and on-treatment monitoring.
- 3) Severity: major

- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Concomitant administration of ivabradine and QT-prolonging drugs, including antiarrhythmic medications, may result in additive prolongation effects on the QT interval and should be avoided. If concomitant use is required, close cardiac monitoring is necessary [318] [319]. Consider a baseline ECG and on-treatment monitoring.
- 7) Probable Mechanism: additive QT-interval prolongation

3.5.1.EO] Ketoconazole

- 1) Interaction Effect: increased citalopram exposure and risk of QT interval prolongation
- 2) Summary: Using ketoconazole together with a CYP3A4 substrate known to prolong the QT interval, such as citalopram, may be contraindicated. Concomitant use may result in elevated plasma concentrations of citalopram, increasing the risk for QT prolongation and life-threatening ventricular tachyarrhythmias, including torsades de pointes [198]. Ketoconazole is a potent inhibitor of CYP3A4 and may be expected to decrease the metabolism of citalopram. However, the concomitant administration of citalopram 40 mg and ketoconazole 200 mg decreased ketoconazole C_{max} by 21% and AUC by 10%, but did not significantly affect the exposure of citalopram [76]. If concomitant use is required, monitor patient for signs and symptoms of increased or prolonged pharmacologic effects of ketoconazole [198] and consider monitoring ECG.
- 3) Severity: contraindicated
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Using ketoconazole together with a CYP3A4 substrate known to prolong the QT interval, such as citalopram, may be contraindicated. Concomitant use may result in elevated plasma concentrations of citalopram, increasing the risk for QT prolongation and life-threatening ventricular tachyarrhythmias, including torsades de pointes. If concomitant use is required, monitor patient for signs and symptoms of increased or prolonged pharmacologic effects of ketoconazole [198] and consider monitoring ECG.
- 7) Probable Mechanism: inhibition of CYP3A4-mediated citalopram metabolism by ketoconazole

3.5.1.EP] Ketoprofen

- 1) Interaction Effect: an increased risk of bleeding
- 2) Summary: Caution is recommended with the concomitant use of NSAIDs and SSRIs due to an increased risk of gastrointestinal bleeding [228] [229]. Bleeding events have included epistaxis, ecchymosis, hematoma, petechiae, and life-threatening hemorrhages [231] [53] [232] [233]. 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: probable
- 6) Clinical Management: Use caution if NSAIDs and SSRIs are coadministered. Concomitant use of NSAIDs and SSRIs may cause an increased risk of bleeding [228] [229]. When an SSRI and an NSAID are given concurrently, monitor the patient for signs of increased bleeding.
- 7) Probable Mechanism: unknown
- 8) Literature Reports

a) SSRIs increase the risk of upper gastrointestinal (GI) bleeding, and this effect is potentiated by concurrent use of NSAIDs or low-dose aspirin. Hospitalizations for upper GI bleeding were searched among 26,005 users of antidepressant medications and compared with the number of hospitalizations in those patients who did not receive prescriptions for antidepressants. The

amount of [upper GI bleeding](#) episodes was 3.6 times more than expected (95% CI, 2.7 to 4.7). Combined use of an SSRI and NSAIDs or low-dose [aspirin](#) increased the risk to 12.2 (95% CI, 7.1 to 19.5) and 5.2 (95% CI, 3.2 to 8), respectively. The findings of this study demonstrate an increased risk of [upper GI bleeding](#) during the use of SSRIs. Combined use of SSRIs and NSAIDs or low-dose [aspirin](#) increased the risk even further [230].

b) The 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 [53].

3.5.1.EQ] Ketorolac

1) Interaction Effect: an increased risk of bleeding

2) Summary: Caution is recommended with the concomitant use of NSAIDs and SSRIs due to an increased risk of [gastrointestinal bleeding](#) [228] [229]. Bleeding events have included [epistaxis](#), ecchymosis, [hematoma](#), [petechiae](#), and life-threatening hemorrhages [231] [53] [232] [233]. 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: probable

6) Clinical Management: Use caution if NSAIDs and SSRIs are coadministered. Concomitant use of NSAIDs and SSRIs may cause an increased risk of bleeding [228] [229]. When an SSRI and an NSAID are given concurrently, monitor the patient for signs of increased bleeding.

7) Probable Mechanism: unknown

8) Literature Reports

a) SSRIs increase the risk of upper gastrointestinal (GI) bleeding, and this effect is potentiated by concurrent use of NSAIDs or low-dose [aspirin](#). Hospitalizations for [upper GI bleeding](#) were searched among 26,005 users of antidepressant medications and compared with the number of hospitalizations in those patients who did not receive prescriptions for antidepressants. The amount of [upper GI bleeding](#) episodes was 3.6 times more than expected (95% CI, 2.7 to 4.7). Combined use of an SSRI and NSAIDs or low-dose [aspirin](#) increased the risk to 12.2 (95% CI, 7.1 to 19.5) and 5.2 (95% CI, 3.2 to 8), respectively. The findings of this study demonstrate an increased risk of [upper GI bleeding](#) during the use of SSRIs. Combined use of SSRIs and NSAIDs or low-dose [aspirin](#) increased the risk even further [230].

b) The 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 [53].

3.5.1.ER] Lansoprazole

1) Interaction Effect: increased [citalopram](#) exposure and risk of QT interval prolongation

2) Summary: In a [pharmacokinetic study](#) in patients who received [citalopram](#) 40 mg/day for 21 days, combined administration with [cimetidine](#) (a potent CYP2C19 inhibitor) 400 mg/day for 8 days resulted in an increase in [citalopram](#) AUC and Cmax of 43% and 39%, respectively. Although the interaction between [citalopram](#) (a CYP2C19 substrate) and [lansoprazole](#) (another CYP2C19 inhibitor) [199] has not been specifically studied, concomitant use may result in increased [citalopram](#) exposure and risk of QT prolongation. If coadministration of [citalopram](#) with [lansoprazole](#) is required, do not exceed [citalopram](#) doses of 20 mg/day. Discontinue [citalopram](#) in patients who have persistent QTc measurements greater than 500 milliseconds [76].

- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: The concomitant use of [citalopram](#), a CYP2C19 substrate, and a CYP2C19 inhibitor, such as [lansoprazole](#), may result in increased [citalopram](#) exposure and risk of QT prolongation. If coadministration of [citalopram](#) with [lansoprazole](#) is required, do not exceed [citalopram](#) doses of 20 mg/day. Discontinue [citalopram](#) in patients who have persistent QTc measurements greater than 500 milliseconds [76].
- 7) Probable Mechanism: inhibition of CYP2C19-mediated [citalopram](#) metabolism by [lansoprazole](#)

3.5.1.ES] Lapatinib

- 1) Interaction Effect: increased risk of QT interval prolongation
- 2) Summary: [Citalopram](#) causes dose-dependent prolongation of the QTc interval [76] and lapatinib has also been associated with QT prolongation [305]. Although this interaction has not been studied, the concomitant use of [citalopram](#) and lapatinib may increase the risk of QT interval prolongation and [torsade de pointes](#) and is, therefore, not recommended. If coadministration is required, do not exceed [citalopram](#) doses of 40 mg/day and monitor for ECG changes. Discontinue [citalopram](#) in patients who have persistent QTc measurements greater than 500 milliseconds. [Torsade de pointes](#) has been reported during postmarketing use of [citalopram](#) [76].
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Concomitant use of [citalopram](#) with other drugs that prolong the QT interval, such as lapatinib [305], is not recommended as concurrent use may increase the risk of cardiac adverse events, including [torsade de pointes](#). If coadministration is required, do not exceed [citalopram](#) doses of 40 mg/day and monitor for ECG changes. Discontinue [citalopram](#) in patients who have persistent QTc measurements greater than 500 milliseconds [76].
- 7) Probable Mechanism: additive effects on the QT interval

3.5.1.ET] Leuprolide

- 1) Interaction Effect: increased risk of QT-interval prolongation
- 2) Summary: Gonadotropin-releasing hormone (GnRH) agonists prolong the QT interval through their androgen-depriving action [261] [262] [263], while [citalopram](#) causes dose-dependent QT-interval prolongation that can lead to life-threatening [ventricular tachycardia](#) or [Torsade de Pointes](#). Avoid concomitant use of [citalopram](#) with GnRH agonists. If concurrent use is essential, [ECG monitoring](#) is recommended. Discontinue [citalopram](#) if persistent QTc measurements above 500 msec occur [38].
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Avoid concomitant use of [citalopram](#) with gonadotropin-releasing hormone (GnRH) agonists, a class of drug known to prolong the QT interval, as additive QT-interval prolongation may occur. If concurrent use is essential, [ECG monitoring](#) is recommended. Discontinue [citalopram](#) if persistent QTc measurements above 500 msec occur [38].
- 7) Probable Mechanism: additive effects on the QT interval

3.5.1.EU] Levofloxacin

- 1) Interaction Effect: increased risk of QT interval prolongation

2)) Summary: Although the interaction has not been studied, both [citalopram](#) and [levofloxacin](#) are known to prolong the QT interval [323] and concurrent use of these agents is not recommended due to a potential for additive effects on the QT interval and an increased risk of serious cardiovascular effects. If coadministration is required, monitor for ECG changes. Do not exceed [citalopram](#) doses of 40 mg/day, and discontinue [citalopram](#) in patients who have persistent QTc measurements greater than 500 milliseconds [76].

3)) Severity: major

4)) Onset: unspecified

5)) Substantiation: theoretical

6)) Clinical Management: Concomitant use of [citalopram](#) and [levofloxacin](#) is not recommended due to a potential for additive effects on the QT interval and an increased risk of serious cardiovascular effects. If coadministration is required, monitor for ECG changes. Do not exceed [citalopram](#) doses of 40 mg/day, and discontinue [citalopram](#) in patients who have persistent QTc measurements greater than 500 milliseconds [76].

7)) Probable Mechanism: additive effects on QT interval

3.5.1.EV] 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 [citalopram](#) that prolong the QT interval [106].

3)) Severity: contraindicated

4)) Onset: delayed

5)) Substantiation: theoretical

6)) Clinical Management: Levomethadyl is contraindicated in patients being treated with [citalopram](#) as it may precipitate QT prolongation and interact with levomethadyl.

7)) Probable Mechanism: unknown

3.5.1.EW] 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 [248].

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 [248].

7)) Probable Mechanism: additive serotonergic effects

3.5.1.EX] 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 [236].
- 3) Severity: moderate
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) 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 [236].
- 7) Probable Mechanism: unknown

3.5.1.EY] Linezolid

- 1) Interaction Effect: an increased risk of [serotonin syndrome](#) ([hypertension](#), [tachycardia](#), [hyperthermia](#), [myoclonus](#), [mental status changes](#))
- 2) Summary: Coadministration of [citalopram](#) and an MAOI, such as [linezolid](#), is contraindicated. If urgent treatment with [linezolid](#) is required, alternatives are not available, and risk/benefit has been evaluated, promptly discontinue [citalopram](#) and then administer [linezolid](#). Monitor for [serotonin syndrome](#) for 2 weeks or until 24 hours after the last dose of [linezolid](#), whichever comes first. Treatment with [citalopram](#) can be resumed within 24 hours of the last [linezolid](#) dose [53].
- 3) Severity: contraindicated
- 4) Onset: unspecified
- 5) Substantiation: probable
- 6) Clinical Management: Concurrent use of [citalopram](#) and an MAOI, such as [linezolid](#), is contraindicated. If urgent treatment with [linezolid](#) is necessary, alternatives are not available, and risk/benefit has been evaluated, promptly discontinue [citalopram](#) and then administer [linezolid](#). Monitor for [serotonin syndrome](#) for 2 weeks or until 24 hours after the last dose of [linezolid](#), whichever comes first. [Citalopram](#) can be resumed 24 hours after the last dose of [linezolid](#) [53].
- 7) Probable Mechanism: additive serotonergic effects
- 8) Literature Reports

a) [Citalopram](#) and [linezolid](#) resulted in [thrombocytopenia](#), [serotonin syndrome](#), and [lactic acidosis](#) and ultimately death in a 81-year-old man. The patient was admitted for surgical [debridement](#) of ankle [osteomyelitis](#) due to MRSA. For 3 weeks prior to admission, he received [citalopram](#) 20 mg twice daily. Other medications included [prednisone](#), [methotrexate](#), [digoxin](#), trinitrate transdermic patch, [torsemide](#), [insulin](#), and [oxazepam](#). The patient began [linezolid](#) 600 mg twice daily following surgery. Changes in the patient's mental status appeared after one week of [linezolid](#) therapy. At week 3, the patient developed fever, [high blood pressure](#), [tachycardia](#), confusion, and tremors without localizable neurologic signs. The patient experienced [cardiac arrest](#) and he was successfully intubated and ventilated without drugs. The patient's serum lactate level rose to 29.1 mmol, and, in addition to severe [lactic acidosis](#) (pH, 6.9), the [hepatic failure](#) worsened. Cardiac [ultrasonography](#) revealed major [ventricular dysfunction](#). The patient died following 3 additional [cardiac arrest](#) events. The autopsy revealed drug [encephalopathy](#) and [myocardial infarction](#). The results of the [bacterial cultures](#) were negative. If [linezolid](#) is the therapy of choice, treatment with the SSRI should be discontinued at least 2 weeks prior to initiating [linezolid](#) therapy [252].

b)) A retrospective chart review identified one highly probable case of [serotonin syndrome](#) in a patient who received concomitant therapy with [linezolid](#) and [venlafaxine](#), followed by [citalopram](#). Charts of 72 inpatients who received [linezolid](#) and an SSRI or [venlafaxine](#) within 14 days of each other were reviewed for a diagnosis of [serotonin syndrome](#) (SS) using the Sternbach and the Hunter serotonin toxicity criteria. Of these patients, 52 (72%) were treated concomitantly with [linezolid](#) and an SSRI or [venlafaxine](#). Four patients met the criteria for having either high or low probability of SS. Of these, one case involved an 81-year-old woman who was determined to have a high probability of SS after receiving concomitant [linezolid](#) and [venlafaxine](#) followed by [citalopram](#). [Linezolid](#) was given for a vancomycin-resistant Enterococcus UTI. When the patient presented, she refused to eat, was confused as to time and place, and began shouting. Although she appeared to have met 6 of the Sternbach criteria and 4 of the Hunter criteria for SS, a diagnosis of SS was not documented in her chart. Her blood pressure was 180 mmHg with a heart rate of 120 beats/min and a respiratory rate of 50 breaths/min. The following day, she barely spoke and could not be aroused; additional symptoms included lethargy, extremity twitching and jerking, eyes rolled back in her head, and labored breathing. [Linezolid](#) was discontinued, and she was sedated and intubated. Five days following onset of symptoms and 2 days after [linezolid](#) was stopped, she was extubated and had returned to baseline mental status with the ability to communicate [253].

c)) [Serotonin syndrome](#) was reported in the case of a 56-year-old woman who was admitted for an allogeneic stem cell transplant. Prior to the transplant, the patient received [fludarabine](#), [melphalan](#), and antithymocyte globulin. She had a medical history of [cystic fibrosis](#), [asthma](#), fungal [sinusitis](#), and depression. Ten days following transplantation, the patient required mechanical ventilation for increasing respiratory distress and was treated empirically with [vancomycin](#) 1 g IV every 24 hours, [ceftazidime](#) 2 g IV every 8 hours, [acyclovir](#) 300 mg IV every 8 hours, and [voriconazole](#) 200 mg orally twice daily for [febrile neutropenia](#) and [aspiration pneumonia](#). Urine culture grew vancomycin-resistant enterococci susceptible to [linezolid](#), so [vancomycin](#) was discontinued and [linezolid](#) 600 mg every 12 hours was initiated. The patient was prescribed [mirtazapine](#) 30 mg orally and [citalopram](#) 40 mg orally daily along with other medications. After 4 days of concomitant therapy with [linezolid](#), [mirtazapine](#), and [citalopram](#), the patient developed [hypertension](#) (160 to 170 mmHg/80 to 100 mmHg), [tachycardia](#) (130 to 140 beats/min), and fever (100.2 degrees F). She became confused, distressed, lethargic, shaky, and weak. Her diagnostic lab values were noted as: lactic dehydrogenase (2931 units/L), AST (52 units/mL), troponin I (0.18 nanogram/milliliter), [alkaline phosphatase](#) (160 units/L), [total bilirubin](#) (2.8 mg/dL), and creatine kinase-myocardial band (8.9 mcg/L). Final [blood culture](#) results reported were negative and [linezolid](#) was discontinued. The patient's symptoms diminished within 2 days of [linezolid](#) being discontinued [254].

d)) In one case report, a 37-year-old man experienced symptoms of [serotonin syndrome](#) after concomitant treatment with [citalopram](#) and [linezolid](#). He was admitted for [cellulitis](#) and [panniculitis](#) in his right leg. His medical history consisted of [hypertension](#), [multiple myeloma](#), [type 2 diabetes](#), depression, [passive-aggressive behavior](#), and adaptation trouble. The patient was treated for suspected MRSA with IV [vancomycin](#). Prior to admission, the patient was receiving oral [citalopram](#) 40 mg daily, [olanzapine](#) 2.5 mg daily, [trazodone](#) 150 mg daily at bedtime, [clonazepam](#) 2 mg 3 times daily, [hydromorphone](#) 125 mg subQ every 4 hours, and other medications. On day 5, the patient's infection improved and [vancomycin](#) was discontinued. He was discharged 2 days later on a regimen of oral [linezolid](#) 600 mg twice daily for 10 days. After 3 days of [linezolid](#) therapy, the patient reported having panic attacks and severe anxiety. After 5 days of [linezolid](#), he was readmitted to the hospital for these symptoms, where he developed hot flashes, tremors, excessive sweating, palpitations, and peribuccal numbness. His blood pressure (206/102

mmHg) and heart rate (112 beats/min) were elevated. On day 2, his blood pressure was 170/80 mmHg, and he was still anxious and experiencing multiple panic attacks. [Methotrimeprazine](#) 12.5 mg twice daily, [bisoprolol](#) 5 mg daily, and [ondansetron](#) 8 mg as needed were introduced; [olanzapine](#) dose was increased to 12.5 mg/day. One day 4, [linezolid](#) was suspected as a possible cause of [serotonin syndrome](#) and was discontinued. Only one dose of [linezolid](#) remained of the 10-day regimen. On day 5, the patient's level of anxiety decreased and blood pressure varied (138/80 to 160/80 mmHg). By day 9, his symptoms subsided and blood pressure (140/80 mmHg) and heart rate (80 beats/min) returned to normal [255].

e) In one case report, an 85-year-old woman experienced symptoms of [serotonin syndrome](#) after concomitant treatment with [citalopram](#) and [linezolid](#). Her medical history included [hypertension](#), depression, essential tremor, and pulmonary embolus. She was admitted to a nursing facility after hospitalization for systemic infection with oxacillin-resistant *Staphylococcus aureus* stemming from tibial [bursitis](#). Her medications included [citalopram](#) and [linezolid](#). Upon examination, the patient showed signs of tremors, confusion, restlessness, and difficulty speaking. No signs of infection were found. Once concurrent use of [citalopram](#) and [linezolid](#) were identified, [citalopram](#) was discontinued. Her mental and physical status improved after 72 hours [256].

3.5.1.EZ] [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 [215]. 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](#) [216] [217]. Two studies have failed to identify a pharmacokinetic interaction between [lithium](#) and [citalopram](#) [218] [219]. 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 [220]. Concurrent use of [fluvoxamine](#) and [lithium](#) has led to case reports of increased [lithium](#) levels and [neurotoxicity](#), [serotonin syndrome](#), somnolence, and mania [215] [221] [222] [223]. No pharmacokinetic interference was apparent during a multiple-dose study of coadministered [lithium](#) and [paroxetine](#) [224]. 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) [221] [215].

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** [207]. **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** [208].

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** [209].

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** [210].

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 [211].

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 [212].

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 [213].

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 [214].

3.5.1.FA] [Lopinavir](#)

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

2) Summary: QT interval prolongation and [torsade de pointes](#) have been reported with both [citalopram](#) [76] and [lopinavir/ritonavir](#) [225]. Due to the potential for additive effects on the QT interval and increased risk of [torsade de pointes](#), avoid the concomitant use of [citalopram](#) with [lopinavir/ritonavir](#) [225]. If coadministration is required, do not exceed [citalopram](#) doses of 40 mg/day and monitor for ECG changes. Discontinue [citalopram](#) in patients who have persistent QTc measurements greater than 500 milliseconds [76].

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Avoid the concomitant use of [lopinavir/ritonavir](#) with other drugs that prolong the QT interval, such as [citalopram](#) [76], as coadministration may result in additive effects on the QT interval and an increased risk of [torsade de pointes](#) [225]. If coadministration is required, do not exceed [citalopram](#) doses of 40 mg/day and monitor for ECG changes. Discontinue [citalopram](#) in patients who have persistent QTc measurements greater than 500 milliseconds [76].

7) Probable Mechanism: additive effects on QT interval prolongation

3.5.1.FB] [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 [92].

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 [92].
- 7) Probable Mechanism: additive serotonergic effects

3.5.1.FC] Lornoxicam

- 1) Interaction Effect: an increased risk of bleeding
- 2) Summary: Caution is recommended with the concomitant use of NSAIDs and SSRIs due to an increased risk of [gastrointestinal bleeding](#) [228] [229]. Bleeding events have included [epistaxis](#), ecchymosis, [hematoma](#), [petechiae](#), and life-threatening hemorrhages [231] [53] [232] [233]. 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: probable
- 6) Clinical Management: Use caution if NSAIDs and SSRIs are coadministered. Concomitant use of NSAIDs and SSRIs may cause an increased risk of bleeding [228] [229]. When an SSRI and an NSAID are given concurrently, monitor the patient for signs of increased bleeding.
- 7) Probable Mechanism: unknown
- 8) Literature Reports

a) SSRIs increase the risk of upper gastrointestinal (GI) bleeding, and this effect is potentiated by concurrent use of NSAIDs or low-dose [aspirin](#). Hospitalizations for [upper GI bleeding](#) were searched among 26,005 users of antidepressant medications and compared with the number of hospitalizations in those patients who did not receive prescriptions for antidepressants. The amount of [upper GI bleeding](#) episodes was 3.6 times more than expected (95% CI, 2.7 to 4.7). Combined use of an SSRI and NSAIDs or low-dose [aspirin](#) increased the risk to 12.2 (95% CI, 7.1 to 19.5) and 5.2 (95% CI, 3.2 to 8), respectively. The findings of this study demonstrate an increased risk of [upper GI bleeding](#) during the use of SSRIs. Combined use of SSRIs and NSAIDs or low-dose [aspirin](#) increased the risk even further [230].

b) The 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 [53].

3.5.1.FD] Loxoprofen

- 1) Interaction Effect: an increased risk of bleeding
- 2) Summary: Caution is recommended with the concomitant use of NSAIDs and SSRIs due to an increased risk of [gastrointestinal bleeding](#) [228] [229]. Bleeding events have included [epistaxis](#), ecchymosis, [hematoma](#), [petechiae](#), and life-threatening hemorrhages [231] [53] [232] [233]. 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: probable

6j) Clinical Management: Use caution if NSAIDs and SSRIs are coadministered. Concomitant use of NSAIDs and SSRIs may cause an increased risk of bleeding [228] [229]. When an SSRI and an NSAID are given concurrently, monitor the patient for signs of increased bleeding.

7j) Probable Mechanism: unknown

8j) Literature Reports

aj) SSRIs increase the risk of upper gastrointestinal (GI) bleeding, and this effect is potentiated by concurrent use of NSAIDs or low-dose aspirin. Hospitalizations for upper GI bleeding were searched among 26,005 users of antidepressant medications and compared with the number of hospitalizations in those patients who did not receive prescriptions for antidepressants. The amount of upper GI bleeding episodes was 3.6 times more than expected (95% CI, 2.7 to 4.7). Combined use of an SSRI and NSAIDs or low-dose aspirin increased the risk to 12.2 (95% CI, 7.1 to 19.5) and 5.2 (95% CI, 3.2 to 8), respectively. The findings of this study demonstrate an increased risk of upper GI bleeding during the use of SSRIs. Combined use of SSRIs and NSAIDs or low-dose aspirin increased the risk even further [230].

bj) The 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 [53].

3.5.1.FE] Lumefantrine

1j) Interaction Effect: increased risk of QT-interval prolongation

2j) Summary: Avoid concomitant use of artemether/lumefantrine and citalopram due to a potential for additive effects on QT-interval prolongation and an increased risk of serious cardiovascular effects, including torsade de pointes. If concomitant use is required, monitor for ECG changes. Do not exceed citalopram doses of 40 mg/day, and discontinue citalopram in patients who have persistent QTc measurements greater than 500 milliseconds [76]. Additionally, caution is advised when administering drugs that prolong the QT interval after completing artemether/lumefantrine therapy, due to the long half-life of lumefantrine (3 to 6 days) [356].

3j) Severity: major

4j) Onset: unspecified

5j) Substantiation: theoretical

6j) Clinical Management: Avoid concomitant use of artemether/lumefantrine and citalopram due to a potential for additive effects on QT-interval prolongation and an increased risk of serious cardiovascular effects, including torsade de pointes. If concomitant use is required, monitor for ECG changes. Do not exceed citalopram doses of 40 mg/day, and discontinue citalopram in patients who have persistent QTc measurements greater than 500 milliseconds [76]. Additionally, caution is advised when administering drugs that prolong the QT interval after completing artemether/lumefantrine therapy, due to the long half-life of lumefantrine (3 to 6 days) [356].

7j) Probable Mechanism: additive effects on the QT interval

3.5.1.FF] Lumiracoxib

1j) Interaction Effect: an increased risk of bleeding

2j) Summary: Caution is recommended with the concomitant use of NSAIDs and SSRIs due to an increased risk of gastrointestinal bleeding [228] [229]. Bleeding events have included epistaxis, ecchymosis, hematoma, petechiae, and life-threatening hemorrhages [231] [53] [232] [233]. When an SSRI and an NSAID are given concurrently, monitor the patient for signs of increased bleeding.

3j) Severity: major

4j) Onset: unspecified

5) Substantiation: probable

6) Clinical Management: Use caution if NSAIDs and SSRIs are coadministered. Concomitant use of NSAIDs and SSRIs may cause an increased risk of bleeding [228] [229]. When an SSRI and an NSAID are given concurrently, monitor the patient for signs of increased bleeding.

7) Probable Mechanism: unknown

8) Literature Reports

a) SSRIs increase the risk of upper gastrointestinal (GI) bleeding, and this effect is potentiated by concurrent use of NSAIDs or low-dose [aspirin](#). Hospitalizations for [upper GI bleeding](#) were searched among 26,005 users of antidepressant medications and compared with the number of hospitalizations in those patients who did not receive prescriptions for antidepressants. The amount of [upper GI bleeding](#) episodes was 3.6 times more than expected (95% CI, 2.7 to 4.7). Combined use of an SSRI and NSAIDs or low-dose [aspirin](#) increased the risk to 12.2 (95% CI, 7.1 to 19.5) and 5.2 (95% CI, 3.2 to 8), respectively. The findings of this study demonstrate an increased risk of [upper GI bleeding](#) during the use of SSRIs. Combined use of SSRIs and NSAIDs or low-dose [aspirin](#) increased the risk even further [230].

b) The 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 [53].

3.5.1.FG| [Meclofenamate](#)

1) Interaction Effect: an increased risk of bleeding

2) Summary: Caution is recommended with the concomitant use of NSAIDs and SSRIs due to an increased risk of [gastrointestinal bleeding](#) [228] [229]. Bleeding events have included [epistaxis](#), ecchymosis, [hematoma](#), [petechiae](#), and life-threatening hemorrhages [231] [53] [232] [233]. 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: probable

6) Clinical Management: Use caution if NSAIDs and SSRIs are coadministered. Concomitant use of NSAIDs and SSRIs may cause an increased risk of bleeding [228] [229]. When an SSRI and an NSAID are given concurrently, monitor the patient for signs of increased bleeding.

7) Probable Mechanism: unknown

8) Literature Reports

a) SSRIs increase the risk of upper gastrointestinal (GI) bleeding, and this effect is potentiated by concurrent use of NSAIDs or low-dose [aspirin](#). Hospitalizations for [upper GI bleeding](#) were searched among 26,005 users of antidepressant medications and compared with the number of hospitalizations in those patients who did not receive prescriptions for antidepressants. The amount of [upper GI bleeding](#) episodes was 3.6 times more than expected (95% CI, 2.7 to 4.7). Combined use of an SSRI and NSAIDs or low-dose [aspirin](#) increased the risk to 12.2 (95% CI, 7.1 to 19.5) and 5.2 (95% CI, 3.2 to 8), respectively. The findings of this study demonstrate an increased risk of [upper GI bleeding](#) during the use of SSRIs. Combined use of SSRIs and NSAIDs or low-dose [aspirin](#) increased the risk even further [230].

b) The 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 [53].

3.5.1.FH] Mefenamic Acid

- 1) Interaction Effect: an increased risk of bleeding
- 2) Summary: Caution is recommended with the concomitant use of NSAIDs and SSRIs due to an increased risk of [gastrointestinal bleeding](#) [228] [229]. Bleeding events have included [epistaxis](#), ecchymosis, [hematoma](#), [petechiae](#), and life-threatening hemorrhages [231] [53] [232] [233]. 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: probable
- 6) Clinical Management: Use caution if NSAIDs and SSRIs are coadministered. Concomitant use of NSAIDs and SSRIs may cause an increased risk of bleeding [228] [229]. When an SSRI and an NSAID are given concurrently, monitor the patient for signs of increased bleeding.
- 7) Probable Mechanism: unknown
- 8) Literature Reports

a) SSRIs increase the risk of upper gastrointestinal (GI) bleeding, and this effect is potentiated by concurrent use of NSAIDs or low-dose [aspirin](#). Hospitalizations for [upper GI bleeding](#) were searched among 26,005 users of antidepressant medications and compared with the number of hospitalizations in those patients who did not receive prescriptions for antidepressants. The amount of [upper GI bleeding](#) episodes was 3.6 times more than expected (95% CI, 2.7 to 4.7). Combined use of an SSRI and NSAIDs or low-dose [aspirin](#) increased the risk to 12.2 (95% CI, 7.1 to 19.5) and 5.2 (95% CI, 3.2 to 8), respectively. The findings of this study demonstrate an increased risk of [upper GI bleeding](#) during the use of SSRIs. Combined use of SSRIs and NSAIDs or low-dose [aspirin](#) increased the risk even further [230].

b) The 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 [53].

3.5.1.FI] Mefloquine

- 1) Interaction Effect: an increased risk of QT interval prolongation
- 2) Summary: [Citalopram](#) causes dose-dependent prolongation of the QTc interval [76] and [mefloquine](#) is known to cause QT interval prolongation [182]. Although the interaction has not been studied, concurrent use of these 2 agents may increase the risk of cardiac adverse events, including [torsade de pointes](#). If coadministration is required, monitor for ECG changes. Do not exceed [citalopram](#) doses of 40 mg/day and discontinue [citalopram](#) in patients who have persistent QTc measurements greater than 500 milliseconds [76].
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: The concomitant use of [citalopram](#) with other drugs that prolong the QT interval, such as [mefloquine](#) [182], is not recommended as concurrent use may increase the risk of cardiac adverse events, including [torsade de pointes](#). If coadministration is required, monitor for ECG changes. Do not exceed [citalopram](#) doses of 40 mg/day and discontinue [citalopram](#) in patients who have persistent QTc measurements greater than 500 milliseconds [76].
- 7) Probable Mechanism: additive effects on the QT interval prolongation

3.5.1.FJ] Meloxicam

- 1) Interaction Effect: an increased risk of bleeding
- 2) Summary: Caution is recommended with the concomitant use of NSAIDs and SSRIs due to an increased risk of [gastrointestinal bleeding](#) [228] [229]. Bleeding events have included [epistaxis](#), ecchymosis, [hematoma](#), [petechiae](#), and life-threatening hemorrhages [231] [53] [232] [233]. 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: probable
- 6) Clinical Management: Use caution if NSAIDs and SSRIs are coadministered. Concomitant use of NSAIDs and SSRIs may cause an increased risk of bleeding [228] [229]. When an SSRI and an NSAID are given concurrently, monitor the patient for signs of increased bleeding.
- 7) Probable Mechanism: unknown
- 8) Literature Reports

a) SSRIs increase the risk of upper gastrointestinal (GI) bleeding, and this effect is potentiated by concurrent use of NSAIDs or low-dose [aspirin](#). Hospitalizations for [upper GI bleeding](#) were searched among 26,005 users of antidepressant medications and compared with the number of hospitalizations in those patients who did not receive prescriptions for antidepressants. The amount of [upper GI bleeding](#) episodes was 3.6 times more than expected (95% CI, 2.7 to 4.7). Combined use of an SSRI and NSAIDs or low-dose [aspirin](#) increased the risk to 12.2 (95% CI, 7.1 to 19.5) and 5.2 (95% CI, 3.2 to 8), respectively. The findings of this study demonstrate an increased risk of [upper GI bleeding](#) during the use of SSRIs. Combined use of SSRIs and NSAIDs or low-dose [aspirin](#) increased the risk even further [230].

b) The 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 [53].

3.5.1.FK] Meperidine

- 1) Interaction Effect: an increased risk of [serotonin syndrome](#)
- 2) Summary: [Serotonin syndrome](#), a potentially life-threatening condition, has been reported with selective serotonin reuptake inhibitors, including [citalopram](#), particularly when used in combination with other serotonergic medications [3]. A 44-year-old female taking [citalopram](#) 40 mg daily developed [serotonin syndrome](#) 10 hours after the initiation of parenteral [meperidine](#); symptoms resolved with 12 hours of [meperidine](#) discontinuation [158]. If concomitant use of [citalopram](#) and [meperidine](#) is required, observe the patient closely for signs and symptoms of [serotonin syndrome](#), including mental status changes, autonomic instability, and neuromuscular and gastrointestinal symptoms. Discontinue treatment if symptoms of [serotonin syndrome](#) occur and institute appropriate symptomatic treatment [3].
- 3) Severity: major
- 4) Onset: rapid
- 5) Substantiation: probable
- 6) Clinical Management: Use caution when using [citalopram](#) and [meperidine](#) concomitantly due to the potential for developing [serotonin syndrome](#) as was reported in one case [158]. Observe the patient closely for mental status changes, autonomic instability or other signs and symptoms of [serotonin syndrome](#). Discontinue treatment if symptoms occur and institute appropriate symptomatic treatment [3].
- 7) Probable Mechanism: additive serotonergic effect
- 8) Literature Reports

a)) A 44-year-old female taking [citalopram](#) 40 mg daily developed [serotonin syndrome](#) 10 hours after the initiation of parenteral [meperidine](#). The patient had been taking [citalopram](#) 20 mg for 9 months when the dose was increased to 40 mg for worsening depression during a hospitalization for a rectal [wound debridement](#). The depressive symptoms improved and 5 weeks later, the patient was given parenteral [meperidine](#) for [patient-controlled analgesia](#) (total dose over 8 hours, 230 mg). Within 10 hours of initiation of [meperidine](#), the patient became acutely agitated, disoriented, paranoid, and had [perceptual disturbances](#) and nausea. Vital signs indicated she had spiked a fever (39.1 degrees C), was hypertensive (161/86 mmHg), tachypneic (22 breaths per minute), and tachycardic (112 beats per minute). A complete metabolic panel was normal and a medical work up, including [computed tomography](#), ECG, and [chest X-ray](#), was not significant. In addition to [meperidine](#), other as-needed medications included [hydromorphone](#), [hydrocodone/acetaminophen](#), and [promethazine](#). The patient's routine daily medication profile consisted of [zolpidem](#), [lansoprazole](#), subcutaneous [enoxaparin](#), [fentanyl](#) patch, and a 10-day course of [gatifloxacin](#) which was initiated 5 days prior to the onset of symptoms. [Meperidine](#) was stopped and her symptoms resolved with 12 hours of discontinuation and did not recur over the next 3 months [158].

3.5.1.FL] [Mesoridazine](#)

- 1)) Interaction Effect: increased risk of QT-interval prolongation
- 2)) Summary: The concomitant use of [mesoridazine](#) with drugs that cause QT-interval prolongation is contraindicated, as coadministration may increase the risk of QT prolongation and serious [ventricular arrhythmias](#) [200].
- 3)) Severity: contraindicated
- 4)) Onset: unspecified
- 5)) Substantiation: established
- 6)) Clinical Management: The concomitant use of [mesoridazine](#) with drugs that cause QT-interval prolongation is contraindicated, as coadministration may increase the risk of QT prolongation and serious [ventricular arrhythmias](#) [200].
- 7)) Probable Mechanism: additive QT-interval prolongation

3.5.1.FM] [Methadone](#)

- 1)) Interaction Effect: increased risk of QT interval prolongation
- 2)) Summary: Although the interaction has not been studied, both [citalopram](#) and [methadone](#) are known cause QT interval prolongation and [torsade de pointes](#) [76] [344]. Concomitant use of [citalopram](#) and [methadone](#) is generally not recommended due to a potential for additive effects on QT interval prolongation and an increased risk of serious cardiovascular effects. If coadministration is required, monitor for ECG changes. Do not exceed [citalopram](#) doses of 40 mg/day, and discontinue [citalopram](#) in patients who have persistent QTc measurements greater than 500 milliseconds [76].
- 3)) Severity: major
- 4)) Onset: unspecified
- 5)) Substantiation: theoretical
- 6)) Clinical Management: Concomitant use of [citalopram](#) and [methadone](#) is generally not recommended due to a potential for additive effects on QT interval prolongation and an increased risk of serious cardiovascular effects, including [torsade de pointes](#). If coadministration is required, monitor for ECG changes. Do not exceed [citalopram](#) doses of 40 mg/day, and discontinue [citalopram](#) in patients who have persistent QTc measurements greater than 500 milliseconds [76].
- 7)) Probable Mechanism: additive effects on the QT interval

3.5.1.FN] Methylene Blue

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

2J) Summary: Concurrent use of [citalopram](#) and IV methylene blue, an MAOI, is contraindicated due to reports of [serotonin syndrome](#) with coadministration of an SSRI and methylene blue 1 to 8 mg/kg administered IV [53]. No cases have been identified in patients receiving methylene blue up to 5 mg for lymphatic mapping in [breast cancer](#) [276], nor with other routes of administration (eg, oral, local tissue injection), or at lower doses; however, the potential for [serotonin syndrome](#) may still exist. If urgent treatment with IV methylene blue is required in a patient receiving [citalopram](#), alternatives are not available, and risk/benefit has been evaluated, promptly discontinue [citalopram](#) and then administer IV methylene blue. Monitor for 14 days or until 24 hours after the last methylene blue dose, whichever comes first. [Citalopram](#) can be resumed 24 hours after the last methylene blue dose [53].

3J) Severity: contraindicated

4J) Onset: unspecified

5J) Substantiation: probable

6J) Clinical Management: Concurrent use of [citalopram](#) and IV methylene blue (an MAOI) is contraindicated. If urgent treatment with IV methylene blue is necessary, alternatives are not available, and risk/benefit has been evaluated, promptly discontinue [citalopram](#) and then administer IV methylene blue. Monitor for [serotonin syndrome](#) for 2 weeks or until 24 hours after the last dose of IV methylene blue, whichever comes first. [Citalopram](#) can be resumed 24 hours after the last dose of methylene blue [53]. While the risk of concurrent [citalopram](#) with other forms of methylene blue is unclear, interactions are possible with methylene blue administered orally, by local injection, or in IV doses lower than 1 mg/kg.

7J) Probable Mechanism: additive serotonergic effect

8J) Literature Reports

aJ) Serious CNS reactions have occurred following administration of methylene blue in a patient currently receiving an SSRI, such as [citalopram](#). In most reported cases, the patient was undergoing [parathyroid surgery](#), with use of methylene blue as a visualizing agent in doses ranging from 1 to 8 mg/kg. The risk of [serotonin syndrome](#) in patients taking SSRIs who receive methylene blue by alternative routes (eg, orally or by local tissue injection) or at doses lower than 1 mg/kg is unknown [275].

bJ) 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, healthcare providers should still be aware of the potential for an interaction between methylene blue and SSRIs in this setting [276].

cJ) Serotonin toxicity, subsequent to concomitant use of [citalopram](#) and methylene blue, occurred in a 44-year-old woman following a partial [parathyroidectomy](#). The patient had been taking [citalopram](#) 20 mg/day as well other maintenance medications, including [aspirin](#), [simvastatin](#), [atenolol](#), [isosorbide](#) mononitrate, and [bendroflumethiazide](#). Prior to surgery, a methylene blue infusion of 560 mg in 500 mL NS was given over 2 hours, in addition to [propofol](#), [remifentanyl](#), rocuronium, [dexamethasone](#), and [morphine](#) analgesia, all administered the day of surgery. Three hours after surgery, symptoms indicating serotonin toxicity manifested, with the patient becoming agitated, restless, staring into space, and making incomprehensible sounds. Her Glasgow coma scale was 11/15, scoring a 2 and 5 for verbal and motor response, respectively, and a 4 for eye

opening. There were no focal deficits on neurological examination; however, both pupils were dilated with a slow response to light, with myoclonic movements in the lower limbs, brisk reflexes throughout, and downgoing plantar responses. Vital signs were all within normal limits and there were no significant findings on a [CT scan of the head](#); the patient had received general [anesthesia](#) in the past without complications. [Citalopram](#) was discontinued and the patient was transferred to the ICU for supportive treatment and was sedated for 12 hours with [propofol](#) and [alfentanil](#). Upon discharge 3 days later, she resumed [citalopram](#) therapy and experienced no long-term effects [277].

3.5.1.FO| [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 [156].
- 3) Severity: moderate
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Use caution when prescribing [methylphenidate](#) to patients who take an selective serotonin reuptake inhibitor (SSRI). Concomitant use of [methylphenidate](#) and an SSRI may cause elevated SSRI plasma concentrations. Consider a decrease in the dose of SSRI when these agents are coadministered. Additionally, consider adjusting the SSRI dose if necessary when initiating or discontinuing [methylphenidate](#) therapy [156].
- 7) Probable Mechanism: inhibition of selective serotonin reuptake inhibitor metabolism by [methylphenidate](#)

3.5.1.FP| [Metoclopramide](#)

- 1) Interaction Effect: an increased risk of extrapyramidal reactions or [neuroleptic malignant syndrome](#)
- 2) Summary: Concomitant use of [citalopram](#) with [metoclopramide](#) may increase the risk of extrapyramidal symptoms, such as [tardive dyskinesia](#) or [neuroleptic malignant syndrome](#), and is contraindicated [363]. 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 [364].
- 3) Severity: contraindicated
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Concomitant use of [citalopram](#) with [metoclopramide](#) is contraindicated [363]. 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 [364].
- 7) Probable Mechanism: unknown

3.5.1.FQ| [Metoprolol](#)

- 1) Interaction Effect: increased [metoprolol](#) plasma concentrations and possible loss of [metoprolol](#) cardioselectivity

- 2)) Summary: [Citalopram](#) 40 mg daily administered for 22 days resulted in a two-fold increase in the plasma levels of [metoprolol](#). No clinically significant changes in blood pressure or heart rate were observed; however, increased [metoprolol](#) plasma levels have been associated with decreased cardioselectivity [297].
- 3)) Severity: moderate
- 4)) Onset: delayed
- 5)) Substantiation: probable
- 6)) Clinical Management: Patients stabilized on [metoprolol](#) who are administered [citalopram](#) should be observed for signs of increased beta blockade such as bradycardia, hypotension or [heart failure](#). At higher [metoprolol](#) concentrations, cardioselectivity may be diminished; monitor appropriate measures of disease control when [citalopram](#) and [metoprolol](#) are used concomitantly in patients with [diabetes](#), [asthma](#), and chronic [bronchitis](#).
- 7)) Probable Mechanism: unknown

3.5.1.FR] [Metronidazole](#)

- 1)) Interaction Effect: increased risk of QT-interval prolongation and [arrhythmias](#)
- 2)) Summary: Concurrent use of [metronidazole](#) with other QT-prolonging drugs was a probable cause of QT-interval prolongation in one study of cardiac ICU patients. Use caution with coadministration of [metronidazole](#) with other QT interval-prolonging drugs, as life-threatening additive effects on the QT interval, including [torsades de pointes](#), may occur. Consider close [ECG monitoring](#) at baseline and during concurrent therapy with QT-interval prolonging drugs [89].
- 3)) Severity: major
- 4)) Onset: unspecified
- 5)) Substantiation: theoretical
- 6)) Clinical Management: Use caution with coadministration of [metronidazole](#) with other QT interval-prolonging drugs, as life-threatening additive effects on the QT interval, including [torsades de pointes](#), may occur. Consider close [ECG monitoring](#) at baseline and during concurrent therapy with QT-interval prolonging drugs [89].
- 7)) Probable Mechanism: additive QT-interval prolongation
- 8)) Literature Reports

a)) In a retrospective study, 164 of 501 patients admitted in cardiac ICUs (87.7%) developed QT-interval prolongation potentially linked to inhibition of CYP450-mediated metabolism. Out of 1027 total interactions that were potentially associated with QT-interval prolonging effects, interactions with [metronidazole](#) (n=22) were some of the most common. No patients developed [torsades de pointes](#) during their ICU stays. Close [ECG monitoring](#) at baseline and during concurrent therapy with drugs known to cause QT-interval prolongation is recommended [89].

b)) A 71-year-old woman with antibiotic-induced [pseudomembranous colitis](#) developed ECG QTc interval prolongation and [torsades de pointes](#) with concurrent [amiodarone](#) 450 mg bolus followed by 900 mg/day IV and [metronidazole](#) 1500 mg/day oral administration. Baseline QTc interval was 440 msec. [Amiodarone](#) was added after trial fibrillation developed with 3 days of [amiodarone](#) therapy. Conversion to sinus rhythm occurred 2 days later; however, the follow-up ECG revealed a QTc interval of 625 msec. Symptoms progressed to sustained torsades de pointes-variant [ventricular tachycardia](#) that required emergent [cardioversion/defibrillation](#) to restore normal sinus rhythm. [Amiodarone](#) and [metronidazole](#) were immediately withdrawn, and the QTc interval slowly returned to baseline values without further clinically significant [arrhythmia](#) events [90].

3.5.1.FS] [Mifepristone](#)

- 1) Interaction Effect: increased risk of QT interval prolongation
- 2) Summary: Both [citalopram](#) and [mifepristone](#) have been associated with dose-dependent QT interval prolongation, and [torsades de pointes](#) has been reported during postmarketing surveillance of [citalopram](#) [127] [76]. Concomitant use of [citalopram](#) and [mifepristone](#) (Korlym(TM)) is not recommended due to the potential for additive QT interval prolongation. [76]. If concomitant use is necessary, monitor for ECG changes. [76]. Wait at least 2 weeks after stopping [mifepristone](#) (Korlym(TM)) before initiating [citalopram](#) therapy or increasing the [citalopram](#) dose [127]. Do not exceed [citalopram](#) doses of 40 mg/day and discontinue [citalopram](#) if persistent QTc measurements greater than 500 milliseconds are noted [76].
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: The concomitant use of [citalopram](#) and [mifepristone](#) (Korlym(TM)) is not recommended as it may increase the risk for additive QT interval prolongation [76]. If concomitant use is necessary, monitor for ECG changes. [76]. Wait at least 2 weeks after stopping [mifepristone](#) (Korlym(TM)) before initiating [citalopram](#) therapy or increasing the [citalopram](#) dose [127]. Do not exceed [citalopram](#) doses of 40 mg/day and discontinue [citalopram](#) if persistent QTc measurements greater than 500 milliseconds are noted [76].
- 7) Probable Mechanism: additive effects on QT interval prolongation

3.5.1.FT] 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 [302].
- 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 [302].
- 7) Probable Mechanism: additive serotonergic effect

3.5.1.FU] 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 [148]. 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 [81].

- 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](#) [148].
- 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 [149].

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 [150].

3.5.1.FV] [Mitotane](#)

- 1) Interaction Effect: decreased exposure of CYP3A4 substrates
- 2) Summary: Concurrent administration of [mitotane](#), a strong CYP3A4 inducer, with a CYP3A4 substrate may decrease the exposure of the CYP3A4 substrate. If concomitant use is required, monitor patients to determine dosage adjustments [271] and loss of efficacy. If possible, substitute the use of CYP3A4 substrates during [mitotane](#) therapy.
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Concurrent administration of [mitotane](#), a strong CYP3A4 inducer, with a CYP3A4 substrate may decrease the exposure of the CYP3A4 substrate. If concomitant use is required, monitor patients to determine dosage adjustments [271] and loss of efficacy. If possible, substitute the use of CYP3A4 substrates during [mitotane](#) therapy.
- 7) Probable Mechanism: induction of CYP3A4-mediated metabolism by [mitotane](#)

3.5.1.FW] [Moclobemide](#)

- 1) Interaction Effect: an increased risk of [serotonin syndrome](#) ([hypertension](#), [tachycardia](#), [hyperthermia](#), [myoclonus](#), mental status changes)
- 2) Summary: Concomitant use of [citalopram](#) and an MAOI is contraindicated. Concurrent administration or overlapping therapy with [citalopram](#) 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, and tremor. A minimum of 14 days should elapse after discontinuing an MAOI intended to treat psychiatric disorders before initiating therapy with [citalopram](#), and a minimum of 14 days should elapse after discontinuing [citalopram](#) before initiating therapy with an MAOI intended to treat psychiatric disorders [53].

3) Severity: contraindicated

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Concurrent use of [citalopram](#) and an MAOI is contraindicated. Wait at least 14 days after discontinuing an MAOI intended to treat psychiatric disorders before initiating [citalopram](#). Wait at least 14 days after discontinuing [citalopram](#) before initiating therapy with an MAOI intended to treat psychiatric disorders [53].

7) Probable Mechanism: additive serotonergic effect

3.5.1.FX] Moclobemide

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

2) Summary: Three fatal cases of [serotonin syndrome](#) were reported involving overdoses of [citalopram](#) (the most selective of the SSRIs) and moclobemide (a reversible inhibitor of MOA-A) [351]. Although a placebo-controlled study of coadministered moclobemide and [fluvoxamine](#) (another SSRI) found no indications of [serotonin syndrome](#) [352], the concurrent administration of [citalopram](#) and a MAO inhibitor is contraindicated [353].

3) Severity: contraindicated

4) Onset: rapid

5) Substantiation: probable

6) Clinical Management: Concurrent use of [citalopram](#) and a MAO inhibitor is contraindicated. Wait at least 14 days after discontinuing a MAO inhibitor before initiating therapy with [citalopram](#). Wait at least 14 days after discontinuing [citalopram](#) before initiating therapy with a MAO inhibitor.

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

8) Literature Reports

a) Five fatal overdose cases were reported due to [serotonin syndrome](#). In three of the five cases, the drug combination that induced the fatal syndrome was moclobemide, a selective monoamine oxidase inhibitor, and [citalopram](#). Of the three patients, blood concentrations of moclobemide ranged from 5 times the therapeutic level to 50 times the therapeutic level, and [citalopram](#) concentrations ranged from normal therapeutic levels to 5 times the therapeutic level [349].

b) Concomitant use of selective serotonin reuptake inhibitors and monoamine oxidase inhibitors can produce a toxic reaction known as [serotonin syndrome](#) [350]. [Serotonin syndrome](#) is a condition of serotonergic hyperstimulation and manifests as restlessness, myoclonus, changes in mental status, hyperreflexia, diaphoresis, shivering, and tremor. If the syndrome is not recognized and correctly treated, death can result.

3.5.1.FY] Modafinil

1) Interaction Effect: increased [citalopram](#) exposure and risk of QT interval prolongation

2) Summary: In a [pharmacokinetic study](#) in patients who received [citalopram](#) 40 mg/day for 21 days, combined administration with [cimetidine](#) (a potent CYP2C19 inhibitor) 400 mg/day for 8 days resulted in an increase in [citalopram](#) AUC and Cmax of 43% and 39%, respectively. Although the interaction between [citalopram](#) (a CYP2C19 substrate) and [modafinil](#) (another CYP2C19 inhibitor) [197] has not

been specifically studied, concomitant use may result in increased [citalopram](#) exposure and risk of QT prolongation. If coadministration of [citalopram](#) with [modafinil](#) is required, do not exceed [citalopram](#) doses of 20 mg/day. Discontinue [citalopram](#) in patients who have persistent QTc measurements greater than 500 milliseconds [76] and monitor for [citalopram](#) toxicity [197].

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: The concomitant use of [citalopram](#), a CYP2C19 substrate [76], with [modafinil](#), a CYP2C19 inhibitor [197], may result in increased [citalopram](#) exposure and risk of QT prolongation. If coadministration of [citalopram](#) with [modafinil](#) is required, do not exceed [citalopram](#) doses of 20 mg/day [76] and monitor for [citalopram](#) toxicity [197]. Discontinue [citalopram](#) in patients who have persistent QTc measurements greater than 500 milliseconds [76].

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

3.5.1.FZ] Morniflumate

1) Interaction Effect: an increased risk of bleeding

2) Summary: Caution is recommended with the concomitant use of NSAIDs and SSRIs due to an increased risk of [gastrointestinal bleeding](#) [228] [229]. Bleeding events have included [epistaxis](#), ecchymosis, [hematoma](#), [petechiae](#), and life-threatening hemorrhages [231] [53] [232] [233]. 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: probable

6) Clinical Management: Use caution if NSAIDs and SSRIs are coadministered. Concomitant use of NSAIDs and SSRIs may cause an increased risk of bleeding [228] [229]. When an SSRI and an NSAID are given concurrently, monitor the patient for signs of increased bleeding.

7) Probable Mechanism: unknown

8) Literature Reports

a) SSRIs increase the risk of upper gastrointestinal (GI) bleeding, and this effect is potentiated by concurrent use of NSAIDs or low-dose [aspirin](#). Hospitalizations for [upper GI bleeding](#) were searched among 26,005 users of antidepressant medications and compared with the number of hospitalizations in those patients who did not receive prescriptions for antidepressants. The amount of [upper GI bleeding](#) episodes was 3.6 times more than expected (95% CI, 2.7 to 4.7). Combined use of an SSRI and NSAIDs or low-dose [aspirin](#) increased the risk to 12.2 (95% CI, 7.1 to 19.5) and 5.2 (95% CI, 3.2 to 8), respectively. The findings of this study demonstrate an increased risk of [upper GI bleeding](#) during the use of SSRIs. Combined use of SSRIs and NSAIDs or low-dose [aspirin](#) increased the risk even further [230].

b) The 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 [53].

3.5.1.GA] Moxifloxacin

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

2) Summary: Both [citalopram](#) and [moxifloxacin](#) are known to cause QT interval prolongation [76] [362] and concomitant use is not recommended [76]. Although the interaction has not been studied, the coadministration of [citalopram](#) with [moxifloxacin](#) may cause an increased risk of QT prolongation and [torsade de pointes](#). If concomitant use is required, monitor for ECG changes. Do not exceed [citalopram](#)

doses of 40 mg/day and discontinue [citalopram](#) in patients who have persistent QTc measurements greater than 500 milliseconds [76]. Do not exceed the recommended dose or infusion rate of [moxifloxacin](#) [362].

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: The concomitant use of [citalopram](#) with [moxifloxacin](#) is not recommended as both agents are known to increase the QT interval resulting in , an increased risk of cardiac adverse events . If coadministration is required, monitor for ECG changes. Do not exceed [citalopram](#) doses of 40 mg/day and discontinue [citalopram](#) in patients who have persistent QTc measurements greater than 500 milliseconds [76]. Do not exceed the recommended dose or infusion rate of [moxifloxacin](#) [362].

7) Probable Mechanism: additive effects on the QT interval prolongation

3.5.1.GB| [Nabumetone](#)

1) Interaction Effect: an increased risk of bleeding

2) Summary: Caution is recommended with the concomitant use of NSAIDs and SSRIs due to an increased risk of [gastrointestinal bleeding](#) [228] [229]. Bleeding events have included [epistaxis](#), ecchymosis, [hematoma](#), [petechiae](#), and life-threatening hemorrhages [231] [53] [232] [233]. 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: probable

6) Clinical Management: Use caution if NSAIDs and SSRIs are coadministered. Concomitant use of NSAIDs and SSRIs may cause an increased risk of bleeding [228] [229]. When an SSRI and an NSAID are given concurrently, monitor the patient for signs of increased bleeding.

7) Probable Mechanism: unknown

8) Literature Reports

a) SSRIs increase the risk of upper gastrointestinal (GI) bleeding, and this effect is potentiated by concurrent use of NSAIDs or low-dose [aspirin](#). Hospitalizations for [upper GI bleeding](#) were searched among 26,005 users of antidepressant medications and compared with the number of hospitalizations in those patients who did not receive prescriptions for antidepressants. The amount of [upper GI bleeding](#) episodes was 3.6 times more than expected (95% CI, 2.7 to 4.7). Combined use of an SSRI and NSAIDs or low-dose [aspirin](#) increased the risk to 12.2 (95% CI, 7.1 to 19.5) and 5.2 (95% CI, 3.2 to 8), respectively. The findings of this study demonstrate an increased risk of [upper GI bleeding](#) during the use of SSRIs. Combined use of SSRIs and NSAIDs or low-dose [aspirin](#) increased the risk even further [230].

b) The 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 [53].

3.5.1.GC| [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 [340] [341] [339]. 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](#) [341] [339].

3) Severity: major

- 4) Onset: unspecified
- 5) Substantiation: probable
- 6) Clinical Management: When [citalopram](#) and an anticoagulant are given concurrently, monitor patients for signs of increased bleeding. Patients who are taking [warfarin](#) should be monitored closely for altered anticoagulant effects, including increased bleeding, when [citalopram](#) therapy is initiated or discontinued [339].
- 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 [340].

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 [341].

c) The pharmacokinetics of [warfarin](#), a CYP3A4 substrate, were not affected by the administration of [citalopram](#) 40 mg/day for 21 days, while the prothrombin time was increased by 5%. The clinical significance of this is unknown [339].

3.5.1.GD] [Nafarelin](#)

- 1) Interaction Effect: increased risk of QT-interval prolongation
- 2) Summary: Gonadotropin-releasing hormone (GnRH) agonists prolong the QT interval through their androgen-depriving action [261] [262] [263], while [citalopram](#) causes dose-dependent QT-interval prolongation that can lead to life-threatening [ventricular tachycardia](#) or [Torsade de Pointes](#). Avoid concomitant use of [citalopram](#) with GnRH agonists. If concurrent use is essential, [ECG monitoring](#) is recommended. Discontinue [citalopram](#) if persistent QTc measurements above 500 msec occur [38].
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical

6) Clinical Management: Avoid concomitant use of [citalopram](#) with gonadotropin-releasing hormone (GnRH) agonists, a class of drug known to prolong the QT interval, as additive QT-interval prolongation may occur. If concurrent use is essential, [ECG monitoring](#) is recommended. Discontinue [citalopram](#) if persistent QTc measurements above 500 msec occur [38].

7) Probable Mechanism: additive effects on the QT interval

3.5.1.GE] [Naproxen](#)

1) Interaction Effect: an increased risk of bleeding

2) Summary: Caution is recommended with the concomitant use of NSAIDs and SSRIs due to an increased risk of [gastrointestinal bleeding](#) [228] [229]. Bleeding events have included [epistaxis](#), ecchymosis, [hematoma](#), [petechiae](#), and life-threatening hemorrhages [231] [53] [232] [233]. 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: probable

6) Clinical Management: Use caution if NSAIDs and SSRIs are coadministered. Concomitant use of NSAIDs and SSRIs may cause an increased risk of bleeding [228] [229]. When an SSRI and an NSAID are given concurrently, monitor the patient for signs of increased bleeding.

7) Probable Mechanism: unknown

8) Literature Reports

a) SSRIs increase the risk of upper gastrointestinal (GI) bleeding, and this effect is potentiated by concurrent use of NSAIDs or low-dose [aspirin](#). Hospitalizations for [upper GI bleeding](#) were searched among 26,005 users of antidepressant medications and compared with the number of hospitalizations in those patients who did not receive prescriptions for antidepressants. The amount of [upper GI bleeding](#) episodes was 3.6 times more than expected (95% CI, 2.7 to 4.7). Combined use of an SSRI and NSAIDs or low-dose [aspirin](#) increased the risk to 12.2 (95% CI, 7.1 to 19.5) and 5.2 (95% CI, 3.2 to 8), respectively. The findings of this study demonstrate an increased risk of [upper GI bleeding](#) during the use of SSRIs. Combined use of SSRIs and NSAIDs or low-dose [aspirin](#) increased the risk even further [230].

b) The 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 [53].

3.5.1.GF] [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 [283]. 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](#) [95].

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.GG| [Nelfinavir](#)

- 1) Interaction Effect: increased exposure of CYP3A4 substrate; increased risk of QT-interval prolongation
- 2) Summary: [Nelfinavir](#) is a strong CYP3A inhibitor. Coadministration of [nelfinavir](#) and a CYP3A4 substrate that may have serious or life-threatening consequences with increased plasma concentrations is contraindicated [338]. [Nelfinavir](#) and these selected CYP3A4 substrates are each independently associated with QT-interval prolongation. Coadministration may result in additive risk for QT-interval prolongation and serious cardiac adverse effects.
- 3) Severity: contraindicated
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: The concomitant use of [nelfinavir](#) and a CYP3A4 substrate that may have serious or life-threatening consequences with increased plasma concentrations is contraindicated [338].
- 7) Probable Mechanism: inhibition of CYP3A4-mediated metabolism by [nelfinavir](#); additive QT interval effects

3.5.1.GH| [Nepafenac](#)

- 1) Interaction Effect: an increased risk of bleeding
- 2) Summary: Caution is recommended with the concomitant use of NSAIDs and SSRIs due to an increased risk of [gastrointestinal bleeding](#) [228] [229]. Bleeding events have included [epistaxis](#), ecchymosis, [hematoma](#), [petechiae](#), and life-threatening hemorrhages [231] [53] [232] [233]. 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: probable
- 6) Clinical Management: Use caution if NSAIDs and SSRIs are coadministered. Concomitant use of NSAIDs and SSRIs may cause an increased risk of bleeding [228] [229]. When an SSRI and an NSAID are given concurrently, monitor the patient for signs of increased bleeding.
- 7) Probable Mechanism: unknown
- 8) Literature Reports

a) SSRIs increase the risk of upper gastrointestinal (GI) bleeding, and this effect is potentiated by concurrent use of NSAIDs or low-dose [aspirin](#). Hospitalizations for [upper GI bleeding](#) were searched among 26,005 users of antidepressant medications and compared with the number of hospitalizations in those patients who did not receive prescriptions for antidepressants. The amount of [upper GI bleeding](#) episodes was 3.6 times more than expected (95% CI, 2.7 to 4.7). Combined use of an SSRI and NSAIDs or low-dose [aspirin](#) increased the risk to 12.2 (95% CI, 7.1 to 19.5) and 5.2 (95% CI, 3.2 to 8), respectively. The findings of this study demonstrate an increased risk of [upper GI bleeding](#) during the use of SSRIs. Combined use of SSRIs and NSAIDs or low-dose [aspirin](#) increased the risk even further [230].

b)) The 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 [53].

3.5.1.GI] Netupitant

1)) Interaction Effect: increased exposure of CYP3A4 substrate

2)) Summary: Caution is advised with the coadministration of netupitant (a CYP3A inhibitor) and a CYP3A substrate, as this may increase plasma concentrations of the CYP3A substrate due to inhibition of CYP3A4-mediated metabolism by netupitant and increase the risk of adverse effects that may persist for days. Examples of CYP3A substrates include IV administered chemotherapeutic agents and benzodiazepines; close monitoring is recommended of the increased adverse effects of these agents [258].

3)) Severity: moderate

4)) Onset: unspecified

5)) Substantiation: theoretical

6)) Clinical Management: Caution is advised with the coadministration of netupitant (a CYP3A inhibitor) and a CYP3A substrate, as this may increase plasma concentrations of the CYP3A substrate and increase the risk of adverse effects that may persist for days. Examples of CYP3A substrates include IV administered chemotherapeutic agents and benzodiazepines; close monitoring is recommended of the increased adverse effects of these agents [258].

7)) Probable Mechanism: inhibition of CYP3A4-mediated metabolism by netupitant

8)) Literature Reports

a)) [Pharmacokinetic studies](#) demonstrated that coadministration of netupitant 300 mg/[palonosetron](#) 0.5 mg and [docetaxel](#), a chemotherapeutic agents metabolized by CYP3A4, increased [docetaxel](#) Cmax by 49% and AUC by 35%, compared with coadministration with [palonosetron](#) alone. Additionally, coadministration with another chemotherapeutic agent, [etoposide](#), increased [etoposide](#) Cmax and AUC by 10% and 28%, respectively. After a single oral dose of the benzodiazepine [midazolam](#) 7.5 mg was coadministered with netupitant 300 mg, mean Cmax and AUC of [midazolam](#) was 36% and 126% higher, respectively [258].

3.5.1.GJ] Nialamide

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

2)) Summary: Concurrent administration or overlapping therapy with [citalopram](#) 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 [120] [121] [122]. Concomitant use is contraindicated [123].

3)) Severity: contraindicated

4)) Onset: rapid

5)) Substantiation: established

6)) Clinical Management: Concurrent use of [citalopram](#) and a MAO inhibitor is contraindicated. Wait at least two weeks after discontinuing a MAO inhibitor before initiating therapy with [citalopram](#). Wait two weeks after discontinuing [citalopram](#) before initiating therapy with a MAO inhibitor.

7)) Probable Mechanism: serotonin reuptake inhibition

8)) Literature Reports

a) Concomitant use of selective serotonin reuptake inhibitors and monoamine oxidase inhibitors can produce a toxic reaction known as [serotonin syndrome](#) [115]. [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 [116].

c) A drug interaction was reported in a 61-year old woman in which [sertraline](#) 100 mg twice daily was added to a regimen of [lithium](#), [phenelzine](#), [thioridazine](#), and [doxepin](#). Three hours after taking the first [sertraline](#) dose, the patient was found in a semicomatose state, with elevated body temperature, increased pulse, increased respiration rate, and a blood pressure of 140/110 mm Hg. After transportation to the hospital, the patient was misdiagnosed as having [neuroleptic malignant syndrome](#) (NMS) which was later changed to [serotonin syndrome](#) due to a reaction between [sertraline](#) and [phenelzine](#). The authors suggest that monoamine oxidase inhibitor (MAOI) therapy should be discontinued for at least two weeks before initiation of therapy with a selective serotonin reuptake inhibitor (SSRI) and that before starting a MAOI, SSRI therapy should be discontinued for at least five half-lives of the parent drug and any active metabolites [117].

d) Two case reports suggested a possible interaction between [fluoxetine](#) and [selegiline](#) [118]. 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.

e) Five fatal overdose cases were reported due to [serotonin syndrome](#). In three of the five cases, the drug combination that induced the fatal syndrome was moclobemide, a selective monoamine oxidase inhibitor, and [citalopram](#). Of the three patients, blood concentrations of moclobemide ranged from 5 times the therapeutic level to 50 times the therapeutic level, and [citalopram](#) concentrations ranged from normal therapeutic levels to 5 times the therapeutic level [119].

3.5.1.GK] Niflumic Acid

1) Interaction Effect: an increased risk of bleeding

2) Summary: Caution is recommended with the concomitant use of NSAIDs and SSRIs due to an increased risk of [gastrointestinal bleeding](#) [228] [229]. Bleeding events have included [epistaxis](#), ecchymosis, [hematoma](#), [petechiae](#), and life-threatening hemorrhages [231] [53] [232] [233]. 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: probable

6) Clinical Management: Use caution if NSAIDs and SSRIs are coadministered. Concomitant use of NSAIDs and SSRIs may cause an increased risk of bleeding [228] [229]. When an SSRI and an NSAID are given concurrently, monitor the patient for signs of increased bleeding.

7) Probable Mechanism: unknown

8) Literature Reports

a) SSRIs increase the risk of upper gastrointestinal (GI) bleeding, and this effect is potentiated by concurrent use of NSAIDs or low-dose aspirin. Hospitalizations for upper GI bleeding were searched among 26,005 users of antidepressant medications and compared with the number of hospitalizations in those patients who did not receive prescriptions for antidepressants. The amount of upper GI bleeding episodes was 3.6 times more than expected (95% CI, 2.7 to 4.7). Combined use of an SSRI and NSAIDs or low-dose aspirin increased the risk to 12.2 (95% CI, 7.1 to 19.5) and 5.2 (95% CI, 3.2 to 8), respectively. The findings of this study demonstrate an increased risk of upper GI bleeding during the use of SSRIs. Combined use of SSRIs and NSAIDs or low-dose aspirin increased the risk even further [230].

b) The 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 [53].

3.5.1.GL] Nilotinib

1) Interaction Effect: an increased risk of QT interval prolongation; increased citalopram exposure

2) Summary: Coadministration of citalopram (a CYP3A4 substrate) [53] with nilotinib (a moderate CYP3A4 inhibitor) is not recommended as both drugs are known to prolong the QT interval and additive QT prolongation is possible. Concurrent use may also increase citalopram exposure. If concomitant use is clinically indicated, monitor for ECG changes. Dose adjustment or discontinuation may be required [359] [53]. .

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Coadministration of citalopram with nilotinib is not recommended as both drugs are known to prolong the QT interval and additive QT prolongation is possible. Concurrent use may also increase citalopram exposure. If concomitant use is clinically indicated, monitor for ECG changes. Dose adjustment or discontinuation may be required [359] [53]. .

7) Probable Mechanism: additive effects on QT interval prolongation; inhibition of CYP3A4-mediated citalopram metabolism

8) Literature Reports

a) Although not specifically studied with the CYP3A4 substrate citalopram [53], multiple doses of nilotinib (a moderate CYP3A4 inhibitor) increased the systemic exposure of midazolam (a CYP3A4 substrate) by 2.6-fold in patients with chronic myeloid leukemia [359].

3.5.1.GM] Nimesulide

1) Interaction Effect: an increased risk of bleeding

2) Summary: Caution is recommended with the concomitant use of NSAIDs and SSRIs due to an increased risk of gastrointestinal bleeding [228] [229]. Bleeding events have included epistaxis, ecchymosis, hematoma, petechiae, and life-threatening hemorrhages [231] [53] [232] [233]. 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: probable
- 6) Clinical Management: Use caution if NSAIDs and SSRIs are coadministered. Concomitant use of NSAIDs and SSRIs may cause an increased risk of bleeding [228] [229]. When an SSRI and an NSAID are given concurrently, monitor the patient for signs of increased bleeding.
- 7) Probable Mechanism: unknown
- 8) Literature Reports

a) SSRIs increase the risk of upper gastrointestinal (GI) bleeding, and this effect is potentiated by concurrent use of NSAIDs or low-dose aspirin. Hospitalizations for upper GI bleeding were searched among 26,005 users of antidepressant medications and compared with the number of hospitalizations in those patients who did not receive prescriptions for antidepressants. The amount of upper GI bleeding episodes was 3.6 times more than expected (95% CI, 2.7 to 4.7). Combined use of an SSRI and NSAIDs or low-dose aspirin increased the risk to 12.2 (95% CI, 7.1 to 19.5) and 5.2 (95% CI, 3.2 to 8), respectively. The findings of this study demonstrate an increased risk of upper GI bleeding during the use of SSRIs. Combined use of SSRIs and NSAIDs or low-dose aspirin increased the risk even further [230].

b) The 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 [53].

3.5.1.GN] Norfloxacin

- 1) Interaction Effect: an increased risk of QT interval prolongation
- 2) Summary: Citalopram causes dose-dependent prolongation of the QTc interval [76] and norfloxacin has also been associated with QT interval prolongation [187]. The concomitant use of citalopram and norfloxacin is not recommended due to a potential for additive effects on QT interval prolongation and an increased risk of cardiac adverse events, including ventricular arrhythmias and/or torsade de pointes. If coadministration is required, monitor for ECG changes. Do not exceed citalopram doses of 40 mg/day and discontinue citalopram in patients who have persistent QTc measurements greater than 500 milliseconds [76].
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: The concomitant use of citalopram and norfloxacin is not recommended due to a potential for additive effects on QT interval prolongation and an increased risk of serious cardiovascular effects. If coadministration is required, monitor for ECG changes. Do not exceed citalopram doses of 40 mg/day and discontinue citalopram in patients who have persistent QTc measurements greater than 500 milliseconds [76].
- 7) Probable Mechanism: additive effects on the QT interval

3.5.1.GO] Nortriptyline

- 1) Interaction Effect: an increased risk of QT interval prolongation
- 2) Summary: Concomitant use of citalopram and nortriptyline is not recommended due to a potential for additive effects on QT interval prolongation and an increased risk of serious cardiovascular effects. If concomitant therapy is required, monitor for ECG changes. Do not exceed citalopram doses of 40 mg/day, and discontinue citalopram in patients who have persistent QTc measurements greater than 500 milliseconds [76].
- 3) Severity: major

- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Concomitant use of [citalopram](#) and [nortriptyline](#) is not recommended due to a potential for additive effects on QT interval prolongation and an increased risk of serious cardiovascular effects. If concomitant therapy is required, monitor for ECG changes. Do not exceed [citalopram](#) doses of 40 mg/day, and discontinue [citalopram](#) in patients who have persistent QTc measurements greater than 500 milliseconds [76].
- 7) Probable Mechanism: additive effects on QT interval prolongation

3.5.1.GP] [Octreotide](#)

- 1) Interaction Effect: an increased risk of QT interval prolongation
- 2) Summary: [Citalopram](#) has been associated with dose-dependent prolongation of the QT interval [76] and QT prolongation has been observed during [octreotide](#) therapy [365]. The concomitant use of [citalopram](#) and [octreotide](#) is not recommended due to a potential for additive effects on QT interval prolongation and an increased risk of serious cardiovascular effects. If concurrent therapy is required, monitor for ECG changes. Do not exceed [citalopram](#) doses of 40 mg/day, and discontinue [citalopram](#) in patients who have persistent QTc measurements greater than 500 milliseconds [76].
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Concomitant use of [citalopram](#) and [octreotide](#) is not recommended due to a potential for additive effects on QT interval prolongation and an increased risk of serious cardiovascular effects. If concurrent therapy is required, monitor for ECG changes. Do not exceed [citalopram](#) doses of 40 mg/day, and discontinue [citalopram](#) in patients who have persistent QTc measurements greater than 500 milliseconds [76].
- 7) Probable Mechanism: additive effects on QT interval prolongation

3.5.1.GQ] [Ofloxacin](#)

- 1) Interaction Effect: an increased risk of QT interval prolongation
- 2) Summary: Concomitant use of [citalopram](#) and [ofloxacin](#) is not recommended due to additive effects on QT interval prolongation and an increased risk of serious cardiovascular effects. If concurrent therapy is required, monitor for ECG changes. Do not exceed [citalopram](#) doses of 40 mg/day, and discontinue [citalopram](#) in patients who have persistent QTc measurements greater than 500 milliseconds [76].
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Coadministration of [citalopram](#) and [ofloxacin](#) is not recommended due to a potential for additive effects on QT interval prolongation and an increased risk of serious cardiovascular effects. If concomitant therapy is required, [monitoring for ECG changes](#). Do not exceed [citalopram](#) doses of 40 mg/day, and discontinue [citalopram](#) in patients who have persistent QTc measurements greater than 500 milliseconds [76].
- 7) Probable Mechanism: additive effects on QT interval prolongation

3.5.1.GR] [Omeprazole](#)

- 1) Interaction Effect: increased [citalopram](#) exposure and risk of QT interval prolongation
- 2) Summary: [Citalopram](#) has been associated with dose-dependent prolongation of the QT interval [76]. In a [pharmacokinetic study](#) in patients who received [citalopram](#) 40 mg/day for 21 days, combined administration with [cimetidine](#) (a potent CYP2C19 inhibitor) 400 mg/day for 8 days resulted in an

increase in [citalopram](#) AUC and Cmax of 43% and 39%, respectively. Although the interaction between [citalopram](#) (a CYP2C19 substrate) and [omeprazole](#) (another CYP2C19 inhibitor) [371] has not been specifically studied, concomitant use may result in increased [citalopram](#) exposure and an increased risk of QT prolongation. If coadministration of [citalopram](#) with [omeprazole](#) is required, do not exceed [citalopram](#) doses of 20 mg/day and discontinue [citalopram](#) in patients who have persistent QTc measurements greater than 500 milliseconds [76].

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: The concomitant use of [citalopram](#) with [omeprazole](#) may result in increased [citalopram](#) exposure and risk of QT prolongation. If coadministration of [citalopram](#) with [omeprazole](#) is required, do not exceed [citalopram](#) doses of 20 mg/day and discontinue [citalopram](#) in patients who have persistent QTc measurements greater than 500 milliseconds [76].

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

3.5.1.GS] [Ondansetron](#)

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

2) Summary: [Citalopram](#) causes dose-dependent prolongation of the QTc interval [76] and [ondansetron](#) has also been associated with QT interval prolongation [196]. The concomitant use of [citalopram](#) and [ondansetron](#) is not recommended due to a potential for additive effects on QT interval prolongation and an increased risk of cardiac adverse events, including [ventricular arrhythmias](#) and/or [torsade de pointes](#). If coadministration is required, monitor for ECG changes. Do not exceed [citalopram](#) doses of 40 mg/day and discontinue [citalopram](#) in patients who have persistent QTc measurements greater than 500 milliseconds [76].

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: The concomitant use of [citalopram](#) and [ondansetron](#) is not recommended due to a potential for additive effects on QT interval prolongation and an increased risk of serious cardiovascular effects. If coadministration is required, monitor for ECG changes. Do not exceed [citalopram](#) doses of 40 mg/day and discontinue [citalopram](#) in patients who have persistent QTc measurements greater than 500 milliseconds [76].

7) Probable Mechanism: additive effects on QT interval prolongation

3.5.1.GT] [Oxaprozin](#)

1) Interaction Effect: an increased risk of bleeding

2) Summary: Caution is recommended with the concomitant use of NSAIDs and SSRIs due to an increased risk of [gastrointestinal bleeding](#) [228] [229]. Bleeding events have included [epistaxis](#), ecchymosis, [hematoma](#), [petechiae](#), and life-threatening hemorrhages [231] [53] [232] [233]. 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: probable

6) Clinical Management: Use caution if NSAIDs and SSRIs are coadministered. Concomitant use of NSAIDs and SSRIs may cause an increased risk of bleeding [228] [229]. When an SSRI and an NSAID are given concurrently, monitor the patient for signs of increased bleeding.

7) Probable Mechanism: unknown

8) Literature Reports

a) SSRIs increase the risk of upper gastrointestinal (GI) bleeding, and this effect is potentiated by concurrent use of NSAIDs or low-dose [aspirin](#). Hospitalizations for [upper GI bleeding](#) were searched among 26,005 users of antidepressant medications and compared with the number of hospitalizations in those patients who did not receive prescriptions for antidepressants. The amount of [upper GI bleeding](#) episodes was 3.6 times more than expected (95% CI, 2.7 to 4.7). Combined use of an SSRI and NSAIDs or low-dose [aspirin](#) increased the risk to 12.2 (95% CI, 7.1 to 19.5) and 5.2 (95% CI, 3.2 to 8), respectively. The findings of this study demonstrate an increased risk of [upper GI bleeding](#) during the use of SSRIs. Combined use of SSRIs and NSAIDs or low-dose [aspirin](#) increased the risk even further [230].

b) The 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 [53].

3.5.1.GU] [Oxcarbazepine](#)

- 1) Interaction Effect: increased [citalopram](#) exposure and risk of QT interval prolongation
- 2) Summary: [Citalopram](#) has been associated with dose-dependent prolongation of the QT interval [76]. In a [pharmacokinetic study](#) in patients who received [citalopram](#) 40 mg/day for 21 days, combined administration with [cimetidine](#) (a potent CYP2C19 inhibitor) 400 mg/day for 8 days resulted in an increase in [citalopram](#) AUC and Cmax of 43% and 39%, respectively. Although the interaction between [citalopram](#) (a CYP2C19 substrate) and [oxcarbazepine](#) (another CYP2C19 inhibitor) [373] has not been specifically studied, concomitant use may result in increased [citalopram](#) exposure and an increased risk of QT prolongation. If coadministration of [citalopram](#) with [oxcarbazepine](#) is required, do not exceed [citalopram](#) doses of 20 mg/day and discontinue [citalopram](#) in patients who have persistent QTc measurements greater than 500 milliseconds [76].
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: The concomitant use of [citalopram](#) with [oxcarbazepine](#) may result in increased [citalopram](#) exposure and risk of QT prolongation. If coadministration of [citalopram](#) with [oxcarbazepine](#) is required, do not exceed [citalopram](#) doses of 20 mg/day and discontinue [citalopram](#) in patients who have persistent QTc measurements greater than 500 milliseconds [76].
- 7) Probable Mechanism: inhibition of CYP2C19-mediated [citalopram](#) metabolism by [oxcarbazepine](#)

3.5.1.GV] [Oxyphenbutazone](#)

- 1) Interaction Effect: an increased risk of bleeding
- 2) Summary: Caution is recommended with the concomitant use of NSAIDs and SSRIs due to an increased risk of [gastrointestinal bleeding](#) [228] [229]. Bleeding events have included [epistaxis](#), ecchymosis, [hematoma](#), [petechiae](#), and life-threatening hemorrhages [231] [53] [232] [233]. 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: probable
- 6) Clinical Management: Use caution if NSAIDs and SSRIs are coadministered. Concomitant use of NSAIDs and SSRIs may cause an increased risk of bleeding [228] [229]. When an SSRI and an NSAID are given concurrently, monitor the patient for signs of increased bleeding.
- 7) Probable Mechanism: unknown
- 8) Literature Reports

a) SSRIs increase the risk of upper gastrointestinal (GI) bleeding, and this effect is potentiated by concurrent use of NSAIDs or low-dose [aspirin](#). Hospitalizations for [upper GI bleeding](#) were searched among 26,005 users of antidepressant medications and compared with the number of hospitalizations in those patients who did not receive prescriptions for antidepressants. The amount of [upper GI bleeding](#) episodes was 3.6 times more than expected (95% CI, 2.7 to 4.7). Combined use of an SSRI and NSAIDs or low-dose [aspirin](#) increased the risk to 12.2 (95% CI, 7.1 to 19.5) and 5.2 (95% CI, 3.2 to 8), respectively. The findings of this study demonstrate an increased risk of [upper GI bleeding](#) during the use of SSRIs. Combined use of SSRIs and NSAIDs or low-dose [aspirin](#) increased the risk even further [230].

b) The 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 [53].

3.5.1.GW] [Paliperidone](#)

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

2) Summary: Although the interaction has not been studied, both [citalopram](#) and [paliperidone](#) are known to prolong the QT interval [76] [324] and concurrent use of these agents is not recommended due to a potential for additive effects on QT interval prolongation and an increased risk of serious cardiovascular effects. If coadministration is required, monitor for ECG changes. Do not exceed [citalopram](#) doses of 40 mg/day, and discontinue [citalopram](#) in patients who have persistent QTc measurements greater than 500 milliseconds [76].

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Concomitant use of [citalopram](#) and [paliperidone](#) is not recommended due to a potential for additive effects on QT interval prolongation and an increased risk of serious cardiovascular effects. If concomitant use is required, monitor for ECG changes. Do not exceed [citalopram](#) doses of 40 mg/day, and discontinue [citalopram](#) in patients who have persistent QTc measurements greater than 500 milliseconds [76].

7) Probable Mechanism: additive effects on QT interval prolongation

3.5.1.GX] [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](#) [206].

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](#) [206].

7) Probable Mechanism: unknown

3.5.1.GY] Panobinostat

- 1) Interaction Effect: increased risk of QT-interval prolongation
- 2) Summary: Concurrent use of panobinostat with QT-prolonging drugs is not recommended, as additive effects on the QT interval may develop. Conduct frequent [ECG monitoring](#) if concurrent use with antiemetics known to prolong the QT interval is warranted. Interrupt treatment if the Fridericia-corrected QT interval increases to 480 msec or more. Discontinue panobinostat if QT-interval prolongation does not resolve after any electrolyte abnormalities are corrected [137].
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Concurrent use of panobinostat with QT-prolonging drugs is not recommended, as additive effects on the QT interval may develop. Conduct frequent [ECG monitoring](#) if concurrent use with antiemetics known to prolong the QT interval is warranted. Interrupt treatment if the Fridericia-corrected QT interval increases to 480 msec or more. Discontinue panobinostat if QT-interval prolongation does not resolve after any electrolyte abnormalities are corrected [137].
- 7) Probable Mechanism: additive QT effects

3.5.1.GZ] Pantoprazole

- 1) Interaction Effect: increased [citalopram](#) exposure and risk of QT interval prolongation
- 2) Summary: In a [pharmacokinetic study](#) in patients who received [citalopram](#) 40 mg/day for 21 days, combined administration with [cimetidine](#) (a potent CYP2C19 inhibitor) 400 mg/day for 8 days resulted in an increase in [citalopram](#) AUC and C_{max} of 43% and 39%, respectively. Although the interaction between [citalopram](#) (a CYP2C19 substrate) and [pantoprazole](#) (another CYP2C19 inhibitor) has not been specifically studied, concomitant use may result in increased [citalopram](#) exposure and an increased risk of QT prolongation. If coadministration of [citalopram](#) with [pantoprazole](#) is required, do not exceed [citalopram](#) doses of 20 mg/day and discontinue [citalopram](#) in patients who have persistent QTc measurements greater than 500 milliseconds [76].
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: The concomitant use of [citalopram](#) with [pantoprazole](#) may result in increased [citalopram](#) exposure and risk of QT prolongation. If coadministration of [citalopram](#) with [pantoprazole](#) is required, do not exceed [citalopram](#) doses of 20 mg/day and discontinue [citalopram](#) in patients who have persistent QTc measurements greater than 500 milliseconds [76].
- 7) Probable Mechanism: inhibition of CYP2C19-mediated [citalopram](#) metabolism by [pantoprazole](#)

3.5.1.HA] Parecoxib

- 1) Interaction Effect: an increased risk of bleeding
- 2) Summary: Caution is recommended with the concomitant use of NSAIDs and SSRIs due to an increased risk of [gastrointestinal bleeding](#) [228] [229]. Bleeding events have included [epistaxis](#), ecchymosis, [hematoma](#), [petechiae](#), and life-threatening hemorrhages [231] [53] [232] [233]. 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: probable

6j) Clinical Management: Use caution if NSAIDs and SSRIs are coadministered. Concomitant use of NSAIDs and SSRIs may cause an increased risk of bleeding [228] [229]. When an SSRI and an NSAID are given concurrently, monitor the patient for signs of increased bleeding.

7j) Probable Mechanism: unknown

8j) Literature Reports

a) SSRIs increase the risk of upper gastrointestinal (GI) bleeding, and this effect is potentiated by concurrent use of NSAIDs or low-dose aspirin. Hospitalizations for upper GI bleeding were searched among 26,005 users of antidepressant medications and compared with the number of hospitalizations in those patients who did not receive prescriptions for antidepressants. The amount of upper GI bleeding episodes was 3.6 times more than expected (95% CI, 2.7 to 4.7). Combined use of an SSRI and NSAIDs or low-dose aspirin increased the risk to 12.2 (95% CI, 7.1 to 19.5) and 5.2 (95% CI, 3.2 to 8), respectively. The findings of this study demonstrate an increased risk of upper GI bleeding during the use of SSRIs. Combined use of SSRIs and NSAIDs or low-dose aspirin increased the risk even further [230].

b) The 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 [53].

3.5.1.HBj Pargyline

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

2j) Summary: Concomitant use of citalopram and an MAOI is contraindicated. Concurrent administration or overlapping therapy with citalopram 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, and tremor. A minimum of 14 days should elapse after discontinuing an MAOI intended to treat psychiatric disorders before initiating therapy with citalopram, and a minimum of 14 days should elapse after discontinuing citalopram before initiating therapy with an MAOI intended to treat psychiatric disorders [53].

3j) Severity: contraindicated

4j) Onset: unspecified

5j) Substantiation: theoretical

6j) Clinical Management: Concurrent use of citalopram and an MAOI is contraindicated. Wait at least 14 days after discontinuing an MAOI intended to treat psychiatric disorders before initiating citalopram. Wait at least 14 days after discontinuing citalopram before initiating therapy with an MAOI intended to treat psychiatric disorders [53].

7j) Probable Mechanism: additive serotonergic effect

3.5.1.HCj Parnaparin

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 [340] [341] [339]. 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 [341] [339].

3j) Severity: major

4j) Onset: unspecified

5j) Substantiation: probable

6j) Clinical Management: When [citalopram](#) and an anticoagulant are given concurrently, monitor patients for signs of increased bleeding. Patients who are taking [warfarin](#) should be monitored closely for altered anticoagulant effects, including increased bleeding, when [citalopram](#) therapy is initiated or discontinued [339].

7j) Probable Mechanism: unknown

8j) 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 [340].

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 [341].

c) The pharmacokinetics of [warfarin](#), a CYP3A4 substrate, were not affected by the administration of [citalopram](#) 40 mg/day for 21 days, while the prothrombin time was increased by 5%. The clinical significance of this is unknown [339].

3.5.1.HDj [Paroxetine](#)

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

2j) Summary: [Serotonin syndrome](#) may result from the concomitant use of [paroxetine](#) and another SSRI, such as [citalopram](#) [79]. 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 [citalopram](#) and [paroxetine](#) and initiate supportive care [53] [79].

3j) Severity: major

4j) Onset: unspecified

5j) Substantiation: theoretical

6J) Clinical Management: Coadministration of [paroxetine](#) and another SSRI, such as [citalopram](#), is not recommended [79], 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 [paroxetine](#) and initiate supportive care [53] [79].

7J) Probable Mechanism: additive serotonergic effect

3.5.1.HE] Pasireotide

1J) Interaction Effect: increased risk of QT prolongation

2J) Summary: Pasireotide is associated with QT-interval prolongation. In 2 studies, QT prolongation occurred at both therapeutic and supratherapeutic doses of pasireotide. Concomitant administration of pasireotide with other drugs that prolong the QT interval, including antiarrhythmic medications, may have additive prolonging effects on the QT interval. ECGs at baseline and at 21 days after treatment initiation are recommended when pasireotide is coadministered with other QT-prolonging agents [320].

3J) Severity: major

4J) Onset: unspecified

5J) Substantiation: theoretical

6J) Clinical Management: Concomitant administration of pasireotide and QT-prolonging drugs, including antiarrhythmic medications, may result in additive prolongation of the QT interval. ECGs at baseline and 21 days after treatment initiation are recommended when pasireotide is coadministered with other QT-prolonging agents [320].

7J) Probable Mechanism: additive QT-interval prolongation

3.5.1.HF] Pazopanib

1J) Interaction Effect: an increased risk of QT interval prolongation

2J) Summary: Although the interaction has not been studied, both [citalopram](#) and pazopanib are known cause QT interval prolongation [76] [308] and concomitant use is not recommended due to a potential for additive effects on QT interval prolongation and an increased risk of serious cardiac adverse events. If concomitant use is required, monitor for ECG changes [76] and maintain electrolytes within normal ranges [308]. Do not exceed [citalopram](#) doses of 40 mg/day, and discontinue [citalopram](#) in patients who have persistent QTc measurements greater than 500 milliseconds [76].

3J) Severity: major

4J) Onset: unspecified

5J) Substantiation: theoretical

6J) Clinical Management: Concomitant use of [citalopram](#) and pazopanib is not recommended due to a potential for additive effects on QT interval prolongation and an increased risk of serious cardiac adverse events. If coadministration of [citalopram](#) with pazopanib is required, monitor for ECG changes [76] and maintain electrolytes (eg, [calcium](#), magnesium, potassium) within normal ranges [308]. Do not exceed [citalopram](#) doses of 40 mg/day, and discontinue [citalopram](#) in patients who have persistent QTc measurements greater than 500 milliseconds [76].

7J) Probable Mechanism: additive effects on QT interval prolongation

3.5.1.HG] Pentosan Polysulfate Sodium

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 [340] [341] [339]. 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](#) [341] [339].

3) Severity: major

4) Onset: unspecified

5) Substantiation: probable

6) Clinical Management: When [citalopram](#) and an anticoagulant are given concurrently, monitor patients for signs of increased bleeding. Patients who are taking [warfarin](#) should be monitored closely for altered anticoagulant effects, including increased bleeding, when [citalopram](#) therapy is initiated or discontinued [339].

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 [340].

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 [341].

c) The pharmacokinetics of [warfarin](#), a CYP3A4 substrate, were not affected by the administration of [citalopram](#) 40 mg/day for 21 days, while the prothrombin time was increased by 5%. The clinical significance of this is unknown [339].

3.5.1.HH] Perflutren Lipid Microsphere

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

2) Summary: Both [citalopram](#) and perflutren may prolong the QT interval [76]. Additionally, serious cardiopulmonary reactions, including fatalities, have been reported during or after administration of perflutren [108]. Due to the potential for additive effects on QT interval prolongation and an increased risk of serious cardiovascular effects, concomitant use of these agents is not recommended. If concomitant

therapy is required, monitor for ECG changes. Do not exceed [citalopram](#) doses of 40 mg/day, and discontinue [citalopram](#) in patients who have persistent QTc measurements greater than 500 milliseconds [76].

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Concomitant use of [citalopram](#) and perflutren is not recommended due to a potential for additive effects on QT interval prolongation and an increased risk of serious cardiovascular effects. If concomitant therapy is required, monitor for ECG changes. Do not exceed [citalopram](#) doses of 40 mg/day, and discontinue [citalopram](#) in patients who have persistent QTc measurements greater than 500 milliseconds [76].

7) Probable Mechanism: additive effects on QT interval prolongation

8) Literature Reports

a) Serious cardiopulmonary reactions, including fatalities, have been reported during or after administration of perflutren-containing microspheres; most serious reactions occurred within 30 minutes of administration. In 221 subjects receiving a perflutren-containing microsphere bolus injection of up to 10 microL/kg, measurement of ECG parameters from 1 hour to 72 hours after administration revealed QTc prolongations of greater than 30 milliseconds in 29% (64/221) of subjects. Among 46 subjects who were further evaluated, 18 (39%) experienced associated cardiac rhythm changes. The effects of concomitant drugs on ECG changes has not been studied [108].

3.5.1.HI] [Phenelzine](#)

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

2) Summary: Concomitant use of [citalopram](#) and an MAOI is contraindicated. Concurrent administration or overlapping therapy with [citalopram](#) 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, and tremor. A minimum of 14 days should elapse after discontinuing an MAOI intended to treat psychiatric disorders before initiating therapy with [citalopram](#), and a minimum of 14 days should elapse after discontinuing [citalopram](#) before initiating therapy with an MAOI intended to treat psychiatric disorders [53].

3) Severity: contraindicated

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Concurrent use of [citalopram](#) and an MAOI is contraindicated. Wait at least 14 days after discontinuing an MAOI intended to treat psychiatric disorders before initiating [citalopram](#). Wait at least 14 days after discontinuing [citalopram](#) before initiating therapy with an MAOI intended to treat psychiatric disorders [53].

7) Probable Mechanism: additive serotonergic effect

3.5.1.HJ] [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 [340] [341] [339]. 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](#) [341] [339].

3) Severity: major

- 4) Onset: unspecified
- 5) Substantiation: probable
- 6) Clinical Management: When [citalopram](#) and an anticoagulant are given concurrently, monitor patients for signs of increased bleeding. Patients who are taking [warfarin](#) should be monitored closely for altered anticoagulant effects, including increased bleeding, when [citalopram](#) therapy is initiated or discontinued [339].
- 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 [340].

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 [341].

c) The pharmacokinetics of [warfarin](#), a CYP3A4 substrate, were not affected by the administration of [citalopram](#) 40 mg/day for 21 days, while the prothrombin time was increased by 5%. The clinical significance of this is unknown [339].

3.5.1.HK] 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 [340] [341] [339]. 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](#) [341] [339].
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: probable

6j) Clinical Management: When [citalopram](#) and an anticoagulant are given concurrently, monitor patients for signs of increased bleeding. Patients who are taking [warfarin](#) should be monitored closely for altered anticoagulant effects, including increased bleeding, when [citalopram](#) therapy is initiated or discontinued [339].

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 [340].

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 [341].

cj) The pharmacokinetics of [warfarin](#), a CYP3A4 substrate, were not affected by the administration of [citalopram](#) 40 mg/day for 21 days, while the prothrombin time was increased by 5%. The clinical significance of this is unknown [339].

3.5.1.HLj [Phenylbutazone](#)

1j) Interaction Effect: an increased risk of bleeding

2j) Summary: Caution is recommended with the concomitant use of NSAIDs and SSRIs due to an increased risk of [gastrointestinal bleeding](#) [228] [229]. Bleeding events have included [epistaxis](#), ecchymosis, [hematoma](#), [petechiae](#), and life-threatening hemorrhages [231] [53] [232] [233]. 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: probable

6j) Clinical Management: Use caution if NSAIDs and SSRIs are coadministered. Concomitant use of NSAIDs and SSRIs may cause an increased risk of bleeding [228] [229]. When an SSRI and an NSAID are given concurrently, monitor the patient for signs of increased bleeding.

7) Probable Mechanism: unknown

8) Literature Reports

a) SSRIs increase the risk of upper gastrointestinal (GI) bleeding, and this effect is potentiated by concurrent use of NSAIDs or low-dose [aspirin](#). Hospitalizations for [upper GI bleeding](#) were searched among 26,005 users of antidepressant medications and compared with the number of hospitalizations in those patients who did not receive prescriptions for antidepressants. The amount of [upper GI bleeding](#) episodes was 3.6 times more than expected (95% CI, 2.7 to 4.7). Combined use of an SSRI and NSAIDs or low-dose [aspirin](#) increased the risk to 12.2 (95% CI, 7.1 to 19.5) and 5.2 (95% CI, 3.2 to 8), respectively. The findings of this study demonstrate an increased risk of [upper GI bleeding](#) during the use of SSRIs. Combined use of SSRIs and NSAIDs or low-dose [aspirin](#) increased the risk even further [230].

b) The 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 [53].

3.5.1.HM] [Piketoprofen](#)

1) Interaction Effect: an increased risk of bleeding

2) Summary: Caution is recommended with the concomitant use of NSAIDs and SSRIs due to an increased risk of [gastrointestinal bleeding](#) [228] [229]. Bleeding events have included [epistaxis](#), ecchymosis, [hematoma](#), [petechiae](#), and life-threatening hemorrhages [231] [53] [232] [233]. 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: probable

6) Clinical Management: Use caution if NSAIDs and SSRIs are coadministered. Concomitant use of NSAIDs and SSRIs may cause an increased risk of bleeding [228] [229]. When an SSRI and an NSAID are given concurrently, monitor the patient for signs of increased bleeding.

7) Probable Mechanism: unknown

8) Literature Reports

a) SSRIs increase the risk of upper gastrointestinal (GI) bleeding, and this effect is potentiated by concurrent use of NSAIDs or low-dose [aspirin](#). Hospitalizations for [upper GI bleeding](#) were searched among 26,005 users of antidepressant medications and compared with the number of hospitalizations in those patients who did not receive prescriptions for antidepressants. The amount of [upper GI bleeding](#) episodes was 3.6 times more than expected (95% CI, 2.7 to 4.7). Combined use of an SSRI and NSAIDs or low-dose [aspirin](#) increased the risk to 12.2 (95% CI, 7.1 to 19.5) and 5.2 (95% CI, 3.2 to 8), respectively. The findings of this study demonstrate an increased risk of [upper GI bleeding](#) during the use of SSRIs. Combined use of SSRIs and NSAIDs or low-dose [aspirin](#) increased the risk even further [230].

b) The 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 [53].

3.5.1.HN] [Pimozide](#)

1) Interaction Effect: increased risk of QT-interval prolongation

- 2) Summary: The concomitant use of [pimozide](#) with drugs that cause QT-interval prolongation is contraindicated, as coadministration may increase the risk of QT prolongation and serious [ventricular arrhythmias](#) [272].
- 3) Severity: contraindicated
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: The concomitant use of [pimozide](#) with drugs that cause QT-interval prolongation is contraindicated, as coadministration may increase the risk of QT prolongation and serious [ventricular arrhythmias](#) [272].
- 7) Probable Mechanism: additive QT-interval prolongation

3.5.1.HO] Piperaquine

- 1) Interaction Effect: increased exposure of [citalopram](#) or escitalopram and an increased risk of QT-interval prolongation
- 2) Summary: Concomitant administration of [citalopram](#) and piperaquine may result in additive prolongation effects on the QT interval and is contraindicated. Recent use of QT-interval prolonging drugs, that may still be circulating at the time of piperaquine administration, is contraindicated. Additionally, concurrent administration of [citalopram](#) (a CYP3A4 and CYP2C19 substrate) and piperaquine (a CYP3A4 and CYP2C19 inhibitor) may increase the exposure of [citalopram](#) and further increase the risk of QT-interval prolongation [369]. The same effects are expected with concomitant use of escitalopram and piperaquine.
- 3) Severity: contraindicated
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Concomitant administration of [citalopram](#) and piperaquine may result in additive prolongation effects on the QT interval and is contraindicated. Recent use of QT-interval prolonging drugs, that may still be circulating at the time of piperaquine administration, is contraindicated. Additionally, concurrent administration of [citalopram](#) (a CYP3A4 and CYP2C19 substrate) and piperaquine (a CYP3A4 and CYP2C19 inhibitor) may increase the exposure of [citalopram](#) and further increase the risk of QT-interval prolongation [369]. The same effects are expected with concomitant use of escitalopram and piperaquine.
- 7) Probable Mechanism: inhibition of CYP3A4 and CYP2C19-mediated metabolism of [citalopram](#) or escitalopram by piperaquine; additive QT-interval prolongation

3.5.1.HP] Piroxicam

- 1) Interaction Effect: an increased risk of bleeding
- 2) Summary: Caution is recommended with the concomitant use of NSAIDs and SSRIs due to an increased risk of [gastrointestinal bleeding](#) [228] [229]. Bleeding events have included [epistaxis](#), ecchymosis, [hematoma](#), [petechiae](#), and life-threatening hemorrhages [231] [53] [232] [233]. 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: probable
- 6) Clinical Management: Use caution if NSAIDs and SSRIs are coadministered. Concomitant use of NSAIDs and SSRIs may cause an increased risk of bleeding [228] [229]. When an SSRI and an NSAID are given concurrently, monitor the patient for signs of increased bleeding.
- 7) Probable Mechanism: unknown
- 8) Literature Reports

a) SSRIs increase the risk of upper gastrointestinal (GI) bleeding, and this effect is potentiated by concurrent use of NSAIDs or low-dose [aspirin](#). Hospitalizations for [upper GI bleeding](#) were searched among 26,005 users of antidepressant medications and compared with the number of hospitalizations in those patients who did not receive prescriptions for antidepressants. The amount of [upper GI bleeding](#) episodes was 3.6 times more than expected (95% CI, 2.7 to 4.7). Combined use of an SSRI and NSAIDs or low-dose [aspirin](#) increased the risk to 12.2 (95% CI, 7.1 to 19.5) and 5.2 (95% CI, 3.2 to 8), respectively. The findings of this study demonstrate an increased risk of [upper GI bleeding](#) during the use of SSRIs. Combined use of SSRIs and NSAIDs or low-dose [aspirin](#) increased the risk even further [230].

b) The 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 [53].

3.5.1.HQ| Posaconazole

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

2) Summary: [Citalopram](#) causes dose-dependent prolongation of the QTc interval [76] and [posaconazole](#) has been associated with QT interval prolongation and rare cases of [torsade de pointes](#) [237]. [Posaconazole](#) is a CYP3A4 inhibitor and may increase [citalopram](#) exposure. The concomitant use of [citalopram](#) with [posaconazole](#) is contraindicated due to a potential for additive effects on QT interval prolongation and an increased risk of cardiac adverse events, including [ventricular arrhythmias](#) and/or [torsade de pointes](#) [237].

3) Severity: contraindicated

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: The concomitant use of [citalopram](#) and [posaconazole](#) is contraindicated due to a potential for additive effects on QT interval prolongation and an increased risk of serious cardiovascular effects [237].

7) Probable Mechanism: additive effects on QT interval prolongation; inhibition of [citalopram](#) CYP3A4-mediated metabolism

3.5.1.HR| Prasugrel

1) Interaction Effect: an increased risk of bleeding

2) Summary: The concomitant use of [citalopram](#) and an antiplatelet drug may increase the risk of bleeding. The release of serotonin by [platelets](#) is important for maintaining hemostasis. Case-controlled and cohort studies have shown that the combined use of selective serotonin reuptake inhibitors and antiplatelet agents has been associated with an increased risk of bleeding. Bleeding events reported have included [epistaxis](#), ecchymosis, [hematoma](#), [petechiae](#), and life-threatening hemorrhages. Monitor patient for signs of increased bleeding when [citalopram](#) is administered concomitantly with an antiplatelet drug [40].

3) Severity: major

4) Onset: unspecified

5) Substantiation: probable

6) Clinical Management: When [citalopram](#) and an antiplatelet agent are given concurrently, monitor patient for signs of increased bleeding [40].

7) Probable Mechanism: unknown

3.5.1.HS| Primidone

1) Interaction Effect: decreased exposure of CYP3A4 substrates

2)) Summary: **Primidone** is metabolized to **phenobarbital** [343] (a strong CYP3A4 inducer). Concomitant use of **primidone** with certain CYP3A4 substrates may result in decreased exposure of the CYP3A4 substrate and should be avoided if clinically possible. 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 concomitant use if clinically possible. If coadministration is required, use caution and monitor the patient closely.

7)) Probable Mechanism: induction of CYP3A4-mediated metabolism by **primidone**

3.5.1.HT] **Probenecid**

1)) Interaction Effect: increased **citalopram** exposure and risk of QT interval prolongation

2)) Summary: **Citalopram** has been associated with dose-dependent prolongation of the QT interval [76]. In a **pharmacokinetic study** in patients who received **citalopram** 40 mg/day for 21 days, combined administration with **cimetidine** (a potent CYP2C19 inhibitor) 400 mg/day for 8 days resulted in an increase in **citalopram** AUC and C_{max} of 43% and 39%, respectively. Although the interaction between **citalopram** (a CYP2C19 substrate) and **probenecid** (another CYP2C19 inhibitor) has not been specifically studied, concomitant use may result in increased **citalopram** exposure and an increased risk of QT prolongation. If coadministration of **citalopram** with **probenecid** is required, do not exceed **citalopram** doses of 20 mg/day. Discontinue **citalopram** in patients who have persistent QTc measurements greater than 500 milliseconds [76].

3)) Severity: major

4)) Onset: unspecified

5)) Substantiation: theoretical

6)) Clinical Management: The concomitant use of **citalopram** with **probenecid** may result in increased **citalopram** exposure and risk of QT prolongation. If coadministration of **citalopram** with **probenecid** is required, do not exceed **citalopram** doses of 20 mg/day. Discontinue **citalopram** in patients who have persistent QTc measurements greater than 500 milliseconds [76].

7)) Probable Mechanism: inhibition of CYP2C19-mediated **citalopram** metabolism by **probenecid**

3.5.1.HU] **Procainamide**

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

2)) Summary: **Citalopram** causes dose-dependent prolongation of the QTc interval [76] and **procainamide** is a class IA antiarrhythmic associated with QT interval prolongation [181]. The concomitant use of **citalopram** and **procainamide** is not recommended due to a potential for additive effects on QT interval prolongation and an increased risk of cardiac adverse events, including **ventricular arrhythmias** and/or **torsade de pointes**. If coadministration is required, monitor for ECG changes. Do not exceed **citalopram** doses of 40 mg/day and discontinue **citalopram** in patients who have persistent QTc measurements greater than 500 milliseconds [76].

3)) Severity: major

4)) Onset: unspecified

5)) Substantiation: theoretical

6)) Clinical Management: The concomitant use of **citalopram** and **procainamide** is not recommended due to a potential for additive effects on QT interval prolongation and an increased risk of serious cardiovascular effects. If coadministration is required, monitor for ECG changes. Do not exceed **citalopram** doses of 40 mg/day and discontinue **citalopram** in patients who have persistent QTc measurements greater than 500 milliseconds [76].

7J) Probable Mechanism: additive effects on QT interval prolongation

3.5.1.HV] Procarbazine

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

2J) Summary: Concomitant use of [citalopram](#) and an MAOI is contraindicated. Concurrent administration or overlapping therapy with [citalopram](#) 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, and tremor. A minimum of 14 days should elapse after discontinuing an MAOI intended to treat psychiatric disorders before initiating therapy with [citalopram](#), and a minimum of 14 days should elapse after discontinuing [citalopram](#) before initiating therapy with an MAOI intended to treat psychiatric disorders [53].

3J) Severity: contraindicated

4J) Onset: unspecified

5J) Substantiation: theoretical

6J) Clinical Management: Concurrent use of [citalopram](#) and an MAOI is contraindicated. Wait at least 14 days after discontinuing an MAOI intended to treat psychiatric disorders before initiating [citalopram](#). Wait at least 14 days after discontinuing [citalopram](#) before initiating therapy with an MAOI intended to treat psychiatric disorders [53].

7J) Probable Mechanism: additive serotonergic effect

3.5.1.HW] Prochlorperazine

1J) Interaction Effect: an increased risk of QT interval prolongation

2J) Summary: [Citalopram](#) has been associated with dose-dependent prolongation of the QT interval [76] and [prochlorperazine](#) is a phenothiazine tranquilizer (some drugs in this class have been associated with distortions of the QT interval) [202]. The concomitant use of [citalopram](#) and [prochlorperazine](#) is not recommended due to a potential for additive effects on QT interval prolongation and an increased risk of cardiac adverse events, including [ventricular arrhythmias](#) and/or [torsade de pointes](#). If coadministration is required, monitor for ECG changes. Do not exceed [citalopram](#) doses of 40 mg/day and discontinue [citalopram](#) in patients who have persistent QTc measurements greater than 500 milliseconds [76].

3J) Severity: major

4J) Onset: unspecified

5J) Substantiation: theoretical

6J) Clinical Management: The concomitant use of [citalopram](#) and [prochlorperazine](#) is not recommended due to a potential for additive effects on QT interval prolongation and an increased risk of serious cardiovascular effects. If coadministration is required, monitor for ECG changes. Do not exceed [citalopram](#) doses of 40 mg/day and discontinue [citalopram](#) in patients who have persistent QTc measurements greater than 500 milliseconds [76].

7J) Probable Mechanism: additive effects on QT interval prolongation

3.5.1.HX] Proglumetacin

1J) Interaction Effect: an increased risk of bleeding

2J) Summary: Caution is recommended with the concomitant use of NSAIDs and SSRIs due to an increased risk of [gastrointestinal bleeding](#) [228] [229]. Bleeding events have included [epistaxis](#), [ecchymosis](#), [hematoma](#), [petechiae](#), and life-threatening hemorrhages [231] [53] [232] [233]. When an SSRI and an NSAID are given concurrently, monitor the patient for signs of increased bleeding.

3J) Severity: major

4J) Onset: unspecified

5) Substantiation: probable

6) Clinical Management: Use caution if NSAIDs and SSRIs are coadministered. Concomitant use of NSAIDs and SSRIs may cause an increased risk of bleeding [228] [229]. When an SSRI and an NSAID are given concurrently, monitor the patient for signs of increased bleeding.

7) Probable Mechanism: unknown

8) Literature Reports

a) SSRIs increase the risk of upper gastrointestinal (GI) bleeding, and this effect is potentiated by concurrent use of NSAIDs or low-dose aspirin. Hospitalizations for upper GI bleeding were searched among 26,005 users of antidepressant medications and compared with the number of hospitalizations in those patients who did not receive prescriptions for antidepressants. The amount of upper GI bleeding episodes was 3.6 times more than expected (95% CI, 2.7 to 4.7). Combined use of an SSRI and NSAIDs or low-dose aspirin increased the risk to 12.2 (95% CI, 7.1 to 19.5) and 5.2 (95% CI, 3.2 to 8), respectively. The findings of this study demonstrate an increased risk of upper GI bleeding during the use of SSRIs. Combined use of SSRIs and NSAIDs or low-dose aspirin increased the risk even further [230].

b) The 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 [53].

3.5.1.HY] Promethazine

1) Interaction Effect: increased risk of QT interval prolongation

2) Summary: Citalopram causes dose-dependent prolongation of the QTc interval. The concomitant use of citalopram and promethazine is not recommended due to a potential for additive effects on QT interval prolongation and an increased risk of cardiac adverse events, including ventricular arrhythmias and/or torsade de pointes. If coadministration is required, monitor for ECG changes. Do not exceed citalopram doses of 40 mg/day and discontinue citalopram in patients who have persistent QTc measurements greater than 500 milliseconds [76].

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: The concomitant use of citalopram and promethazine is not recommended due to a potential for additive effects on QT interval prolongation and an increased risk of serious cardiovascular effects. If coadministration is required, monitor for ECG changes. Do not exceed citalopram doses of 40 mg/day and discontinue citalopram in patients who have persistent QTc measurements greater than 500 milliseconds [76].

7) Probable Mechanism: additive effects on the QT interval prolongation

3.5.1.HZ] Propafenone

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

2) Summary: Both citalopram and propafenone have been associated with QT interval prolongation [204]. Therefore, concomitant use of citalopram and propafenone is not recommended due to a potential for additive effects on QT interval prolongation and an increased risk of serious cardiovascular effects. However, if concurrent therapy is required, monitor for ECG changes. Do not exceed citalopram doses of 40 mg/day, and discontinue citalopram in patients who have persistent QTc measurements greater than 500 milliseconds [76].

3) Severity: major

4) Onset: unspecified

- 5) Substantiation: theoretical
- 6) Clinical Management: Concomitant use of [citalopram](#) and [propafenone](#) is not recommended due to a potential for additive effects on QT interval prolongation and an increased risk of serious cardiovascular effects. However, if concurrent therapy is required, monitor for ECG changes. Do not exceed [citalopram](#) doses of 40 mg/day, and discontinue [citalopram](#) in patients who have persistent QTc measurements greater than 500 milliseconds [76].
- 7) Probable Mechanism: additive effects on QT interval prolongation

3.5.1.IA) [Propionic Acid](#)

- 1) Interaction Effect: an increased risk of bleeding
- 2) Summary: Caution is recommended with the concomitant use of NSAIDs and SSRIs due to an increased risk of [gastrointestinal bleeding](#) [228] [229]. Bleeding events have included [epistaxis](#), ecchymosis, [hematoma](#), [petechiae](#), and life-threatening hemorrhages [231] [53] [232] [233]. 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: probable
- 6) Clinical Management: Use caution if NSAIDs and SSRIs are coadministered. Concomitant use of NSAIDs and SSRIs may cause an increased risk of bleeding [228] [229]. When an SSRI and an NSAID are given concurrently, monitor the patient for signs of increased bleeding.
- 7) Probable Mechanism: unknown
- 8) Literature Reports

a) SSRIs increase the risk of upper gastrointestinal (GI) bleeding, and this effect is potentiated by concurrent use of NSAIDs or low-dose [aspirin](#). Hospitalizations for [upper GI bleeding](#) were searched among 26,005 users of antidepressant medications and compared with the number of hospitalizations in those patients who did not receive prescriptions for antidepressants. The amount of [upper GI bleeding](#) episodes was 3.6 times more than expected (95% CI, 2.7 to 4.7). Combined use of an SSRI and NSAIDs or low-dose [aspirin](#) increased the risk to 12.2 (95% CI, 7.1 to 19.5) and 5.2 (95% CI, 3.2 to 8), respectively. The findings of this study demonstrate an increased risk of [upper GI bleeding](#) during the use of SSRIs. Combined use of SSRIs and NSAIDs or low-dose [aspirin](#) increased the risk even further [230].

b) The 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 [53].

3.5.1.IB) [Propyphenazone](#)

- 1) Interaction Effect: an increased risk of bleeding
- 2) Summary: Caution is recommended with the concomitant use of NSAIDs and SSRIs due to an increased risk of [gastrointestinal bleeding](#) [228] [229]. Bleeding events have included [epistaxis](#), ecchymosis, [hematoma](#), [petechiae](#), and life-threatening hemorrhages [231] [53] [232] [233]. 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: probable
- 6) Clinical Management: Use caution if NSAIDs and SSRIs are coadministered. Concomitant use of NSAIDs and SSRIs may cause an increased risk of bleeding [228] [229]. When an SSRI and an NSAID are given concurrently, monitor the patient for signs of increased bleeding.

7) Probable Mechanism: unknown

8) Literature Reports

a) SSRIs increase the risk of upper gastrointestinal (GI) bleeding, and this effect is potentiated by concurrent use of NSAIDs or low-dose [aspirin](#). Hospitalizations for [upper GI bleeding](#) were searched among 26,005 users of antidepressant medications and compared with the number of hospitalizations in those patients who did not receive prescriptions for antidepressants. The amount of [upper GI bleeding](#) episodes was 3.6 times more than expected (95% CI, 2.7 to 4.7). Combined use of an SSRI and NSAIDs or low-dose [aspirin](#) increased the risk to 12.2 (95% CI, 7.1 to 19.5) and 5.2 (95% CI, 3.2 to 8), respectively. The findings of this study demonstrate an increased risk of [upper GI bleeding](#) during the use of SSRIs. Combined use of SSRIs and NSAIDs or low-dose [aspirin](#) increased the risk even further [230].

b) The 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 [53].

3.5.1.IC] Proquazone

1) Interaction Effect: an increased risk of bleeding

2) Summary: Caution is recommended with the concomitant use of NSAIDs and SSRIs due to an increased risk of [gastrointestinal bleeding](#) [228] [229]. Bleeding events have included [epistaxis](#), ecchymosis, [hematoma](#), [petechiae](#), and life-threatening hemorrhages [231] [53] [232] [233]. 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: probable

6) Clinical Management: Use caution if NSAIDs and SSRIs are coadministered. Concomitant use of NSAIDs and SSRIs may cause an increased risk of bleeding [228] [229]. When an SSRI and an NSAID are given concurrently, monitor the patient for signs of increased bleeding.

7) Probable Mechanism: unknown

8) Literature Reports

a) SSRIs increase the risk of upper gastrointestinal (GI) bleeding, and this effect is potentiated by concurrent use of NSAIDs or low-dose [aspirin](#). Hospitalizations for [upper GI bleeding](#) were searched among 26,005 users of antidepressant medications and compared with the number of hospitalizations in those patients who did not receive prescriptions for antidepressants. The amount of [upper GI bleeding](#) episodes was 3.6 times more than expected (95% CI, 2.7 to 4.7). Combined use of an SSRI and NSAIDs or low-dose [aspirin](#) increased the risk to 12.2 (95% CI, 7.1 to 19.5) and 5.2 (95% CI, 3.2 to 8), respectively. The findings of this study demonstrate an increased risk of [upper GI bleeding](#) during the use of SSRIs. Combined use of SSRIs and NSAIDs or low-dose [aspirin](#) increased the risk even further [230].

b) The 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 [53].

3.5.1.ID] Protriptyline

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

2) Summary: [Citalopram](#) has been associated with QT interval prolongation [76]. [Protriptyline](#) has a tendency to produce [arrhythmias](#) and prolongation of conduction time [342]. Therefore, the concomitant use of [citalopram](#) and [protriptyline](#) is not recommended due to a potential for additive effects on QT interval prolongation and an increased risk of serious cardiovascular effects. If coadministration is required, monitor for ECG changes. Do not exceed [citalopram](#) doses of 40 mg/day, and discontinue [citalopram](#) in patients who have persistent QTc measurements greater than 500 milliseconds [76].

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Concomitant use of [citalopram](#) and [protriptyline](#) is not recommended due to a potential for additive effects on QT interval prolongation and an increased risk of serious cardiovascular effects. If coadministration is required, monitor for ECG changes. Do not exceed [citalopram](#) doses of 40 mg/day, and discontinue [citalopram](#) in patients who have persistent QTc measurements greater than 500 milliseconds [76].

7) Probable Mechanism: additive effects on QT interval prolongation

3.5.1.IE] [Quetiapine](#)

1) Interaction Effect: increased risk of QT interval prolongation

2) Summary: [Citalopram](#) causes dose-dependent prolongation of the QTc interval [76] and [quetiapine](#) has also been associated with QT interval prolongation [157]. Although this interaction has not been evaluated, the concomitant use of [citalopram](#) and [quetiapine](#) is not recommended due to a potential for additive effects on QT interval prolongation and an increased risk of cardiac adverse events, including [ventricular arrhythmias](#) and/or [torsade de pointes](#). If coadministration is required, monitor for ECG changes. Do not exceed [citalopram](#) doses of 40 mg/day, and discontinue [citalopram](#) in patients who have persistent QTc measurements greater than 500 milliseconds [76].

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: The concomitant use of [citalopram](#) and [quetiapine](#) is not recommended as concurrent use may increase the risk of cardiac adverse events, including [torsade de pointes](#). If coadministration is required, monitor for ECG changes. Do not exceed [citalopram](#) doses of 40 mg/day, and discontinue [citalopram](#) in patients who have persistent QTc measurements greater than 500 milliseconds [76].

7) Probable Mechanism: additive effects on the QT interval

3.5.1.IF] [Quinidine](#)

1) Interaction Effect: increased risk of QT interval prolongation

2) Summary: [Citalopram](#) causes dose-dependent prolongation of the QTc interval [76] and [quinidine](#) is also known to prolong the QT interval [358]. Although this interaction has not been evaluated, the concomitant use of [citalopram](#) and [quinidine](#) is not recommended due to a potential for additive effects on QT interval prolongation and an increased risk of cardiac adverse events, including [ventricular arrhythmias](#) and/or [torsade de pointes](#). If coadministration is required, monitor for ECG changes. Do not exceed [citalopram](#) doses of 40 mg/day, and discontinue [citalopram](#) in patients who have persistent QTc measurements greater than 500 milliseconds [76].

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6J) Clinical Management: The concomitant use of [citalopram](#) and [quinidine](#) is not recommended due to a potential for additive effects on QT interval prolongation and an increased risk of serious cardiovascular effects. If coadministration is required, monitor for ECG changes. Do not exceed [citalopram](#) doses of 40 mg/day, and discontinue [citalopram](#) in patients who have persistent QTc measurements greater than 500 milliseconds [76].

7J) Probable Mechanism: additive effects on the QT interval

3.5.1.IGJ [Quinine](#)

1J) Interaction Effect: an increased risk of QT interval prolongation

2J) Summary: Both [citalopram](#) and [quinine](#) may prolong the QT interval [76] [372]. Although this interaction has not been evaluated, due to the potential for additive effects on QT interval prolongation and an increased risk of serious cardiac events, the concomitant use of [citalopram](#) and [quinine](#) is not recommended. If concomitant therapy is required, monitor for ECG changes. Do not exceed [citalopram](#) doses of 40 mg/day, and discontinue [citalopram](#) in patients who have persistent QTc measurements greater than 500 milliseconds [76].

3J) Severity: major

4J) Onset: unspecified

5J) Substantiation: theoretical

6J) Clinical Management: Concomitant use of [citalopram](#) and [quinine](#) is not recommended due to a potential for additive effects on QT interval prolongation and an increased risk of serious cardiac events. If concomitant therapy is required, monitor for ECG changes. Do not exceed [citalopram](#) doses of 40 mg/day, and discontinue [citalopram](#) in patients who have persistent QTc measurements greater than 500 milliseconds [76].

7J) Probable Mechanism: additive effects on QT interval prolongation

3.5.1.IHJ [Rabeprazole](#)

1J) Interaction Effect: increased [citalopram](#) exposure and risk of QT interval prolongation

2J) Summary: [Citalopram](#) is associated with dose-dependent increase in the QT interval. In a [pharmacokinetic study](#) in patients who received [citalopram](#) 40 mg/day for 21 days, combined administration with [cimetidine](#) (a potent CYP2C19 inhibitor) 400 mg/day for 8 days resulted in an increase in [citalopram](#) AUC and Cmax of 43% and 39%, respectively. Although the interaction between [citalopram](#) (a CYP2C19 substrate) and [rabeprazole](#) (another CYP2C19 inhibitor) has not been specifically studied, concomitant use may result in increased [citalopram](#) exposure and an increased risk of QT prolongation. If coadministration of [citalopram](#) with [rabeprazole](#) is required, do not exceed [citalopram](#) doses of 20 mg/day and discontinue [citalopram](#) in patients who have persistent QTc measurements greater than 500 ms [76].

3J) Severity: major

4J) Onset: unspecified

5J) Substantiation: theoretical

6J) Clinical Management: The concomitant use of [citalopram](#) (a CYP2C19 substrate) with [rabeprazole](#), a potent CYP2C19 inhibitor, may result in increased [citalopram](#) exposure and risk of QT prolongation. If coadministration of [citalopram](#) with [rabeprazole](#) is required, do not exceed [citalopram](#) doses of 20 mg/day and discontinue [citalopram](#) in patients who have persistent QTc measurements greater than 500 ms [76].

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

3.5.1.IIJ [Ranolazine](#)

1J) Interaction Effect: increased risk of QT interval prolongation

2J) Summary: [Citalopram](#) causes dose-dependent prolongation of the QTc interval [76] and [ranolazine](#) has been associated with QT interval prolongation [333]. Although this interaction has not been evaluated,

the concomitant use of [citalopram](#) and [ranolazine](#) is not recommended due to a potential for additive effects on QT interval prolongation and an increased risk of cardiac adverse events, including [ventricular arrhythmias](#) and/or [torsade de pointes](#). If coadministration is required, monitor for ECG changes. Do not exceed [citalopram](#) doses of 40 mg/day, and discontinue [citalopram](#) in patients who have persistent QTc measurements greater than 500 milliseconds [76].

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: The concomitant use of [citalopram](#) and [ranolazine](#) is not recommended due to a potential for additive effects on QT interval prolongation and an increased risk of serious cardiovascular effects. If coadministration is required, monitor for ECG changes. Do not exceed [citalopram](#) doses of 40 mg/day, and discontinue [citalopram](#) in patients who have persistent QTc measurements greater than 500 milliseconds [76].

7) Probable Mechanism: additive effects on the QT interval

3.5.1.IJ] [Rasagiline](#)

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

2) Summary: Concomitant use of [citalopram](#) and an MAOI is contraindicated. Concurrent administration or overlapping therapy with [citalopram](#) 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, and tremor. A minimum of 14 days should elapse after discontinuing an MAOI intended to treat psychiatric disorders before initiating therapy with [citalopram](#), and a minimum of 14 days should elapse after discontinuing [citalopram](#) before initiating therapy with an MAOI intended to treat psychiatric disorders [53].

3) Severity: contraindicated

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Concurrent use of [citalopram](#) and an MAOI is contraindicated. Wait at least 14 days after discontinuing an MAOI intended to treat psychiatric disorders before initiating [citalopram](#). Wait at least 14 days after discontinuing [citalopram](#) before initiating therapy with an MAOI intended to treat psychiatric disorders [53].

7) Probable Mechanism: additive serotonergic effect

3.5.1.IK] [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 [340] [341] [339]. 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](#) [341] [339].

3) Severity: major

4) Onset: unspecified

5) Substantiation: probable

6) Clinical Management: When [citalopram](#) and an anticoagulant are given concurrently, monitor patients for signs of increased bleeding. Patients who are taking [warfarin](#) should be monitored closely for altered anticoagulant effects, including increased bleeding, when [citalopram](#) therapy is initiated or discontinued [339].

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 [340].

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 [341].

cJ) The pharmacokinetics of [warfarin](#), a CYP3A4 substrate, were not affected by the administration of [citalopram](#) 40 mg/day for 21 days, while the prothrombin time was increased by 5%. The clinical significance of this is unknown [339].

3.5.1.ILJ [Rifampin](#)

1J) Interaction Effect: decreased [citalopram](#) plasma concentrations with a risk of decreased [citalopram](#) efficacy

2J) Summary: CYP3A4 is involved in an estimated 70% of [citalopram](#) N-demethylation, the major pathway of its metabolism. [Rifampin](#), as a potent inducer of CYP3A4, may have a significant effect upon [citalopram](#) metabolism, resulting in decreased plasma concentrations and efficacy. Patients using concurrent [citalopram](#) and [rifampin](#) should be monitored for [citalopram](#) efficacy. An upward dosage adjustment of [citalopram](#) should be considered [107].

3J) Severity: moderate

4J) Onset: unspecified

5J) Substantiation: probable

6J) Clinical Management: Coadministration of [rifampin](#) with [citalopram](#) may increase the metabolism of [citalopram](#) resulting in decreased [citalopram](#) efficacy. Monitor patients who are taking both [rifampin](#) and [citalopram](#) for a lack of response to [citalopram](#) therapy. Consider an increase in [citalopram](#) dosing when these medication are prescribed concomitantly.

7J) Probable Mechanism: [rifampin](#) induction of CYP3A4-mediated [citalopram](#) metabolism

8) Literature Reports

a) A case report of a 55 year old male receiving concomitant [citalopram](#) and [rifampin](#) therapy supports a probable interaction between the two drugs due to [rifampin](#) induction of CYP3A4-mediated metabolism of [citalopram](#). While being treated for [osteomyelitis](#) the patient was prescribed a regimen of double strength [sulfamethoxazole/trimethoprim](#) twice daily with [rifampin](#) 600 mg twice daily. The patient was also given a regimen of [citalopram](#) 40 mg once daily and [clonazepam](#) 1 mg twice daily for the treatment of panic attacks. One month later the patient complained of gastrointestinal irritation and was advised to discontinue both antibiotics. He misunderstood and continued [rifampin](#) as a single therapy. A one week follow-up visit to the psychiatric clinic revealed the patient was experiencing increased incidents of crying spells and panic attacks and had increased his [clonazepam](#) from 1 mg twice daily to 5 mg daily due to a perceived decreased in efficacy. At this time the patient was switch to escitalopram under the incorrect assumption that escitalopram was not susceptible to CYP3A4 induction by [rifampin](#). Two weeks later the misunderstanding regarding continuation of [rifampin](#) was corrected with its discontinuation and the patient was switched back to a regimen of [citalopram](#) 60 mg daily and [clonazepam](#) 1mg twice daily. During a follow-up visit a few weeks later the patient reported he was doing well with only one or two panic attacks after the discontinuation of [rifampin](#) [107].

3.5.1.IM] [Risperidone](#)

1) Interaction Effect: an increased risk of QT interval prolongation and [torsade de pointes](#)

2) Summary: [Citalopram](#) has been associated with dose-dependent QT interval prolongation [76]. In a case report, [torsade de pointes](#) occurred in a 77-year-old woman who received both [citalopram](#) and [risperiDONE](#) for delusional [depressive episodes](#) [159]. The concomitant use of [citalopram](#) and [risperiDONE](#) is not recommended due to a potential for additive effects on QT interval prolongation and an increased risk of cardiac adverse events, including [ventricular arrhythmias](#) and/or [torsade de pointes](#). If coadministration is required, monitor for ECG changes. Do not exceed [citalopram](#) doses of 40 mg/day, and discontinue [citalopram](#) in patients who have persistent QTc measurements greater than 500 milliseconds [76].

3) Severity: major

4) Onset: unspecified

5) Substantiation: probable

6) Clinical Management: The concomitant use of [citalopram](#) and [risperiDONE](#) is not recommended due to a potential for additive effects on QT interval prolongation and an increased risk of serious cardiovascular effects. If coadministration is required, monitor for ECG changes. Do not exceed [citalopram](#) doses of 40 mg/day, and discontinue [citalopram](#) in patients who have persistent QTc measurements greater than 500 milliseconds [76].

7) Probable Mechanism: additive effects on QT interval prolongation

8) Literature Reports

a) [Torsade de pointes](#) (TdP) occurred in a 77-year-old woman who received both [citalopram](#) and [risperiDONE](#) for delusional [depressive episodes](#). During a routine Holter ECG, TdP was discovered and the patient was admitted for medical management. Approximately 3 months prior, [citalopram](#) 20 mg/day and [risperiDONE](#) 2 mg/day were initiated, at which time an ECG showed a normal heart rate (66 beats per minute) and corrected QT (QTc) interval (410 milliseconds). The patient's past medical history included latent [hypothyroidism](#), [type 2 diabetes](#), [hypertension](#), and a cerebral insult 3 months prior to admission resulting in paresis of the hypoglossus nerve, [dysphagia](#), [dysarthria](#), and motor dysfunction. On admission, physical exam, vital signs, and laboratory values, including serum potassium, were all normal. An ECG showed QT and QTc

intervals of 510 milliseconds and 490 milliseconds, respectively, and evidence of [sinus bradycardia](#) (48 beats per minute) and [AV block I](#) (PR 260 milliseconds). Citalopram and [risperidone](#) were discontinued and the QTc interval normalized (398 milliseconds), the heart rate returned to normal (80 beats per minute), and no further TdP episodes were detected on ECG telemetry. Later during hospitalization, the patient developed a [cystitis](#) for which [sulfamethoxazole/trimethoprim](#) was started. Although no [arrhythmias](#) were detected, after 3 doses, the QTc interval was again prolonged (500 milliseconds) and [sulfamethoxazole/trimethoprim](#) was replaced with a cephalosporin. The QTc interval normalized, and the patient was discharged home and advised to avoid all QT-prolonging medications [159].

3.5.1.IN] [Ritonavir](#)

- 1) Interaction Effect: increased [citalopram](#) serum concentrations
- 2) Summary: The concurrent administration of [citalopram](#), a selective serotonin reuptake inhibitor and CYP3A4 substrate [3], with [ritonavir](#), a CYP3A inhibitor, may result in increased [citalopram](#) plasma levels. If coadministration is indicated, reduction in [citalopram](#) dosage may be necessary [293] [294].
- 3) Severity: moderate
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Use caution with concomitant administration of [citalopram](#) and [ritonavir](#) as this may result in increased [citalopram](#) plasma levels. A [citalopram](#) dose reduction may be necessary [293] [294].
- 7) Probable Mechanism: inhibition of CYP3A-mediated [citalopram](#) metabolism

3.5.1.IO] [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) [287]. Because [rizatriptan](#) is a 5HT 1B/1D receptor agonist, a similar interaction between SSRIs and [rizatriptan](#) may occur [288]. 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](#) [95].
- 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](#) [286].

3.5.1.IP] Rofecoxib

- 1) Interaction Effect: an increased risk of bleeding
- 2) Summary: Caution is recommended with the concomitant use of NSAIDs and SSRIs due to an increased risk of [gastrointestinal bleeding](#) [228] [229]. Bleeding events have included [epistaxis](#), ecchymosis, [hematoma](#), [petechiae](#), and life-threatening hemorrhages [231] [53] [232] [233]. 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: probable
- 6) Clinical Management: Use caution if NSAIDs and SSRIs are coadministered. Concomitant use of NSAIDs and SSRIs may cause an increased risk of bleeding [228] [229]. When an SSRI and an NSAID are given concurrently, monitor the patient for signs of increased bleeding.
- 7) Probable Mechanism: unknown
- 8) Literature Reports

a) SSRIs increase the risk of upper gastrointestinal (GI) bleeding, and this effect is potentiated by concurrent use of NSAIDs or low-dose [aspirin](#). Hospitalizations for [upper GI bleeding](#) were searched among 26,005 users of antidepressant medications and compared with the number of hospitalizations in those patients who did not receive prescriptions for antidepressants. The amount of [upper GI bleeding](#) episodes was 3.6 times more than expected (95% CI, 2.7 to 4.7). Combined use of an SSRI and NSAIDs or low-dose [aspirin](#) increased the risk to 12.2 (95% CI, 7.1 to 19.5) and 5.2 (95% CI, 3.2 to 8), respectively. The findings of this study demonstrate an increased risk of [upper GI bleeding](#) during the use of SSRIs. Combined use of SSRIs and NSAIDs or low-dose [aspirin](#) increased the risk even further [230].

b) The 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 [53].

3.5.1.IQ] Salicylic Acid

- 1) Interaction Effect: an increased risk of bleeding
- 2) Summary: Caution is recommended with the concomitant use of NSAIDs and SSRIs due to an increased risk of [gastrointestinal bleeding](#) [228] [229]. Bleeding events have included [epistaxis](#), ecchymosis, [hematoma](#), [petechiae](#), and life-threatening hemorrhages [231] [53] [232] [233]. 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: probable
- 6) Clinical Management: Use caution if NSAIDs and SSRIs are coadministered. Concomitant use of NSAIDs and SSRIs may cause an increased risk of bleeding [228] [229]. When an SSRI and an NSAID are given concurrently, monitor the patient for signs of increased bleeding.
- 7) Probable Mechanism: unknown
- 8) Literature Reports

a) SSRIs increase the risk of upper gastrointestinal (GI) bleeding, and this effect is potentiated by concurrent use of NSAIDs or low-dose [aspirin](#). Hospitalizations for [upper GI bleeding](#) were searched among 26,005 users of antidepressant medications and compared with the number of hospitalizations in those patients who did not receive prescriptions for antidepressants. The

amount of [upper GI bleeding](#) episodes was 3.6 times more than expected (95% CI, 2.7 to 4.7). Combined use of an SSRI and NSAIDs or low-dose [aspirin](#) increased the risk to 12.2 (95% CI, 7.1 to 19.5) and 5.2 (95% CI, 3.2 to 8), respectively. The findings of this study demonstrate an increased risk of [upper GI bleeding](#) during the use of SSRIs. Combined use of SSRIs and NSAIDs or low-dose [aspirin](#) increased the risk even further [230].

b) The 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 [53].

3.5.1.IR| Salmeterol

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

2) Summary: Both [citalopram](#) and salmeterol have been associated with QT prolongation [76] [238]. Although this interaction has not been evaluated, the concomitant use of [citalopram](#) with salmeterol is not recommended due to a potential for additive effects on QT interval prolongation and an increased risk of serious cardiac events. If coadministration is required, monitor for ECG changes. Do not exceed [citalopram](#) doses of 40 mg/day, and discontinue [citalopram](#) in patients who have persistent QTc measurements greater than 500 milliseconds [76].

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Both [citalopram](#) and salmeterol are known to increase the QT interval [76] [238], and concurrent use of these agents is not recommended due to a potential for additive effects on QT interval prolongation and an increased risk of serious cardiac events. If coadministration is required, monitor for ECG changes. Do not exceed [citalopram](#) doses of 40 mg/day, and discontinue [citalopram](#) in patients who have persistent QTc measurements greater than 500 milliseconds [76].

7) Probable Mechanism: additive effects on QT interval prolongation

3.5.1.IS| Salsalate

1) Interaction Effect: an increased risk of bleeding

2) Summary: Caution is recommended with the concomitant use of NSAIDs and SSRIs due to an increased risk of [gastrointestinal bleeding](#) [228] [229]. Bleeding events have included [epistaxis](#), ecchymosis, [hematoma](#), [petechiae](#), and life-threatening hemorrhages [231] [53] [232] [233]. 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: probable

6) Clinical Management: Use caution if NSAIDs and SSRIs are coadministered. Concomitant use of NSAIDs and SSRIs may cause an increased risk of bleeding [228] [229]. When an SSRI and an NSAID are given concurrently, monitor the patient for signs of increased bleeding.

7) Probable Mechanism: unknown

8) Literature Reports

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

7.1 to 19.5) and 5.2 (95% CI, 3.2 to 8), respectively. The findings of this study demonstrate an increased risk of [upper GI bleeding](#) during the use of SSRIs. Combined use of SSRIs and NSAIDs or low-dose [aspirin](#) increased the risk even further [230].

b)) The 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 [53].

3.5.1.IT] [Saquinavir](#)

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

2)) Summary: The concomitant use of [citalopram](#) and ritonavir-boosted [saquinavir](#) is not recommended due to additive effects on QT interval prolongation and an increased risk of serious cardiovascular effects, including [ventricular arrhythmias](#) [76]. These drugs should be used concomitantly only when no alternatives are available and the potential benefits outweigh the potential risks. Do not initiate concomitant therapy in patients with a baseline QT interval of greater than 450 milliseconds. In patients with a baseline QT interval of less than 450 milliseconds, perform an on-treatment ECG approximately 3 to 4 days after therapy is initiated. During concomitant therapy, if a subsequent QT interval reading is greater than 480 milliseconds or has increased by more than 20 milliseconds from baseline, evaluate whether to discontinue either [citalopram](#) or ritonavir-boosted [saquinavir](#) or both [265]. [Saquinavir](#) is also a CYP3A4 inhibitor and has the potential to increase [citalopram](#) exposure. If coadministration is required, monitor for ECG changes. Do not exceed [citalopram](#) doses of 40 mg/day and discontinue [citalopram](#) in patients who have persistent QTc measurements greater than 500 milliseconds [76].

3)) Severity: major

4)) Onset: unspecified

5)) Substantiation: theoretical

6)) Clinical Management: The concomitant use of [citalopram](#) and ritonavir-boosted [saquinavir](#) is not recommended due to additive effects on QT interval prolongation and an increased risk of serious cardiovascular effects, including [ventricular arrhythmias](#) [76]. These drugs should be used concomitantly only when no alternatives are available and the potential benefits outweigh the potential risks. Do not initiate concomitant therapy in patients with a baseline QT interval of greater than 450 milliseconds. In patients with a baseline QT interval of less than 450 milliseconds, perform an on-treatment ECG approximately 3 to 4 days after therapy is initiated. During concomitant therapy, if a subsequent QT interval reading is greater than 480 milliseconds or has increased by more than 20 milliseconds from baseline, evaluate whether to discontinue either [citalopram](#) or ritonavir-boosted [saquinavir](#) or both [265]. If coadministration is required, monitor for ECG changes. Do not exceed [citalopram](#) doses of 40 mg/day, and discontinue [citalopram](#) in patients who have persistent QTc measurements greater than 500 milliseconds [76].

7)) Probable Mechanism: inhibition of [citalopram](#) CYP3A4-mediated metabolism; additive effects on QT interval prolongation

3.5.1.IU] [Selegiline](#)

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

2)) Summary: Concomitant use of [citalopram](#) and an MAOI is contraindicated. Concurrent administration or overlapping therapy with [citalopram](#) 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, and tremor. A minimum of 14 days should elapse after discontinuing an MAOI intended to treat psychiatric disorders before initiating therapy with [citalopram](#),

and a minimum of 14 days should elapse after discontinuing [citalopram](#) before initiating therapy with an MAOI intended to treat psychiatric disorders [53].

3) Severity: contraindicated

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Concurrent use of [citalopram](#) and an MAOI is contraindicated. Wait at least 14 days after discontinuing an MAOI intended to treat psychiatric disorders before initiating [citalopram](#). Wait at least 14 days after discontinuing [citalopram](#) before initiating therapy with an MAOI intended to treat psychiatric disorders [53].

7) Probable Mechanism: additive serotonergic effect

3.5.1.IV] [Sertraline](#)

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

2) Summary: The concomitant use of 2 SSRIs, such as [citalopram](#) and [sertraline](#), increases the risk of [serotonin syndrome](#). The risk of [serotonin syndrome](#) is greater during treatment initiation and dose increases. Discontinue any concomitant serotonergic agents immediately and initiate supportive treatment if [serotonin syndrome](#) is suspected. Patients should be monitored 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) [274] [38].

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: The concomitant use of 2 SSRIs, such as [citalopram](#) and [sertraline](#), increases the risk of [serotonin syndrome](#). The risk of [serotonin syndrome](#) is greater during treatment initiation and dose increases. Discontinue any concomitant serotonergic agents immediately and initiate supportive treatment if [serotonin syndrome](#) is suspected. 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) [274] [38].

7) Probable Mechanism: additive serotonergic effects

3.5.1.IW] [Sevoflurane](#)

1) Interaction Effect: increased risk of QT-interval prolongation

2) Summary: [Sevoflurane](#) is a QT-interval-prolonging drug. Use caution with concurrent use of other QT-interval-prolonging agents, due to increased risk of additive QT-interval prolongation and [torsade de pointes](#) [268].

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: [Sevoflurane](#) is a QT-interval-prolonging drug. Use caution with concurrent use of other QT-interval-prolonging agents, due to increased risk of additive QT-interval prolongation and [torsade de pointes](#) [268].

7) Probable Mechanism: additive effects on QT interval

3.5.1.IX] [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 [337].
- 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 [336].

3.5.1.IY] Siltuximab

- 1) Interaction Effect: decreased effectiveness of CYP3A4 substrate
- 2) Summary: Coadministration of siltuximab and a CYP3A4 substrate may result in increased metabolism and decreased effectiveness of the substrate. Approach concurrent use with caution. The effects of siltuximab on CYP450 enzyme activity may persist for several weeks after discontinuation [267]. If coadministration is required, monitoring and dose adjustments may be warranted.
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Coadministration of siltuximab and a CYP3A4 substrate may increase the metabolism of the substrate and decrease its effectiveness. Use caution when coadministering siltuximab and a CYP3A4 substrate. The effects of siltuximab on CYP450 enzyme activity may persist for several weeks after discontinuation [267]. If coadministration is required, monitoring and dose adjustments may be warranted.
- 7) Probable Mechanism: inhibition of interleukin-6 by siltuximab increases CYP450 levels leading to increased metabolism of CYP450 substrates

3.5.1.IZ] Sodium Phosphate

- 1) Interaction Effect: increased risk of QT interval prolongation
- 2) Summary: Both [citalopram](#) and [sodium phosphate](#) have been associated with QT prolongation [76] [322]. Although this interaction has not been evaluated, the concomitant use of [citalopram](#) with [sodium phosphate](#) is not recommended due to a potential for additive effects on QT interval prolongation and increased risk of serious cardiac adverse events. If coadministration is required, monitor for ECG changes. Do not exceed [citalopram](#) doses of 40 mg/day, and discontinue [citalopram](#) in patients who have persistent QTc measurements greater than 500 milliseconds [76].
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Concomitant use of [citalopram](#) with [sodium phosphate](#) is not recommended due to a potential for additive effects on QT interval prolongation and increased risk of serious cardiac

adverse events. If concomitant use is required, monitor for ECG changes. Do not exceed [citalopram](#) doses of 40 mg/day, and discontinue [citalopram](#) in patients who have persistent QTc measurements greater than 500 milliseconds [76].

7) Probable Mechanism: additive effects on the QT interval

3.5.1.JA] [Sodium Phosphate, Dibasic](#)

1) Interaction Effect: increased risk of QT interval prolongation

2) Summary: Both [citalopram](#) and [sodium phosphate](#) have been associated with QT prolongation [76] [322]. Although this interaction has not been evaluated, the concomitant use of [citalopram](#) with [sodium phosphate](#) is not recommended due to a potential for additive effects on QT interval prolongation and increased risk of serious cardiac adverse events. If coadministration is required, monitor for ECG changes. Do not exceed [citalopram](#) doses of 40 mg/day, and discontinue [citalopram](#) in patients who have persistent QTc measurements greater than 500 milliseconds [76].

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Concomitant use of [citalopram](#) with [sodium phosphate](#) is not recommended due to a potential for additive effects on QT interval prolongation and increased risk of serious cardiac adverse events. If concomitant use is required, monitor for ECG changes. Do not exceed [citalopram](#) doses of 40 mg/day, and discontinue [citalopram](#) in patients who have persistent QTc measurements greater than 500 milliseconds [76].

7) Probable Mechanism: additive effects on the QT interval

3.5.1.JB] [Sodium Phosphate, Monobasic](#)

1) Interaction Effect: increased risk of QT interval prolongation

2) Summary: Both [citalopram](#) and [sodium phosphate](#) have been associated with QT prolongation [76] [322]. Although this interaction has not been evaluated, the concomitant use of [citalopram](#) with [sodium phosphate](#) is not recommended due to a potential for additive effects on QT interval prolongation and increased risk of serious cardiac adverse events. If coadministration is required, monitor for ECG changes. Do not exceed [citalopram](#) doses of 40 mg/day, and discontinue [citalopram](#) in patients who have persistent QTc measurements greater than 500 milliseconds [76].

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Concomitant use of [citalopram](#) with [sodium phosphate](#) is not recommended due to a potential for additive effects on QT interval prolongation and increased risk of serious cardiac adverse events. If concomitant use is required, monitor for ECG changes. Do not exceed [citalopram](#) doses of 40 mg/day, and discontinue [citalopram](#) in patients who have persistent QTc measurements greater than 500 milliseconds [76].

7) Probable Mechanism: additive effects on the QT interval

3.5.1.JC] [Sodium Salicylate](#)

1) Interaction Effect: an increased risk of bleeding

2) Summary: Caution is recommended with the concomitant use of NSAIDs and SSRIs due to an increased risk of [gastrointestinal bleeding](#) [228] [229]. Bleeding events have included [epistaxis](#), ecchymosis, [hematoma](#), [petechiae](#), and life-threatening hemorrhages [231] [53] [232] [233]. 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: probable
- 6) Clinical Management: Use caution if NSAIDs and SSRIs are coadministered. Concomitant use of NSAIDs and SSRIs may cause an increased risk of bleeding [228] [229]. When an SSRI and an NSAID are given concurrently, monitor the patient for signs of increased bleeding.
- 7) Probable Mechanism: unknown
- 8) Literature Reports

a) SSRIs increase the risk of upper gastrointestinal (GI) bleeding, and this effect is potentiated by concurrent use of NSAIDs or low-dose [aspirin](#). Hospitalizations for [upper GI bleeding](#) were searched among 26,005 users of antidepressant medications and compared with the number of hospitalizations in those patients who did not receive prescriptions for antidepressants. The amount of [upper GI bleeding](#) episodes was 3.6 times more than expected (95% CI, 2.7 to 4.7). Combined use of an SSRI and NSAIDs or low-dose [aspirin](#) increased the risk to 12.2 (95% CI, 7.1 to 19.5) and 5.2 (95% CI, 3.2 to 8), respectively. The findings of this study demonstrate an increased risk of [upper GI bleeding](#) during the use of SSRIs. Combined use of SSRIs and NSAIDs or low-dose [aspirin](#) increased the risk even further [230].

b) The 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 [53].

3.5.1.JD| [Solifenacin](#)

- 1) Interaction Effect: an increased risk of QT interval prolongation
- 2) Summary: [Citalopram](#) causes dose-dependent prolongation of the QTc interval [76] and [solifenacin](#) has also been associated with QT interval prolongation [226]. Although this interaction has not been evaluated, the concomitant use of [citalopram](#) and [solifenacin](#) is not recommended due to a potential for additive effects on QT interval prolongation and an increased risk of cardiac adverse events, including [ventricular arrhythmias](#) and/or [torsade de pointes](#). If coadministration is required, monitor for ECG changes. Do not exceed [citalopram](#) doses of 40 mg/day, and discontinue [citalopram](#) in patients who have persistent QTc measurements greater than 500 milliseconds [76].
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: The concomitant use of [citalopram](#) and [solifenacin](#) is not recommended due to a potential for additive effects on QT interval prolongation and an increased risk of serious cardiovascular effects. If coadministration is required, monitor for ECG changes. Do not exceed [citalopram](#) doses of 40 mg/day, and discontinue [citalopram](#) in patients who have persistent QTc measurements greater than 500 milliseconds [76].
- 7) Probable Mechanism: additive effects on QT interval prolongation

3.5.1.JE| [Sorafenib](#)

- 1) Interaction Effect: increased risk of QT interval prolongation and risk of [ventricular arrhythmias](#)
- 2) Summary: Both [citalopram](#) and [sorafenib](#) have been associated with QT prolongation [166]. Although this interaction has not been evaluated, the concomitant use of [citalopram](#) with [sorafenib](#) is not recommended due to a potential for additive effects on QT interval prolongation and an increased risk of serious cardiac adverse events, including [ventricular arrhythmias](#). If concomitant use of [citalopram](#) with [sorafenib](#) is required, monitor for ECG changes [76] and electrolyte ([calcium](#), magnesium, and potassium)

abnormalities [166]. Do not exceed [citalopram](#) doses of 40 mg/day, and discontinue [citalopram](#) in patients who have persistent QTc measurements greater than 500 milliseconds [76].

3J) Severity: major

4J) Onset: unspecified

5J) Substantiation: theoretical

6J) Clinical Management: Both [citalopram](#) and [sorafenib](#) are known to prolong the QT interval [166] and concurrent use of these agents is not recommended due to a potential for additive effects on QT interval prolongation and an increased risk of serious cardiac adverse events, including [ventricular arrhythmias](#). If concomitant use of [citalopram](#) with [sorafenib](#) is required, monitor for ECG changes [76] and electrolyte ([calcium](#), magnesium, and potassium) abnormalities [166]. Do not exceed [citalopram](#) doses of 40 mg/day, and discontinue [citalopram](#) in patients who have persistent QTc measurements greater than 500 milliseconds [76].

7J) Probable Mechanism: additive effects on QT interval

3.5.1.JF] [Sotalol](#)

1J) Interaction Effect: increased risk of QT interval prolongation

2J) Summary: [Sotalol](#) can cause serious [ventricular arrhythmias](#), primarily [torsade de pointes](#), a [polymorphic ventricular tachycardia](#) associated with QT interval prolongation. Although the interaction has not been studied, the concurrent use of [citalopram](#) (a dose-dependent QT interval-prolonging drug) with [sotalol](#) is not recommended due to an increased risk of QT prolongation and torsades [299]. If coadministration is required, monitor for ECG changes. Do not exceed [citalopram](#) doses of 40 mg/day, and discontinue [citalopram](#) in patients who have persistent QTc measurements greater than 500 milliseconds [76].

3J) Severity: major

4J) Onset: unspecified

5J) Substantiation: theoretical

6J) Clinical Management: Concurrent use of [citalopram](#) and [sotalol](#) is not recommended due to an increased risk of QT prolongation and [torsade de pointes](#) [299]. If coadministration is required, monitor for ECG changes. Do not exceed [citalopram](#) doses of 40 mg/day, and discontinue [citalopram](#) in patients who have persistent QTc measurements greater than 500 milliseconds [76].

7J) Probable Mechanism: additive effects on the QT interval

3.5.1.JG] [Sparfloxacin](#)

1J) Interaction Effect: increased risk of QT-interval prolongation

2J) Summary: The concomitant use of [sparfloxacin](#) with drugs that cause QT-interval prolongation is contraindicated, as coadministration may increase the risk of QT prolongation and serious [ventricular arrhythmias](#) [296].

3J) Severity: contraindicated

4J) Onset: unspecified

5J) Substantiation: theoretical

6J) Clinical Management: The concomitant use of [sparfloxacin](#) with drugs that cause QT-interval prolongation is contraindicated, as coadministration may increase the risk of QT prolongation and serious [ventricular arrhythmias](#) [296].

7J) Probable Mechanism: additive QT interval effects

3.5.1.JH] [St John's Wort](#)

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

2j) 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 [174] [175] [176] [177]. A patient exhibited a syndrome resembling sedative/[hypnotic intoxication](#) after adding St. John's Wort to [paroxetine](#) therapy [178]. St. John's Wort is thought to inhibit serotonin reuptake and may have mild monoamine oxidase inhibitory activity [179] [180], which when added to selective serotonin reuptake inhibitors may result in [serotonin syndrome](#).

3j) Severity: major

4j) Onset: rapid

5j) Substantiation: probable

6j) 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.

7j) Probable Mechanism: additive serotonergic effect

8j) 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 [169].

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 [170].

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 [171].

d) A 28-year-old male developed a manic syndrome following comedication with St. John's Wort and [sertraline](#). The patient was also on [testosterone](#) replacement therapy following [bilateral orchiectomy](#) 2 years earlier, but [testosterone](#) levels were subtherapeutic. The patient was prescribed [sertraline](#) 50 milligrams daily for depression following a 2 week trial of St. John's Wort per patient preference (dose not specified). Before [sertraline](#) was started, the patient was instructed to discontinue St. John's Wort, but continued it despite this advice. The patient experienced improved mood so did not see his physician, believing that he did not need further treatment. Over 2 months, the patient had elated mood, was irritable, and overspent, buying a car he could not afford, and was ultimately arrested for stealing fuel for the car. On arrest, he was referred to psychiatric services due to irritability and disinhibition. He was observed to be over-aroused, distractible, have flight of ideas, and [grandiose delusions](#), leading to a diagnosis of a [manic episode](#). The authors state the possibility of the manic state resulting from [sertraline](#) therapy alone, and that St. John's Wort may have increased the risk as a result of monoamine oxidase inhibition. Since the patient's [testosterone](#) level was subnormal, the possibility of its contribution to the manic state was considered low. However, the patient had elevated gonadotropin levels ([luteinizing hormone](#) and [follicle-stimulating hormone](#)) which may have predisposed the patient to mania [172].

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 [173].

3.5.1.JI] [Sulindac](#)

1) Interaction Effect: an increased risk of bleeding

2) Summary: Caution is recommended with the concomitant use of NSAIDs and SSRIs due to an increased risk of [gastrointestinal bleeding](#) [228] [229]. Bleeding events have included [epistaxis](#), ecchymosis, [hematoma](#), [petechiae](#), and life-threatening hemorrhages [231] [53] [232] [233]. 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: probable

6) Clinical Management: Use caution if NSAIDs and SSRIs are coadministered. Concomitant use of NSAIDs and SSRIs may cause an increased risk of bleeding [228] [229]. When an SSRI and an NSAID are given concurrently, monitor the patient for signs of increased bleeding.

7) Probable Mechanism: unknown

8) Literature Reports

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

Combined use of an SSRI and NSAIDs or low-dose [aspirin](#) increased the risk to 12.2 (95% CI, 7.1 to 19.5) and 5.2 (95% CI, 3.2 to 8), respectively. The findings of this study demonstrate an increased risk of [upper GI bleeding](#) during the use of SSRIs. Combined use of SSRIs and NSAIDs or low-dose [aspirin](#) increased the risk even further [230].

b) The 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 [53].

3.5.1.JJ] [Sumatriptan](#)

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

2) Summary: There have been case reports of weakness, hyperreflexia, and incoordination following concomitant use of [sumatriptan](#) and a serotonin specific reuptake inhibitor (SSRI) [93] [94]. 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](#) [95].

3) Severity: major

4) Onset: delayed

5) Substantiation: established

6) Clinical Management: Coadministration of a triptan, such as [sumatriptan](#), and an SSRI, such as [citalopram](#), 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.JK] [Sunitinib](#)

1) Interaction Effect: increased risk of QT interval prolongation

2) Summary: Both [citalopram](#) and [sunitinib](#) have been associated with QT interval prolongation and [torsade de pointes](#) [348]. Although this interaction has not been evaluated, the concomitant use of [citalopram](#) with [sunitinib](#) is not recommended due to a potential for additive effects on QT interval prolongation and an increased risk of serious cardiac adverse events. If coadministration is required, monitor for ECG changes. Do not exceed [citalopram](#) doses of 40 mg/day, and discontinue [citalopram](#) in patients who have persistent QTc measurements greater than 500 milliseconds [76].

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Both [citalopram](#) and [sunitinib](#) are known to increase the QT interval [348] and concurrent use of these agents is not recommended due to a potential for additive effects on QT interval prolongation and an increased risk of serious cardiac adverse events. If coadministration is required, monitor for ECG changes. Do not exceed [citalopram](#) doses of 40 mg/day, and discontinue [citalopram](#) in patients who have persistent QTc measurements greater than 500 milliseconds [76].

7) Probable Mechanism: additive effects on the QT interval

3.5.1.JL] Tacrolimus

- 1) Interaction Effect: increased risk of QT-interval prolongation
- 2) Summary: Citalopram and tacrolimus are CYP3A4 substrates and are known to prolong the QT interval. Concurrent use of these agents may result in additive effects on QT-interval prolongation [240], and concurrent use is not recommended [53].
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Concomitant use of citalopram and tacrolimus is not recommended [53] since it may result in additive QT prolongation [240] [53].
- 7) Probable Mechanism: additive effects on QT-interval prolongation

3.5.1.JM] 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 [235].
- 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 [235].
- 7) Probable Mechanism: additive serotonergic effect

3.5.1.JN] Telithromycin

- 1) Interaction Effect: increased risk of QT interval prolongation
- 2) Summary: Citalopram causes dose-dependent prolongation of the QTc interval [76] and telithromycin has also been associated with QT interval prolongation [332]. Although this interaction has not been evaluated, the concomitant use of citalopram and telithromycin is not recommended due to a potential for additive effects on QT interval prolongation and an increased risk of cardiac adverse events, including ventricular arrhythmias and/or torsade de pointes. If coadministration is required, monitor for ECG changes. Do not exceed citalopram doses of 40 mg/day, and discontinue citalopram in patients who have persistent QTc measurements greater than 500 milliseconds [76].
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: The concomitant use of citalopram and telithromycin is not recommended due to a potential for additive effects on QT interval prolongation and an increased risk of serious cardiovascular effects. If coadministration is required, monitor for ECG changes. Do not exceed citalopram doses of 40 mg/day, and discontinue citalopram in patients who have persistent QTc measurements greater than 500 milliseconds [76].
- 7) Probable Mechanism: additive effects on the QT interval

3.5.1.JO| Tenoxicam

- 1) Interaction Effect: an increased risk of bleeding
- 2) Summary: Caution is recommended with the concomitant use of NSAIDs and SSRIs due to an increased risk of [gastrointestinal bleeding](#) [228] [229]. Bleeding events have included [epistaxis](#), ecchymosis, [hematoma](#), [petechiae](#), and life-threatening hemorrhages [231] [53] [232] [233]. 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: probable
- 6) Clinical Management: Use caution if NSAIDs and SSRIs are coadministered. Concomitant use of NSAIDs and SSRIs may cause an increased risk of bleeding [228] [229]. When an SSRI and an NSAID are given concurrently, monitor the patient for signs of increased bleeding.
- 7) Probable Mechanism: unknown
- 8) Literature Reports

a) SSRIs increase the risk of upper gastrointestinal (GI) bleeding, and this effect is potentiated by concurrent use of NSAIDs or low-dose [aspirin](#). Hospitalizations for [upper GI bleeding](#) were searched among 26,005 users of antidepressant medications and compared with the number of hospitalizations in those patients who did not receive prescriptions for antidepressants. The amount of [upper GI bleeding](#) episodes was 3.6 times more than expected (95% CI, 2.7 to 4.7). Combined use of an SSRI and NSAIDs or low-dose [aspirin](#) increased the risk to 12.2 (95% CI, 7.1 to 19.5) and 5.2 (95% CI, 3.2 to 8), respectively. The findings of this study demonstrate an increased risk of [upper GI bleeding](#) during the use of SSRIs. Combined use of SSRIs and NSAIDs or low-dose [aspirin](#) increased the risk even further [230].

b) The 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 [53].

3.5.1.JP| Terfenadine

- 1) Interaction Effect: increased risk of QT-interval prolongation
- 2) Summary: The concomitant use of [terfenadine](#) with drugs that cause QT-interval prolongation is contraindicated, as coadministration may increase the risk of QT prolongation and serious [ventricular arrhythmias](#) [295].
- 3) Severity: contraindicated
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: The concomitant use of [terfenadine](#) with drugs that cause QT-interval prolongation is contraindicated, as coadministration may increase the risk of QT prolongation and serious [ventricular arrhythmias](#) [295].
- 7) Probable Mechanism: additive QT interval effects

3.5.1.JQ| Tetrabenazine

- 1) Interaction Effect: increased risk of QT interval prolongation
- 2) Summary: Although the interaction has not been studied, both [citalopram](#) and tetrabenazine are known to prolong the QT interval [76] [345] and concurrent use of these agents is not recommended due to a potential for additive effects on QT interval prolongation and increased risk of serious cardiovascular

effects. If coadministration is required, monitor for ECG changes. Do not exceed [citalopram](#) doses of 40 mg/day, and discontinue [citalopram](#) in patients who have persistent QTc measurements greater than 500 milliseconds [76].

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Concomitant use of [citalopram](#) and tetrabenazine is not recommended due to a potential for additive effects on QT interval prolongation and increased risk of serious cardiovascular effects. If coadministration is required, monitor for ECG changes. Do not exceed [citalopram](#) doses of 40 mg/day, and discontinue [citalopram](#) in patients who have persistent QTc measurements greater than 500 milliseconds [76].

7) Probable Mechanism: additive effects on the QT interval

3.5.1.JR| [Thioridazine](#)

1) Interaction Effect: increased risk of QT-interval prolongation

2) Summary: The concomitant use of [thioridazine](#) with drugs that cause QT-interval prolongation is contraindicated, as coadministration may increase the risk of QT prolongation and serious [ventricular arrhythmias](#) [264].

3) Severity: contraindicated

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: The concomitant use of [thioridazine](#) with drugs that cause QT-interval prolongation is contraindicated, as coadministration may increase the risk of QT prolongation and serious [ventricular arrhythmias](#) [264].

7) Probable Mechanism: additive QT interval effects

3.5.1.JS| [Tiaprofenic Acid](#)

1) Interaction Effect: an increased risk of bleeding

2) Summary: Caution is recommended with the concomitant use of NSAIDs and SSRIs due to an increased risk of [gastrointestinal bleeding](#) [228] [229]. Bleeding events have included [epistaxis](#), ecchymosis, [hematoma](#), [petechiae](#), and life-threatening hemorrhages [231] [53] [232] [233]. 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: probable

6) Clinical Management: Use caution if NSAIDs and SSRIs are coadministered. Concomitant use of NSAIDs and SSRIs may cause an increased risk of bleeding [228] [229]. When an SSRI and an NSAID are given concurrently, monitor the patient for signs of increased bleeding.

7) Probable Mechanism: unknown

8) Literature Reports

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

increased risk of [upper GI bleeding](#) during the use of SSRIs. Combined use of SSRIs and NSAIDs or low-dose [aspirin](#) increased the risk even further [230].

b) The 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 [53].

3.5.1.JT] [Ticlopidine](#)

1) Interaction Effect: an increased risk of bleeding

2) Summary: The concomitant use of [citalopram](#) and an antiplatelet drug may increase the risk of bleeding. The release of serotonin by [platelets](#) is important for maintaining hemostasis. Case-controlled and cohort studies have shown that the combined use of selective serotonin reuptake inhibitors and antiplatelet agents has been associated with an increased risk of bleeding. Bleeding events reported have included [epistaxis](#), ecchymosis, [hematoma](#), [petechiae](#), and life-threatening hemorrhages. Monitor patient for signs of increased bleeding when [citalopram](#) is administered concomitantly with an antiplatelet drug [40].

3) Severity: major

4) Onset: unspecified

5) Substantiation: probable

6) Clinical Management: When [citalopram](#) and an antiplatelet agent are given concurrently, monitor patient for signs of increased bleeding [40].

7) Probable Mechanism: unknown

3.5.1.JU] [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 [340] [341] [339]. 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](#) [341] [339].

3) Severity: major

4) Onset: unspecified

5) Substantiation: probable

6) Clinical Management: When [citalopram](#) and an anticoagulant are given concurrently, monitor patients for signs of increased bleeding. Patients who are taking [warfarin](#) should be monitored closely for altered anticoagulant effects, including increased bleeding, when [citalopram](#) therapy is initiated or discontinued [339].

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 [340].

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 [341].

c) The pharmacokinetics of [warfarin](#), a CYP3A4 substrate, were not affected by the administration of [citalopram](#) 40 mg/day for 21 days, while the prothrombin time was increased by 5%. The clinical significance of this is unknown [339].

3.5.1.JV] [Tirofiban](#)

1) Interaction Effect: an increased risk of bleeding

2) Summary: The concomitant use of [citalopram](#) and an antiplatelet drug may increase the risk of bleeding. The release of serotonin by [platelets](#) is important for maintaining hemostasis. Case-controlled and cohort studies have shown that the combined use of selective serotonin reuptake inhibitors and antiplatelet agents has been associated with an increased risk of bleeding. Bleeding events reported have included [epistaxis](#), ecchymosis, [hematoma](#), [petechiae](#), and life-threatening hemorrhages. Monitor patient for signs of increased bleeding when [citalopram](#) is administered concomitantly with an antiplatelet drug [40].

3) Severity: major

4) Onset: unspecified

5) Substantiation: probable

6) Clinical Management: When [citalopram](#) and an antiplatelet agent are given concurrently, monitor patient for signs of increased bleeding [40].

7) Probable Mechanism: unknown

3.5.1.JW] [Tizanidine](#)

1) Interaction Effect: increased risk of QT-interval prolongation

2) Summary: [Tizanidine](#) has the potential to cause QT-interval prolongation [328] [329]. Concomitant administration of [tizanidine](#) with other drugs that prolong the QT interval, including antiarrhythmic medications, may increase the risk of QT-interval prolongation. Consider a baseline ECG and on-treatment monitoring when [tizanidine](#) is coadministered with other QT interval-prolonging agents.

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Concomitant administration of [tizanidine](#) and QT interval-prolonging drugs, including antiarrhythmic medications, may result in an increased risk of QT-interval prolongation. Consider a baseline ECG and on-treatment monitoring when [tizanidine](#) is coadministered with other QT interval-prolonging agents.

7J) Probable Mechanism: additive QT interval effects

3.5.1.JX| Tolfenamic Acid

1J) Interaction Effect: an increased risk of bleeding

2J) Summary: Caution is recommended with the concomitant use of NSAIDs and SSRIs due to an increased risk of [gastrointestinal bleeding](#) [228] [229]. Bleeding events have included [epistaxis](#), ecchymosis, [hematoma](#), [petechiae](#), and life-threatening hemorrhages [231] [53] [232] [233]. 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: probable

6J) Clinical Management: Use caution if NSAIDs and SSRIs are coadministered. Concomitant use of NSAIDs and SSRIs may cause an increased risk of bleeding [228] [229]. When an SSRI and an NSAID are given concurrently, monitor the patient for signs of increased bleeding.

7J) Probable Mechanism: unknown

8J) Literature Reports

aJ) SSRIs increase the risk of upper gastrointestinal (GI) bleeding, and this effect is potentiated by concurrent use of NSAIDs or low-dose [aspirin](#). Hospitalizations for [upper GI bleeding](#) were searched among 26,005 users of antidepressant medications and compared with the number of hospitalizations in those patients who did not receive prescriptions for antidepressants. The amount of [upper GI bleeding](#) episodes was 3.6 times more than expected (95% CI, 2.7 to 4.7). Combined use of an SSRI and NSAIDs or low-dose [aspirin](#) increased the risk to 12.2 (95% CI, 7.1 to 19.5) and 5.2 (95% CI, 3.2 to 8), respectively. The findings of this study demonstrate an increased risk of [upper GI bleeding](#) during the use of SSRIs. Combined use of SSRIs and NSAIDs or low-dose [aspirin](#) increased the risk even further [230].

bJ) The 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 [53].

3.5.1.JY| Tolmetin

1J) Interaction Effect: an increased risk of bleeding

2J) Summary: Caution is recommended with the concomitant use of NSAIDs and SSRIs due to an increased risk of [gastrointestinal bleeding](#) [228] [229]. Bleeding events have included [epistaxis](#), ecchymosis, [hematoma](#), [petechiae](#), and life-threatening hemorrhages [231] [53] [232] [233]. 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: probable

6J) Clinical Management: Use caution if NSAIDs and SSRIs are coadministered. Concomitant use of NSAIDs and SSRIs may cause an increased risk of bleeding [228] [229]. When an SSRI and an NSAID are given concurrently, monitor the patient for signs of increased bleeding.

7J) Probable Mechanism: unknown

8J) Literature Reports

aJ) SSRIs increase the risk of upper gastrointestinal (GI) bleeding, and this effect is potentiated by concurrent use of NSAIDs or low-dose [aspirin](#). Hospitalizations for [upper GI bleeding](#) were searched among 26,005 users of antidepressant medications and compared with the number

of hospitalizations in those patients who did not receive prescriptions for antidepressants. The amount of [upper GI bleeding](#) episodes was 3.6 times more than expected (95% CI, 2.7 to 4.7). Combined use of an SSRI and NSAIDs or low-dose [aspirin](#) increased the risk to 12.2 (95% CI, 7.1 to 19.5) and 5.2 (95% CI, 3.2 to 8), respectively. The findings of this study demonstrate an increased risk of [upper GI bleeding](#) during the use of SSRIs. Combined use of SSRIs and NSAIDs or low-dose [aspirin](#) increased the risk even further [230].

b) The 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 [53].

3.5.1.JZ] Toloxatone

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

2) Summary: Concurrent administration or overlapping therapy with [citalopram](#) 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 [133][134][135]. As a reversible and selective monoamine oxidase inhibitor, toloxatone may not potentiate the effects of selective serotonin reuptake inhibitors to the same frequency, extent, and duration observed with other MAO inhibitors. Nonetheless, concurrent use of [citalopram](#) with a MAO inhibitor is contraindicated [136].

3) Severity: contraindicated

4) Onset: rapid

5) Substantiation: established

6) Clinical Management: Concurrent use of [citalopram](#) and a MAO inhibitor is contraindicated. Wait at least two weeks after discontinuing a MAO inhibitor before initiating therapy with [citalopram](#). Wait two weeks after discontinuing [citalopram](#) before initiating therapy with a MAO inhibitor.

7) Probable Mechanism: serotonin reuptake inhibition

8) Literature Reports

a) Concomitant use of selective serotonin reuptake inhibitors and monoamine oxidase inhibitors can produce a toxic reaction known as [serotonin syndrome](#) [128]. [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 [129].

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

[syndrome](#) (NMS) which was later changed to [serotonin syndrome](#) due to a reaction between [sertraline](#) and [phenelzine](#). The authors suggest that monoamine oxidase inhibitor (MAOI) therapy should be discontinued for at least two weeks before initiation of therapy with a selective serotonin reuptake inhibitor (SSRI) and that before starting a MAOI, SSRI therapy should be discontinued for at least five half-lives of the parent drug and any active metabolites [130].

d) Two cases reports suggested a possible interaction between [fluoxetine](#) and [selegiline](#) [131]. 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.

e) Five fatal overdose cases were reported due to [serotonin syndrome](#). In three of the five cases, the drug combination that induced the fatal syndrome was moclobemide, a selective monoamine oxidase inhibitor, and [citalopram](#). Of the three patients, blood concentrations of moclobemide ranged from 5 times the therapeutic level to 50 times the therapeutic level, and [citalopram](#) concentrations ranged from normal therapeutic levels to 5 times the therapeutic level [132].

3.5.1.KA] [Topiramate](#)

1) Interaction Effect: increased [citalopram](#) exposure and risk of QT interval prolongation

2) Summary: In a [pharmacokinetic study](#) in patients who received [citalopram](#) 40 mg/day for 21 days, combined administration with [cimetidine](#) (a potent CYP2C19 inhibitor) 400 mg/day for 8 days resulted in an increase in [citalopram](#) AUC and Cmax of 43% and 39%, respectively. Although the interaction between [citalopram](#) (a CYP2C19 substrate) and [topiramate](#) (a mild CYP2C19 inhibitor) [195] has not been specifically studied, concomitant use may result in increased [citalopram](#) exposure and an increased risk of QT prolongation. If coadministration of [citalopram](#) with [topiramate](#) is required, do not exceed [citalopram](#) doses of 20 mg/day, and discontinue [citalopram](#) in patients who have persistent QTc measurements greater than 500 milliseconds (ms) [76].

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: The concomitant use of [citalopram](#) with [topiramate](#) may result in increased [citalopram](#) exposure and risk of QT prolongation. If coadministration of [citalopram](#) (a CYP2C19 substrate) with [topiramate](#) (a mild CYP2C19 inhibitor) is required [195], do not exceed [citalopram](#) doses of 20 mg/day, and discontinue [citalopram](#) in patients who have persistent QTc measurements greater than 500 milliseconds (ms) [76].

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

3.5.1.KB] [Toremifene](#)

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

2) Summary: Both [citalopram](#) and [toremifene](#) can prolong the QT interval in a dose-dependent manner [76] [310]. Due to the potential for additive effects on QT interval prolongation and an increased risk of serious cardiovascular effects, the concomitant use of these agents is not recommended [76]. If coadministration is required, interrupt [toremifene](#) therapy; however, if interruption of [toremifene](#) is not possible, closely monitor for QT interval prolongation (ECG and electrolytes) [310]. Do not exceed [citalopram](#) doses of 40 mg/day, and discontinue [citalopram](#) in patients who have persistent QTc measurements greater than 500 milliseconds [76].

- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Concomitant use of [citalopram](#) and [toremifene](#) is not recommended due to a potential for additive effects on QT interval prolongation and an increased risk of serious cardiovascular effects [76]. If coadministration is required, interruption of [toremifene](#) is recommended; however, if interruption of [toremifene](#) is not possible, closely monitor for QT interval prolongation (ECG and electrolytes) [310]. Do not exceed [citalopram](#) doses of 40 mg/day, and discontinue [citalopram](#) in patients who have persistent QTc measurements greater than 500 milliseconds [76].
- 7) Probable Mechanism: additive effects on QT interval prolongation

3.5.1.KC] [Tramadol](#)

- 1) Interaction Effect: an increased risk of seizures and [serotonin syndrome](#) (hypertension, hyperthermia, myoclonus, mental status changes)
- 2) Summary: Seizures and [serotonin syndrome](#) have been reported in patients using [tramadol](#). The risk of seizures and [serotonin syndrome](#) may be enhanced when [citalopram](#) and [tramadol](#) therapy are combined [317] [316].
- 3) Severity: major
- 4) Onset: rapid
- 5) Substantiation: theoretical
- 6) Clinical Management: Caution should be used if [tramadol](#) is to be administered to patients receiving concomitant [citalopram](#) therapy. If possible, avoid this combination, especially in patients with underlying conditions that might predispose them to seizures. Observe the patient closely for signs and symptoms of [serotonin syndrome](#).
- 7) Probable Mechanism: increased concentration of serotonin in the nervous system and periphery
- 8) Literature Reports

a) Drug-induced [serotonin syndrome](#) developed in a 70 year-old Caucasian woman when [tramadol](#) 50 milligrams per day was added to her chronic regimen of [citalopram](#) 10 milligrams per day, which she was taking for three years. Symptoms of tremors, restlessness, fever, confusion, and visual hallucinations returned with re-exposure to [tramadol](#) one year later. [Genotyping](#) later revealed that the patient had deficient CYP2D6 and CYP2C19 enzyme activity, contributing to decreased metabolism of both drugs [316].

3.5.1.KD] [Tranylcypromine](#)

- 1) Interaction Effect: an increased risk of [serotonin syndrome](#) (hypertension, tachycardia, hyperthermia, myoclonus, mental status changes)
- 2) Summary: Concomitant use of [citalopram](#) and an MAOI is contraindicated. Concurrent administration or overlapping therapy with [citalopram](#) 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, and tremor. A minimum of 14 days should elapse after discontinuing an MAOI intended to treat psychiatric disorders before initiating therapy with [citalopram](#), and a minimum of 14 days should elapse after discontinuing [citalopram](#) before initiating therapy with an MAOI intended to treat psychiatric disorders [53].
- 3) Severity: contraindicated
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Concurrent use of [citalopram](#) and an MAOI is contraindicated. Wait at least 14 days after discontinuing an MAOI intended to treat psychiatric disorders before initiating [citalopram](#).

Wait at least 14 days after discontinuing [citalopram](#) before initiating therapy with an MAOI intended to treat psychiatric disorders [53].

7J) Probable Mechanism: additive serotonergic effect

3.5.1.KE] [Trazodone](#)

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

2J) Summary: QT/QTc interval prolongation and postmarketing cases of [torsade de pointes](#) have been reported with both [citalopram](#) and [trazodone](#) [76] [162]. Although this interaction has not been evaluated, concomitant use may result in additive effects on QT interval prolongation and an increased risk of serious [ventricular arrhythmias](#), including [torsade de pointes](#) [162]. A potentially life-threatening [serotonin syndrome](#) and neuroleptic malignant syndrome-like reactions (eg, hyperreflexia, incoordination, [tachycardia](#), labile blood pressure, [hyperthermia](#), agitation, hallucinations, coma) have occurred with [citalopram](#) alone, and the risk was increased when combined with other serotonergic drugs such as [trazodone](#) [162]. If coadministration is required, monitor for ECG changes. Do not exceed [citalopram](#) doses of 40 mg/day, and discontinue [citalopram](#) in patients who have persistent QTc measurements greater than 500 milliseconds [76]. Patients should also be monitored for signs/symptoms of [serotonin syndrome](#) or neuroleptic malignant syndrome-like reactions, especially during initiation of treatment and dose increases, and therapy should be discontinued in patients who develop these symptoms [162] [76].

3J) Severity: major

4J) Onset: unspecified

5J) Substantiation: theoretical

6J) Clinical Management: The concomitant use of [citalopram](#) and [trazodone](#) is not recommended due to a potential for additive effects on QT interval prolongation with an increased risk of serious cardiovascular effects. Both agents also have the potential to cause a life-threatening [serotonin syndrome](#) or neuroleptic malignant syndrome-like reactions. If coadministration is required, monitor for ECG changes and signs/symptoms of [serotonin syndrome](#) or neuroleptic malignant syndrome-like reactions, especially during initiation of treatment and dose increases. Do not exceed [citalopram](#) doses of 40 mg/day, and discontinue [citalopram](#) in patients who have persistent QTc measurements greater than 500 milliseconds. Discontinue therapy immediately and initiate treatment in patients who have symptoms of [serotonin syndrome](#) or neuroleptic malignant-syndrome-like reactions [162] [76]. 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 [81].

7J) Probable Mechanism: additive effects on QT interval prolongation and serotonergic effects

3.5.1.KF] [Trifluoperazine](#)

1J) Interaction Effect: an increased risk of QT interval prolongation

2J) Summary: [Citalopram](#) causes dose-dependent QT prolongation and has been associated with postmarketing reports of [torsade de pointes](#). Although this interaction has not been evaluated, concomitant use of [citalopram](#) and [trifluoperazine](#) due to a potential for additive effects on the QT interval prolongation and an increased risk of serious cardiovascular effects. If coadministration is required, monitor for ECG changes. Do not exceed [citalopram](#) doses of 40 mg/day, and discontinue [citalopram](#) in patients who have persistent QTc measurements greater than 500 milliseconds [76].

3J) Severity: major

4J) Onset: unspecified

5J) Substantiation: theoretical

6J) Clinical Management: Concomitant use of [citalopram](#) and [trifluoperazine](#) is not recommended due to a potential for additive effects on QT interval prolongation and an increased risk of serious cardiovascular effects. If coadministration is required, monitor for ECG changes. Do not exceed [citalopram](#) doses of 40 mg/day, and discontinue [citalopram](#) in patients who have persistent QTc measurements greater than 500 milliseconds [76].

7J) Probable Mechanism: additive effects on QT interval prolongation

3.5.1.KG] [Trimipramine](#)

1J) Interaction Effect: an increased risk of QT interval prolongation

2J) Summary: [Citalopram](#) causes dose-dependent prolongation of the QTc interval. Although this interaction has not been evaluated, the concomitant use of [citalopram](#) and [trimipramine](#) is not recommended due to a potential for additive effects on QT interval prolongation and an increased risk of cardiac adverse events, including [ventricular arrhythmias](#) and/or [torsade de pointes](#). If coadministration is required, monitor for ECG changes. Do not exceed [citalopram](#) doses of 40 mg/day, and discontinue [citalopram](#) in patients who have persistent QTc measurements greater than 500 milliseconds [76].

3J) Severity: major

4J) Onset: unspecified

5J) Substantiation: theoretical

6J) Clinical Management: The concomitant use of [citalopram](#) and [trimipramine](#) is not recommended due to a potential for additive effects on QT interval prolongation and an increased risk of serious cardiovascular effects. If coadministration is required, monitor for ECG changes. Do not exceed [citalopram](#) doses of 40 mg/day, and discontinue [citalopram](#) in patients who have persistent QTc measurements greater than 500 milliseconds [76].

7J) Probable Mechanism: additive effects on the QT interval

3.5.1.KH] [Triptorelin](#)

1J) Interaction Effect: increased risk of QT-interval prolongation

2J) Summary: Gonadotropin-releasing hormone (GnRH) agonists prolong the QT interval through their androgen-depriving action [261] [262] [263], while [citalopram](#) causes dose-dependent QT-interval prolongation that can lead to life-threatening [ventricular tachycardia](#) or [Torsade de Pointes](#). Avoid concomitant use of [citalopram](#) with GnRH agonists. If concurrent use is essential, [ECG monitoring](#) is recommended. Discontinue [citalopram](#) if persistent QTc measurements above 500 msec occur [38].

3J) Severity: major

4J) Onset: unspecified

5J) Substantiation: theoretical

6J) Clinical Management: Avoid concomitant use of [citalopram](#) with gonadotropin-releasing hormone (GnRH) agonists, a class of drug known to prolong the QT interval, as additive QT-interval prolongation may occur. If concurrent use is essential, [ECG monitoring](#) is recommended. Discontinue [citalopram](#) if persistent QTc measurements above 500 msec occur [38].

7J) Probable Mechanism: additive effects on the QT interval

3.5.1.KI] [Tryptophan](#)

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

2J) 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 [76].

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 [76].

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 [82].

3.5.1.KJ] [Valdecixib](#)

1) Interaction Effect: an increased risk of bleeding

2) Summary: Caution is recommended with the concomitant use of NSAIDs and SSRIs due to an increased risk of [gastrointestinal bleeding](#) [228] [229]. Bleeding events have included [epistaxis](#), ecchymosis, [hematoma](#), [petechiae](#), and life-threatening hemorrhages [231] [53] [232] [233]. 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: probable

6) Clinical Management: Use caution if NSAIDs and SSRIs are coadministered. Concomitant use of NSAIDs and SSRIs may cause an increased risk of bleeding [228] [229]. When an SSRI and an NSAID are given concurrently, monitor the patient for signs of increased bleeding.

7) Probable Mechanism: unknown

8) Literature Reports

a) SSRIs increase the risk of upper gastrointestinal (GI) bleeding, and this effect is potentiated by concurrent use of NSAIDs or low-dose [aspirin](#). Hospitalizations for [upper GI bleeding](#) were searched among 26,005 users of antidepressant medications and compared with the number of hospitalizations in those patients who did not receive prescriptions for antidepressants. The amount of [upper GI bleeding](#) episodes was 3.6 times more than expected (95% CI, 2.7 to 4.7). Combined use of an SSRI and NSAIDs or low-dose [aspirin](#) increased the risk to 12.2 (95% CI, 7.1 to 19.5) and 5.2 (95% CI, 3.2 to 8), respectively. The findings of this study demonstrate an increased risk of [upper GI bleeding](#) during the use of SSRIs. Combined use of SSRIs and NSAIDs or low-dose [aspirin](#) increased the risk even further [230].

b) The 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 [53].

3.5.1.KK] [Vandetanib](#)

1) Interaction Effect: an increased risk of QT interval prolongation and [torsade de pointes](#)

2) Summary: Vandetanib can prolong the QT interval in a concentration-dependent manner, while [citalopram](#) may cause dose-dependent QT prolongation. The concomitant administration of [citalopram](#) and other drugs that prolong the QT interval, such as vandetanib [289], is not recommended. If these drugs must be coadministered, monitor for ECG changes. Do not exceed [citalopram](#) doses of 40 mg/day, and discontinue [citalopram](#) in patients who have persistent QTc measurements greater than 500 milliseconds (ms) [76]. If the corrected QT interval (Fridericia; QTcF) is greater than 500 ms, discontinue vandetanib therapy until QTcF returns to less than 450 ms. Dosing can then be resumed at a reduced dose [289].

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Concomitant use of [citalopram](#) and vandetanib, both drugs that prolong the QT interval, is not recommended, as it may result in additive effects on the QT interval and an increased risk of [torsade de pointes](#) and [ventricular tachycardia](#). If these agents must be given together, monitor for ECG changes. Do not exceed [citalopram](#) doses of 40 mg/day, and discontinue [citalopram](#) in patients who have persistent QTc measurements greater than 500 milliseconds (ms) [76]. If the corrected QT interval (Fridericia; QTcF) is greater than 500 ms, discontinue vandetanib therapy until QTcF returns to less than 450 ms and then resume at a reduced dose [289].

7) Probable Mechanism: additive effects on the QT interval prolongation

3.5.1.KL] [Vardenafil](#)

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

2) Summary: [Citalopram](#) causes dose-dependent prolongation of the QTc interval [76] and [vardenafil](#) has also been associated with QT interval prolongation [269] [270]. The concomitant use of [citalopram](#) and [vardenafil](#) is not recommended due to a potential for additive effects on QT interval prolongation and an increased risk of cardiac adverse events, including [ventricular arrhythmias](#) and/or [torsade de pointes](#). If coadministration is required, monitor for ECG changes. Do not exceed [citalopram](#) doses of 40 mg/day, and discontinue [citalopram](#) in patients who have persistent QTc measurements greater than 500 milliseconds [76].

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: The concomitant use of [citalopram](#) and [vardenafil](#) is not recommended due to a potential for additive effects on QT interval prolongation and an increased risk of serious cardiovascular effects. If concurrent therapy is required, monitor for ECG changes. Do not exceed [citalopram](#) doses of 40 mg/day, and discontinue [citalopram](#) in patients who have persistent QTc measurements greater than 500 milliseconds [76].

7) Probable Mechanism: additive effects on QT interval prolongation

3.5.1.KM] [Vemurafenib](#)

1) Interaction Effect: increased risk of QT-interval prolongation

2) Summary: Avoid coadministration of [citalopram](#) with vemurafenib [257]. Both [citalopram](#) and vemurafenib have been associated with QT-interval prolongation [257] [76], and although this specific interaction has not been evaluated, coadministration may lead to an increased risk of prolonged QT interval and serious cardiac adverse events, including [torsade de pointes](#) [257]. If coadministration is required, do not exceed [citalopram](#) doses of 40 mg/day, and discontinue [citalopram](#) in patients who have persistent QTc measurements greater than 500 ms [76]. Assess baseline electrolytes and ECG and monitor carefully for QT-interval prolongation. Dosage adjustment of vemurafenib may also be warranted.

3) Severity: major

- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Coadministration of vemurafenib with a drug known to prolong the QT interval [257], such as [citalopram](#) [76], should be avoided, as additive effects on the QT interval may result [257]. If coadministration is required, do not exceed [citalopram](#) doses of 40 mg/day, and discontinue [citalopram](#) in patients who have persistent QTc measurements greater than 500 ms [76]. Assess baseline electrolytes and ECG and monitor carefully for QT-interval prolongation. Dosage adjustment of vemurafenib may also be warranted.
- 7) Probable Mechanism: additive effects on the QT interval

3.5.1.KN] Vilanterol

- 1) Interaction Effect: increased risk of [ventricular arrhythmias](#)
- 2) Summary: Vilanterol (a beta-agonist) has potential to prolong the QT interval; therefore, concomitant use with other drugs that can prolong the QT interval may cause an increased risk of [ventricular arrhythmias](#). [Electrocardiograph](#) changes, such as QT-interval prolongation, have been reported with beta-agonists. Use extreme caution during coadministration of vilanterol with a QT-interval prolonging drug or when using vilanterol within 2 weeks of discontinuation of a QT-interval prolonging drug [278]. [ECG monitoring](#) may be warranted if vilanterol and QT-interval prolonging drugs are used concurrently.
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Concomitant administration of vilanterol and QT-interval prolonging drugs may potentiate cardiovascular effects, such as QT-interval prolongation, and increase the risk of [ventricular arrhythmias](#). Use extreme caution when coadministering vilanterol and QT-interval prolonging drugs, or if using vilanterol within 2 weeks of discontinuation of a QT interval-prolonging drug [278]. If coadministration is required, [ECG monitoring](#) may be warranted.
- 7) Probable Mechanism: additive QT-interval prolongation

3.5.1.KO] 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](#) [80]. 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 [81]. 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 [80].
- 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 [80].

7J) Probable Mechanism: additive serotonergic effects

3.5.1.KP] Vinflunine

1J) Interaction Effect: increased risk of QT-interval prolongation

2J) Summary: Vinflunine is associated with QT-interval prolongation. Concomitant administration of vinflunine with other drugs that prolong the QT interval may have additive prolonging effects on the QT interval and is not recommended [105]. If concomitant use is required, consider a baseline ECG and on-treatment monitoring when vinflunine is coadministered with other QT-prolonging agents.

3J) Severity: major

4J) Onset: unspecified

5J) Substantiation: theoretical

6J) Clinical Management: Concomitant administration of vinflunine and QT-prolonging drugs may result in additive QT-interval prolongation effects and is therefore not recommended [105]. If concomitant use is required, consider a baseline ECG and on-treatment monitoring.

7J) Probable Mechanism: additive QT interval effects

3.5.1.KQ] Voriconazole

1J) Interaction Effect: increased risk of QT interval prolongation

2J) Summary: [Citalopram](#) causes dose-dependent prolongation of the QTc interval [76] and [voriconazole](#) has also been associated with QT interval prolongation [301]. Although this interaction has not been evaluated, the concomitant use of [citalopram](#) and [voriconazole](#) is not recommended due to a potential for additive effects on QT interval prolongation and an increased risk of cardiac adverse events, including [ventricular arrhythmias](#) and/or [torsade de pointes](#). If coadministration is required, monitor for ECG changes. Do not exceed [citalopram](#) doses of 40 mg/day and discontinue [citalopram](#) in patients who have persistent QTc measurements greater than 500 milliseconds [76].

3J) Severity: major

4J) Onset: unspecified

5J) Substantiation: theoretical

6J) Clinical Management: The concomitant use of [citalopram](#) and [voriconazole](#) is not recommended due to a potential for additive effects on QT interval prolongation and an increased risk of serious cardiovascular effects. If coadministration is required, monitor for ECG changes. Do not exceed [citalopram](#) doses of 40 mg/day and discontinue [citalopram](#) in patients who have persistent QTc measurements greater than 500 milliseconds [76].

7J) Probable Mechanism: additive effects on the QT interval

3.5.1.KR] Vortioxetine

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

2J) 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 [239].

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) 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 [239].

7) Probable Mechanism: additive serotonergic effects

3.5.1.KS] [Warfarin](#)

1) Interaction Effect: an increased risk of bleeding

2) Summary: The release of serotonin by [platelets](#) is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs and anticoagulants has been associated with an increased risk of bleeding [340] [341] [339]. 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](#) [341] [339].

3) Severity: major

4) Onset: unspecified

5) Substantiation: probable

6) Clinical Management: When [citalopram](#) and an anticoagulant are given concurrently, monitor patients for signs of increased bleeding. Patients who are taking [warfarin](#) should be monitored closely for altered anticoagulant effects, including increased bleeding, when [citalopram](#) therapy is initiated or discontinued [339].

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 [340].

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 [341].

c) The pharmacokinetics of [warfarin](#), a CYP3A4 substrate, were not affected by the administration of [citalopram](#) 40 mg/day for 21 days, while the prothrombin time was increased by 5%. The clinical significance of this is unknown [339].

3.5.1.KT] [Ziprasidone](#)

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

2) Summary: The concomitant use of [ziprasidone](#) with other drugs that prolong the QT interval is contraindicated because coadministration may result in additive risk for QT-interval prolongation. [Serotonin syndrome](#) has also been reported with [ziprasidone](#) monotherapy and in combination with other serotonergic drugs [303] [304]; coadministration with another serotonergic drug may increase the risk for [serotonin syndrome](#).

3) Severity: contraindicated

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: The concomitant use of [ziprasidone](#) with other drugs that prolong the QT interval is contraindicated because coadministration may result in additive risk for QT-interval prolongation. [Serotonin syndrome](#) has also been reported with [ziprasidone](#) monotherapy and in combination with other serotonergic drugs [303] [304]; coadministration with another serotonergic drug may increase the risk for [serotonin syndrome](#).

7) Probable Mechanism: additive QT interval effects; additive serotonergic effect

3.5.1.KU] [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 [334]. 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](#) [95]. Discontinue use of [zolmitriptan](#) if [serotonin syndrome](#) is suspected [334].

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 [334]. Consider potential intermittent use of triptans in patients who receive SSRIs and closely monitor patients receiving both medications for symptoms of [serotonin syndrome](#) [95]. Discontinue [zolmitriptan](#) if [serotonin syndrome](#) is suspected [334].

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 [335].

3.5.2] Drug-Food Combinations

3.5.2.A] Ethanol

- 1)) Interaction Effect: potentiation of the cognitive and motor effects of alcohol
- 2)) Summary: [Citalopram](#) did not potentiate the cognitive and motor effects of alcohol in a clinical trial, as with other psychotropic medications. The concomitant use, however, is not recommended [93].
- 3)) Severity: moderate
- 4)) Onset: unspecified
- 5)) Substantiation: theoretical
- 6)) Clinical Management: The use of alcohol by patients taking [citalopram](#) is not recommended.
- 7)) Probable Mechanism: unknown

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)) [Citalopram](#) Hydrobromide

1)) Therapeutic

a)) Alleviation of symptoms of depression is indicative of a therapeutic response to [citalopram](#) in patients with major [depressive illness](#). In patients receiving [citalopram](#) for extended periods, re-evaluate periodically for long-term efficacy [76].

2)) Toxic

a)) Laboratory Parameters

1)) Monitor electrolytes (especially potassium and magnesium) prior to therapy initiation and periodically during treatment with citalopram in patients at risk for significant electrolyte disturbances [76].

b)) Physical Findings

1)) Monitor patients receiving antidepressants for worsening of depression, suicidality, or unusual changes in behavior, especially during the initial few months of therapy or when the dose increases or decreases [76]. Such monitoring should include at least weekly face-to-face contact with patients or their family members or caregivers during the initial 4 weeks

of treatment, then visits every other week for the next 4 weeks, then at 12 weeks, and then as clinically indicated beyond 12 weeks [70] [68].

2j) Monitor ECG in patients with congenital long QT syndrome, bradycardia, hypokalemia or hypomagnesemia, recent acute myocardial infarction, uncompensated heart failure, or concomitant use of other QT-prolonging drugs [76].

3j) Monitor weight and growth regularly during therapy in children and adolescents [76].

4.2j Patient Instructions

Aj) Citalopram (By mouth)

Citalopram

Treats depression.

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 [citalopram](#).

How to Use This Medicine:

Liquid, Tablet

Take this medicine as directed. You may need to take it for a month or more before you feel better. Your dose may need to be changed to find out what works best for you.

Measure the oral liquid medicine with a marked measuring spoon, oral syringe, or medicine cup.

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 this medicine together with [pimozide](#). Do not use this medicine and an MAO inhibitor (MAOI) within 14 days of each other.

Some medicines can affect how [citalopram](#) works. Tell your doctor if you are using the following:

[Buspirone](#), [carbamazepine](#), [chlorpromazine](#), [cimetidine](#), [fentanyl](#), [levomethadyl](#), [lithium](#), [tramadol](#), [methadone](#), [omeprazole](#), [pentamidine](#), St John's wort, [thioridazine](#), tryptophan supplements
Medicine for heart rhythm problems ([amiodarone](#), [procainamide](#), [quinidine](#), [sotalol](#)), antibiotics ([gatifloxacin](#), [moxifloxacin](#)), NSAID pain or [arthritis](#) medicine (such as [aspirin](#), [diclofenac](#), [ibuprofen](#), [naproxen](#)), triptan medicine to treat migraine headaches, a blood thinner (such as [warfarin](#)), or a diuretic (water pill)

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 [kidney disease](#), liver disease, bleeding problems, [glaucoma](#), heart problems, or a seizure disorder. Tell your doctor if you or anyone in your family has a heart rhythm problem such as QT prolongation or a slow heartbeat.

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](#) (more likely when used with certain other medicines)

Heart rhythm problems

Increased risk of bleeding problems

Low sodium levels

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.

Your doctor may want to monitor your child's weight and height, because this medicine may cause decreased appetite and weight loss in children.

Do not stop using this medicine suddenly. Your doctor will need to slowly decrease your dose before you stop it completely.

Your doctor will check your progress and the effects of this medicine at regular visits. Keep all appointments.

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

Chest pain, trouble breathing

Confusion, weakness, and muscle twitching

Fast, pounding, or uneven heartbeat

Feeling more excited or energetic than usual, trouble sleeping, racing thoughts

Eye pain, vision changes, seeing halos around lights

Lightheadedness, dizziness, or fainting

Thoughts of hurting yourself or others, unusual behavior

Unusual bleeding or bruising

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

Dry mouth, mild nausea

Sexual problems

Sleepiness or drowsiness

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

4.3] Place In Therapy

A) [Citalopram](#)

1) [Citalopram](#) hydrobromide is indicated for the treatment of depression. Efficacy was established in studies of outpatients and has not been established in hospitalized patients with depression [3].

2) [Citalopram](#) appears to offer the same advantages over tricyclic antidepressants as other serotonin (5-HT) reuptake inhibitors, including a lesser propensity for cardiovascular toxicity and potentially fewer anticholinergic effects; however, direct comparisons of the drug with other 5-HT reuptake inhibitors are

required to determine its place in therapy. Hospital formulary consideration should be delayed until further studies with this agent are completed.

3j) As a class, selective serotonin (5-HT) reuptake inhibitors ([fluoxetine](#), [fluvoxamine](#), [sertraline](#), [paroxetine](#), [citalopram](#)) offer advantages over tricyclic antidepressants by virtue of minimal or no [cardiotoxicity](#), a lower propensity to induce anticholinergic effects, potentially less sedation, and either no effect or a decrease in body weight during therapy. However, the therapeutic efficacy of these agents in [major depression](#) has usually been equivalent to that of tricyclic antidepressants. Thus, they are becoming preferred first-line agents in the treatment of [major depression](#). Other indications have included patients in whom weight gain should be avoided, patients unresponsive to other antidepressants, depressed patients with concomitant [obsessive-compulsive disorders](#), and elderly patients (due to lesser cardiovascular and anticholinergic adverse effects). However, some disadvantages of 5-HT reuptake inhibitors are emerging, and include a relatively high incidence of gastrointestinal disturbances, insomnia, headache, restlessness or anxiety and sexual dysfunction; a propensity to induce [akathisia](#) has been reported [60]. These adverse effects may limit therapy in some patients.

4j) The clinical profile of [citalopram](#) is similar to that of other inhibitors of 5-HT reuptake. The drug appears to lack significant cardiovascular effects, and its propensity to induce seizures appears low. However, despite evidence for lack of significant effects on muscarinic receptors in preclinical investigations, [citalopram](#) clearly induces anticholinergic effects when given in clinically effective doses [60] [50] [49]; the incidence of these effects has been less than with tricyclic antidepressants in some but not all studies. Similar to other 5-HT reuptake inhibitors, the clinical efficacy of [citalopram](#) has not always been equivalent to that of tricyclic antidepressants.

5j) Overall experience with [citalopram](#) in [major depression](#) is still limited compared to other antidepressants. Comparisons with other agents have involved only small numbers of patients. Further studies are needed to evaluate the efficacy and safety of [citalopram](#) in the long-term use and in comparison with tricyclic and tetracyclic agents. There are few studies comparing the drug with other 5-HT reuptake inhibitors and therefore [citalopram's](#) ultimate place in therapy is yet to be determined. Consideration of [citalopram](#) for hospital formularies should be postponed until controlled comparisons with other SSRIs are completed. Data are insufficient to recommend [citalopram](#) in the treatment of other disorders including [dementia](#), [obsessive-compulsive disorder](#), [diabetic neuropathy](#), or alcohol abuse.

Bj) Citalopram Hydrobromide

See Drug Consult reference: CLASS COMPARISON: SSRIs AND SEROTONIN [NOREPINEPHRINE](#) REUPTAKE INHIBITORS (SNRIs) (SELECTED)

4.4j Mechanism of Action / Pharmacology

Aj) Citalopram Hydrobromide

1j) Mechanism of Action

a)j) [Citalopram](#) hydrobromide is a highly selective serotonin reuptake inhibitor (SSRI) with minimal effects on neuronal reuptake of [norepinephrine](#) (NE) and [dopamine](#) (DA). It acts as an antidepressant by potentiating the serotonergic activity in the CNS [76].

b)j) In vitro and in vivo studies have confirmed potent and specific 5-HT reuptake inhibitory properties of [citalopram](#). Its selectivity for serotonin reuptake inhibition is greater than other antidepressants, including [fluoxetine](#), [paroxetine](#), and tricyclic agents [397] [392]. The drug essentially has no effect on [norepinephrine](#) or [dopamine](#) reuptake. [Citalopram](#) does not inhibit monoamine oxidase [397] [398]. It has a low affinity for muscarinic [acetylcholine](#) receptors, and

has shown no significant effect on alpha- or beta-adrenergic receptors or [dopamine-1](#), [dopamine-2](#), [histamine](#), 5HT1A, 5HT1B, [gamma-aminobutyric acid](#), opioid, or benzodiazepine receptors [397] [392].

4.5] Therapeutic Uses

4.5.A] [Citalopram](#) Hydrobromide

4.5.A.1] Alcoholism

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:

[Citalopram](#) therapy was associated with modest reductions in alcohol consumption in relatively heavy drinkers [21] [22]

c)] Adult:

1)] Oral [citalopram](#) 40 mg once daily for 1 to 4 weeks has been effective in reducing alcohol consumption in placebo-controlled studies involving nondepressed alcohol-dependent drinkers (n=52; at least 28 drinks/week). A decrease in daily alcoholic drinks and an increase in the number of abstinent days were observed [21] [22]. The number of daily drinks was only reduced by an average of 16% or 17%. In one study, a decrease in interest, desire, craving, and liking for alcohol was documented during [citalopram](#) therapy; there appeared to be internal validation of these effects, as variations in each were significantly associated with alcohol consumption. These data suggest that [citalopram](#) acts by decreasing the desire for alcohol as well as its rewarding effects [21].

4.5.A.2] [Binging - Eating disorder](#)

a)] Overview

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

Efficacy: Adult, Evidence is inconclusive

Recommendation: Adult, Class IIb

Strength of Evidence: Adult, Category B

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

b)] Summary:

[Citalopram](#) therapy reduced the frequency of binge-eating episodes in patients with [binge-eating disorder](#) [23]

c)] Adult:

1j) The frequency of weekly binge-eating episodes was reduced following [citalopram](#) treatment in patients with [binge-eating disorder](#). In a randomized, double-blind, placebo-controlled study, patients having at least 3 binge-eating episodes each week for at least 6 months received [citalopram](#) (initial, 20 mg/day titrated, as tolerated, in 20 mg increments at weekly intervals to 60 mg/day; mean dose, 57.9 mg/day) or placebo for 6 weeks. According to a time trend analysis, patients treated with [citalopram](#) had significantly fewer binge-eating episodes per week following 6 weeks of therapy as compared with patients given placebo (mean, 1.7 vs 3.4, respectively; $p=0.003$), however, in the endpoint analysis, this primary outcome measure did not reach statistical significance. The time trend analysis also showed significantly greater reductions for the [citalopram](#) group as compared with placebo for frequency of binge-eating days per week, body mass index, and weight (p less than 0.001, all values). [Citalopram](#) was well tolerated with only sweating and fatigue being reported significantly more often with [citalopram](#) treatment than with placebo. Larger, longer-term studies are needed to further evaluate the efficacy of [citalopram](#) in the treatment of patients with [binge-eating disorder](#) [23].

4.5.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:

[Citalopram](#) therapy reduced symptoms of [body dysmorphic disorder](#) in a small, open-label study [25]

c) Adult:

1j) [Citalopram](#) appeared to reduce symptoms of [body dysmorphic disorder](#) (BDD) in a small study. In a 12-week, open-label study, patients ($n=15$) with BDD or delusional disorder, somatic type received [citalopram](#) 20 mg/day for 2 weeks, titrated to 40 mg/day for 2 weeks, then increased to 60 mg/day (if tolerated) for 8 weeks (mean dose at endpoint, 51.3 mg/day; range, 10 to 60 mg/day). Mean scores on the Yale-Brown Obsessive-Compulsive Scale Modified for BDD (BDD-YBOCS) were reduced by 51% from baseline to endpoint (30.7 vs. 10.6, p less than 0.001). Eleven (73.3%) patients were considered responders (response defined as at least a 30% reduction in BDD-YBOCS score). The most common adverse events included nausea, fatigue, constipation, headache, insomnia, and dry mouth. Larger, placebo- controlled trials are needed to substantiate these results [25].

4.5.A.4] [Chronic fatigue syndrome](#)

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:

[Citalopram](#) therapy may be effective in the treatment of idiopathic chronic fatigue in certain groups of patients [26]

c) Adult:

1) [Citalopram](#) treatment appeared to offer relief of symptoms associated with fatigue for some patients suffering from chronic idiopathic fatigue. In an observational study, patients with unexplained chronic fatigue for at least 6 months received open-label [citalopram](#) (20 to 40 mg/day) treatment for 2 months following a 1-week placebo run-in phase (n=31). Patient response to [citalopram](#) treatment was compared with response of patients to an ineffective treatment (placebo/ginseng) in a concurrent randomized control trial (n=96). In the analysis of open-label therapy, fatigue (as measured by the Rand Vitality Index) was significantly reduced at one and two months after patients were switched from placebo to [citalopram](#) (p less than 0.05). This effect was strongest at 2 months for women (p less than 0.01) and for patients with a history of fatigue for 5 years or less (p less than 0.01). When [citalopram](#) was compared to control groups, no significant difference was found overall between treatment groups for change in fatigue, however, subgroup analyses did find significant reductions in fatigue at 2 months in patients who were less severely fatigued at baseline (p=0.005). [Citalopram](#) did not reduce depressive symptoms in patients, overall, but did improve depressive symptoms in women at one month (p=0.01). For all patients, [citalopram](#) treatment was associated with fewer muscles aches (p=0.005) and less severe headaches (p=0.01). The most frequently reported adverse events were moderate to severe insomnia and sexual dysfunction. Further research is needed to delineate the clinical efficacy of [citalopram](#) for the treatment of chronic fatigue [26].

4.5.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:

[Citalopram](#) treatment reduced gambling behavior in patients in a small, open study [31]

c) Adult:

1) [Citalopram](#) treatment reduced gambling behavior and improved quality of life in patients involved in pathological gambling. In an open study, 15 patients who met the DSM-IV criteria for pathological gambling were given [citalopram](#) for 3 months. Approximately half of the patients were also diagnosed with [major depressive disorder](#). Dosing was flexible and started at 10

milligrams (mg) per day, with possible increases to a maximum of 60 mg/day, depending on response and side effects. The mean daily dose at the final evaluation was 34.7 mg/day. At baseline, all subjects were gambling at least 1 day per week, and gambling debt ranged from \$400 to \$150,000. The primary form of problem gambling was machine gambling. Nine patients finished the study. One patient withdrew because of side effects and 1 for lack of efficacy; reasons were not known for the other 4 dropouts. Using last-observation-carried forward, 13 patients (87%) were rated as "much" or "very much" improved on the Clinical Global Impressions of Improvement scale in gambling behavior. At baseline, 67% rated their quality of life as "poor" or "very poor", whereas at study completion, 73% rated their quality of life as "good" or "very good". Patients' level of depression also improved. There was no difference in improvement of gambling behavior between those patients who were depressed at baseline and those who were not. Most of the improvement occurred within the first 2 weeks. Five of the 6 patients who were rated as much or very much improved at the first 2-week follow-up visit maintained that improvement throughout the 12- week study period [31].

4.5.A.6] **Coronary arteriosclerosis - Depression**

a) Overview

FDA Approval: Adult, no; **Pediatric, no**

Efficacy: Adult, Evidence favors efficacy

Recommendation: Adult, Class IIb

Strength of Evidence: Adult, Category B

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

b) Summary:

Effective for the treatment of [major depression](#) in patients with [coronary artery disease](#) in a randomized, controlled, 12-week, parallel-group, 2 x 2 factorial study of 284 patients

4.5.A.7] **Dementia**

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:

Cognitive functioning may be improved with [citalopram](#) therapy [27] [28]

Studies have not been conclusive

See Drug Consult reference: [BEHAVIORAL AND PSYCHOLOGICAL SYMPTOMS OF DEMENTIA](#)

c) Adult:

1)) [Citalopram](#) therapy (20 to 30 milligrams daily) was associated with significant improvement in depressed mood, irritability, confusion, anxiety, agitation, suicidal impulses, fear, panic, and emotional bluntness [27] [28]. However, improvement of depression alone could contribute to improvement in other symptoms.

2)) In one study [27], a significant improvement in cognitive function was reported with [citalopram](#) compared to placebo (Gottfries-Brane-Steen [dementia](#) scale); however, this was not observed in another study [28]. Patients in the latter study had more severe [dementia](#), which was considered to contribute to the differences observed [27].

4.5.A.8] Depressed bipolar I 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:

[Citalopram](#) therapy reduced depression in patients in depressive phase of [bipolar disorder](#); prevention of mood swings was noted during the 16-week extended therapy [24]

c) Adult:

1)) In a study of patients in the depressive phase of [bipolar disorder](#), a majority were responsive to [citalopram](#) as an add-on therapy to their mood stabilizer therapy. Thirty-three patients meeting DSM-IV criteria for bipolar I or bipolar II depression completed 8 weeks of treatment with [citalopram](#), starting at 20 milligrams (mg) per day and increasing to a maximum of 80 mg/day, in addition their ongoing treatment with [lithium](#), [divalproex](#) sodium, [carbamazepine](#), or the combination of [lithium](#) with one of the other two. The average dose for all subjects was 34.7 mg. Twenty-one patients (64%) were responders, as indicated by a 50% reduction in score on the 17-item Hamilton Rating Scale for Depression (HAM-D). Among responders, 11 had responded by week 4 and 15 by week 6. Responders continued treatment with [citalopram](#) for another 16 weeks. Of those continuing, 14 had sustained remission, 3 did not achieve remission before the end of the 16 weeks, 2 patients experienced a [relapse](#), and 2 patients dropped out. There was no difference in outcome between bipolar I and bipolar II patients. Most patients (82%) experienced at least one adverse event, although no patient discontinued the study because of an adverse event. The most frequent adverse events were headache, gastrointestinal disturbances, drowsiness, and sexual dysfunction. There was no discussion of patients experiencing an immediate cycle switch, although one patient did discontinue therapy during a [manic episode](#) [24].

4.5.A.9] Depression

FDA Labeled Indication

a) Overview

FDA Approval: Adult, yes; [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:

[Citalopram](#) hydrobromide is indicated for the treatment of depression. Efficacy was established in studies of outpatients and has not been established in hospitalized patients with depression [3]. Appeared to be effective in the treatment of depression in patients unable to tolerate [fluoxetine](#) [4]. Among geriatric patients with [clinical depression](#) with or without concomitant [dementia](#), [citalopram](#) was more effective than placebo in improving depression on 4 rating scales according to a 6-week, randomized, double-blind trial (n=133) [5].

In a small study, [citalopram](#) was more effective than placebo for treating depression after a [stroke](#) [6]

See Drug Consult reference: CLASS COMPARISON: SSRIs AND SEROTONIN [NOREPINEPHRINE](#) REUPTAKE INHIBITORS (SNRIs) (SELECTED)

c) Adult:

1)) Short-Term Studies

a)) [Citalopram](#) was effective for treating depression in patients with [Hepatitis C](#), without worsening of liver function. In an open-label study, 15 patients with [hepatitis C](#) and severe depression were treated for 8 weeks with [citalopram](#), beginning at 20 mg per day. At the end of the study, the average dose of [citalopram](#) was 26.7 mg. Four of the patients were receiving interferon alfa therapy, known to cause depression, during the study. Seven subjects had never received treatment with interferon. Scores on the Hamilton depression scale (HAM-D) improved significantly over the 8- week period, with no evident difference between scores of those receiving interferon and those not. Thirteen of the 15 patients were regarded as responders, showing a 50% or greater improvement in their HAM-D scores from baseline. Quality-of- life measures, including measures of mental health, emotional well-being, and social functioning, somatization, obsessiveness-compulsiveness, interpersonal sensitivity, depression, anxiety, insomnia, and anger/ hostility, were improved (p=0.001). Liver function tests ([aspartate aminotransferase](#), [alanine aminotransferase](#), and gamma- glutamyltransferase plasma levels) were not changed by [citalopram](#) treatment. In addition to easing the symptoms of depression, [citalopram](#) therapy may improve the likelihood of a patient completing [interferon therapy](#) for [hepatitis C](#) [7].

b)) Treatment of depression with [citalopram](#) was better in middle-aged and elderly male [schizophrenia](#) patients than was no augmentation treatment. In a 10-week, single-blind study, 19 patients meeting DSM-IV criteria for [schizophrenia](#) were randomized to receive [citalopram](#) (n=9, mean age 65.4 years) or no augmentation treatment (n=10, mean age 59.2 years). Scores on the Hamilton Depression Scale (HAM-D) and Clinical Global Improvement (CGI) scale improved for both groups, but significantly more so for the group receiving [citalopram](#) (p less than 0.0001 for HAM-D and p less than 0.0054 for CGI). Final HAM-D scores were 8.8 for the [citalopram](#) group and 16.7 for the non-[citalopram](#) group [8].

c) Citalopram was significantly more effective than placebo for treating depression [9]. In a 6-week, double-blind trial, patients (n=650) were randomly assigned to receive placebo or a fixed dose of citalopram 10, 20, 40, or 60 mg per day. Pooled data for all citalopram doses showed a significant reduction in the Montgomery-Asberg Depression Rating Scale, the Hamilton Rating Scale for Depression (HAM-D), the Clinical Global Impressions (CGI)-Severity scale, and the CGI-Improvement scale. Only citalopram 40 and 60 mg produced a significant reduction in the HAM-D total score compared to placebo. The overall completion rate was 67%. Discontinuation due to adverse effects was reported in 6% of placebo-treated patients and 8% to 18% of citalopram-treated patients. Citalopram was effective for acute treatment of major depression.

d) In one double-blind trial (n=143), citalopram 20 to 80 mg once daily was superior to placebo over a 4-week period in patients with major depression. The mean dose of citalopram was 61 mg/day by week 4. Overall responses suggested improvement in approximately 65% of citalopram-treated patients and 33% of those receiving placebo. A quantitative meta-analysis of published and unpublished studies comparing citalopram with placebo over 4 to 6 weeks revealed similar findings with responses being seen in approximately 70% and 25% of patients, respectively [10].

e) Citalopram therapy appeared to be effective in reducing depressive symptoms in patients intolerant to fluoxetine treatment. In a multicenter, open-label study, patients (n=55) with major depressive disorder who could not tolerate fluoxetine at a minimum dose of 20 mg/day for at least one week received 6 weeks of citalopram therapy (10 to 20 mg/day for 4 weeks, then 20 to 40 milligrams/day; final mean dose, 33.8 mg/day) following a 2-week placebo washout period. Evaluation of response was performed at weeks 0, 1, 2, 4, and 6 using the 24-item Hamilton Rating Scale for Depression (HAM-D-24) and the Clinical Global Impressions Scale (CGI). Response was defined as an improvement score of a 1 or 2 (very much improved or much improved) on the CGI. Significant improvement in the HAM-D-24 score was seen at weeks 1, 2, 4, and 6 (p less than 0.001, all timepoints). At endpoint, 36 (65%) patients were considered responders. Citalopram was generally well tolerated with the common adverse events being pharyngitis (15%) and constipation (11%). Recurrence of adverse events that led to termination of fluoxetine treatment was low (those with the greatest recurrence rates were headache (27%), nausea (22%), and decreased libido (18%)) and no patients discontinued treatment due to adverse effects [4].

f) Citalopram was effective in treating poststroke depression in a 6-week, double-blind, placebo-controlled study [6]. Patients received either placebo (n=33) or citalopram 10 to 40 mg (n=33). Greater improvement on the Hamilton Depression Scale was seen in the citalopram group at 3 and 6 weeks (p less than 0.05).

2) Long-Term Maintenance Studies

a) Maintenance therapy with citalopram effectively reduced the rate of recurrence of depression in elderly patients. In a 3-phase study, patients, 65 years of age or older, suffering a unipolar depressive episode and scoring at least 22 on the Montgomery-Asberg Depression Rating Scale (MADRS) were openly treated with citalopram 20 to 40 mg/day for 8 weeks. Patients scoring 11 or less on the MADRS at week 8 entered period II, in which they received open, continuation treatment for 16 weeks at the same dose that was reached during the first period. At the end of period II, patients with a MADRS score of 11 or less were randomized to receive placebo (n=61) or citalopram (same dose as in period

II) (n=60) during period III, which was a minimum of 48 weeks. There were 19 recurrences (32%) in the [citalopram](#) group as compared with 41 recurrences (67%) in the placebo group during period III. Time to recurrence during period III was significantly different between the two treatment groups in favor of [citalopram](#) (p less than 0.0001). During period III, only increased sweating, tremor, and fatigue were reported at a statistically higher rate in citalopram-treated patients as compared with placebo. Two patients reported weight gain or loss [11].

b) [Citalopram](#) was more effective than placebo for preventing recurrences of depression in patients with unipolar, recurrent depression. In a 3-phase study, patients with a history of at least 2 [major depressive episodes](#) and currently suffering unipolar [major depression](#) (DSM-IV) were openly treated for 6 to 9 weeks with [citalopram](#), beginning with 20 mg/day and stepping up by 20 mg/day at weeks 3 and 6, if necessary. If scores on the Montgomery-Asberg Depression Rating Scale (MADRS) were 11 or less at week 6, patients entered period II, open continuation treatment at the same dose, to consolidate remission. If MADRS scores were higher than 11, patients were treated for 3 more weeks, at which time they met criteria and entered period II or were removed from the study. Patients experiencing no recurrence during period II (16 weeks) were randomized to receive [citalopram](#) (same dose as in period II) (n=132) or placebo (n=132) for period III, which was 48 weeks or more. There were 24 recurrences in the [citalopram](#) group and 59 in the placebo during period III (p less than 0.001 by log rank test). When length of treatment was taken into account, the recurrence rate with [citalopram](#) was 0.22 recurrences/person-years at risk and with placebo 0.76 recurrences/person-years at risk. During period III, the adverse event profiles were similar for the 2 groups, except for a higher rate of certain symptoms (dizziness, headache, and nausea) in the placebo group during the first few weeks, suggesting drug- discontinuation phenomena. No patients reported weight gain with [citalopram](#) treatment [12].

c) Recurrence of depression occurred in 50% of patients who received [citalopram](#) [13]. Fifty hospitalized patients with [major depression](#) received [citalopram](#) 40 mg per day for 6 weeks. When the Hamilton Rating Scale for Depression (HAM-D) score fell to less than or equal to 8 for 3 consecutive weeks, the patients were considered stable and continued treatment for an additional 4 months. During this period, there were no [relapses](#). Of the original 50 patients, 32 entered a 2-year maintenance study with [citalopram](#) 20 mg per day. Side effects were generally mild and transient. The incidence of recurrent depression was similar to that reported in other studies that used no therapy or placebo as maintenance therapy. This study is limited by the absence of a placebo group; however, the participating institution considered this unethical.

3) Geriatric

a) [Citalopram](#) was more effective than placebo in improving depression on 4 rating scales among in geriatric patients with [clinical depression](#) with or without concomitant [dementia](#) according to a 6-week, randomized, double-blind trial (n=133). The efficacy analysis was based on results of the 17-item Hamilton Rating Scale for Depression (HRSD), the Clinical Global Impression Scale (CGI), the Montgomery-Asberg Depression Rating Scale (MADRAS), and the Gottfries-Brane-Steen (GBS) geriatric rating scale. Inpatients and outpatients of 65 to 91 years (mean, 76.7 years) with [clinical depression](#) and a baseline total HRSD score of at least 14 were enrolled. While mild to moderate [dementia](#) and somatic disorders were allowed, patients with a history of [schizophrenia](#) or severe

[dementia](#) were excluded. There were 98 patients with [major depression](#) based on DMS-III criteria and 29 patients with comorbid [dementia](#). Patients were randomized to receive either placebo (n=51) or [citalopram](#) 10 mg/day for 2 days, then 20 mg/day for 2 weeks (n=98). After 2 weeks, if needed the [citalopram](#) dose could be adjusted to either 10 mg/day or 30 mg/day depending on clinical response and adverse events. [Citalopram](#) was discontinued in patients deemed nonresponders at week 4. Concomitant neuroleptics and a benzodiazepine or somatic treatment agent were permitted, but other antidepressants were prohibited. Both treatment arms demonstrated improvement in the mean total HRSD scores from a baseline as early as week 2 (p less than 0.05). After 6 weeks of treatment, [citalopram](#) resulted in a lower mean total HRSD (12.2 +/- 6.8 vs 16 +/- 7.6; p less than 0.05) and greater improvement difference (-9.9 vs -5.1; p less than 0.01) compared with placebo. Similarly, the mean total MADRAS score was significantly lower in the [citalopram](#) group compared with placebo at week 6 (13.1 +/- 10 vs 17.5 +/- 8.5; p less than 0.05). On the CGI scale, the difference in the severity of illness mean score (1.9 vs 2.6; p less than 0.05) and improvement (p less than 0.01) were significant. Relative to placebo, [citalopram](#) was associated with significant improvements (p less than 0.05) on items of the GBS items of orientation in time, impaired recent memory, inability to increase tempo, and fear-panic. In the subgroup of patients with [major depression](#), the differences between [citalopram](#) and placebo was statistically significant in the mean total HRSD and mean total CGI score, but not in the mean total CGI score. [Citalopram](#) was associated with higher frequency of asthenia/tiredness/lassitude (18 vs 3) and emotional indifference (8 vs 0; both p less than 0.05) compared with placebo. Reduction in heart rate of 4 to 6 beats/min occurred in the [citalopram](#) group and no decrease was noted in placebo. The geriatric population may require longer duration of treatment compared with younger patients to assess response [5].

d) Pediatric:

1) [Citalopram](#) improved symptoms of depression in 16 of 21 adolescents treated naturalistically in a community mental health center. In this retrospective study, adolescents with [major depression](#), bipolar, depression, or [dysthymia](#), had been treated with [citalopram](#) 10 to 60 mg per day (mean 26.5 mg/day) for an average of 128 days. According to the Clinical Global Impression (CGI) Improvement scale, 16 patients were "much" or "very much" improved by the end of treatment. The CGI-Severity scale showed significant reduction in severity symptoms (from 4.1 to 2.9, p less than 0.0026, intent-to-treat analysis). Of 10 patients who responded inadequately to previous trials of SSRIs (selective serotonin reuptake inhibitors), 7 responded to [citalopram](#). Thirty-three percent of subjects reported mild side effects (headache, dizziness, nausea, sedation, agitation, and sweating). Three patients discontinued due to adverse effects [14].

4.5.A.10] Nicotine dependence

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:

Citalopram therapy had no effect on smoking behavior [34] [21]

c) Adult:

1) Oral citalopram 20 to 40 milligrams daily had no effect on smoking behavior in heavy drinkers in a placebo-controlled study [34]. The number of cigarettes smoked was also not affected by citalopram therapy in another study investigating benefits of the drug in reducing alcohol consumption [21].

4.5.A.11] Obsessive-compulsive disorder**a) Overview**

FDA Approval: Adult, no; Pediatric, no

Efficacy: Adult, Evidence favors efficacy; Pediatric, Evidence is inconclusive

Recommendation: Adult, Class IIb; Pediatric, Class IIb

Strength of Evidence: Adult, Category B; Pediatric, Category B

See Drug Consult reference: **RECOMMENDATION AND EVIDENCE RATINGS**

b) Summary:

Citalopram appears to be a safe and effective treatment for obsessive-compulsive disorder [15]

Minimum effective dose for depression is also effective for OCD [15]

c) Adult:

1) In a large, randomized, double-blind, placebo-controlled trial, citalopram at 3 different doses was significantly more effective than placebo for improving symptoms of obsessive-compulsive disorder (OCD). Four hundred and one patients were randomized to receive placebo, citalopram 20 mg, citalopram 40 mg, or citalopram 60 mg daily for 12 weeks. Scores on the Yale-Brown Obsessive Compulsive Scale (YBOCS) at week 12 had decreased significantly more for all citalopram groups than for placebo (p less than 0.01 for citalopram 20 mg vs placebo; p less than 0.001 for each of the other 2 citalopram groups vs placebo). Significant differences from placebo occurred at week 3 for the group taking citalopram 60 mg and from week 7 for the other 2 citalopram groups. The percentage of responders (ie, 25% or greater improvement in YBOCS scores) were 57%, 52%, and 65% in the citalopram 20-, 40-, and 60-mg groups, respectively. The mean change from baseline in YBOCS increased with time for all 4 treatment groups. All 4 treatment groups showed a decrease in depression scores, although citalopram showed a greater effect on OCD in non-depressed subjects than in depressed subjects. Adverse events occurred in approximately 70% of patients in the citalopram groups and in 58% of patients in the placebo group. Nausea, insomnia, fatigue, increased sweating, dry mouth, ejaculation failure, and diarrhea occurred significantly more frequently in the citalopram groups than in the placebo group. Although there was a dose-response relationship with citalopram, there were no significant differences between doses on any measure. The lowest dose, which is the minimum effective dose for treating depression, was shown unequivocally to be effective for treating OCD [15].

2) Shorter duration of obsessive-compulsive disorder (OCD), lower severity of symptoms, and no history of treatment with a selective serotonin-reuptake inhibitor (SSRI) were predictive of higher likelihood of successful treatment with citalopram. Data from a randomized, double-blind, placebo-controlled trial were analyzed to determine predictors of response of patients who met

DSM-IV criteria for OCD. Patients had experienced OCD symptoms for at least 12 months and had a baseline score on the Yale-Brown Obsessive-Compulsive Scale (YBOCS) of at least 20 to be included in the study; subjects with more than mild depression were not included. Patients (n=393) received placebo, [citalopram](#) 20 mg, 40 mg, or 60 mg daily for 12 weeks. The odds of responding were 3 times higher for [citalopram](#) 20 or 40 mg than for placebo and 4 times higher for [citalopram](#) 60 mg than for placebo. Higher baseline scores on the YBOCS and longer duration of illness were both negatively associated with likelihood of positive response. The odds ratio of response in patients who had previously tried an SSRI over that in patients who had never before tried an SSRI was 0.31 if the previous trial had met with failure and 0.41 if it had not. The duration of treatment (more or less than 56 days) was also a significant predictor. The odds ratio of patients with shorter treatment over those with longer treatment was 0.04 (p less than 0.001). Sex and age were not predictors of success. The linear regression analysis from this study yielded equations, which, with the insertion of an individual's values for these predictors, can calculate the prognosis of that patient [16].

3j) [Citalopram](#) was beneficial for 22 of 27 (76%) patients with [obsessive compulsive disorder](#) in an open pilot study [17]. Patients (19 to 63 years old) were started on [citalopram](#) 20 mg daily and increased to 40 mg during the second week. The dose was further escalated to 60 mg if no improvement was seen. After 24 weeks, patients showed a significant improvement on the Yale-Brown Obsessive Compulsive Scale from their baseline scores (p=0.042). Adverse effects included: decreased sleep (10%), increased dreaming (6%), [orgasmic dysfunction](#) (8%), and reduced sexual desire (5%).

4j) [Citalopram](#) (mean dose 44 mg daily) was effective in 67% of evaluable patients with [obsessive-compulsive disorder](#) in a naturalistic, open label 12-week study. Adverse reactions by week 12 were few and minimal in severity; one of four dropouts was due to intolerable anxiety within the first 2 weeks of treatment [18]. Conclusions of this trial are limited by its design.

5j) Improvement in symptoms of [obsessive-compulsive disorder](#) was observed in one patient after 5 weeks of therapy with [citalopram](#) (up to 80 mg daily). This patient had been refractory to previous therapy with [desipramine](#), [tranylcypromine](#), [lithium](#), [carbamazepine](#), and neuroleptics. However, almost uncontrollable mania accompanied the reduction in [obsessive-compulsive behavior](#) during [citalopram](#) therapy, limiting its overall usefulness [19].

dj) Pediatric:

1j) In an open study, [citalopram](#) was useful for [obsessive compulsive disorder](#) in 22 of 23 children/adolescents (9 to 18 years old) [20]. [Citalopram](#) was started at 10 mg daily and titrated to 40 mg. Due to side effects, 2 patients were maintained on 20 mg and 1 on 10 mg. Therapeutic effects were observable after 2 to 6 weeks of therapy. After 10 weeks, 4 patients showed a marked improvement in the Yale-Brown Obsessive-Compulsive Scale (Y-BOCS), 14 patients showed a moderate improvement, and 4 had a slight improvement. Social functioning scores were also significantly increased (Children's Global Assessment Scale, p less than 0.001). Adverse events included 4 patients with restlessness and 2 with anxiety.

4.5.A.12] Panic disorder

a) Overview

FDA Approval: Adult, no; **Pediatric, no**

Efficacy: Adult, Evidence favors efficacy; Pediatric, Evidence is inconclusive

Recommendation: Adult, Class IIb; **Pediatric, Class IIb**

Strength of Evidence: Adult, Category B; Pediatric, Category C

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

b) Summary:

[Citalopram](#), at doses of 20 to 60 mg/day, was effective compared with placebo; although, [citalopram](#) 20 mg to 30 mg/day appeared to be the optimal dose in treating [panic disorder](#) in a 1-year continuation study [29]

Low-dose [citalopram](#) (20 milligrams/day) therapy over 8 to 15 months was useful in treating panic attacks in 3 children [30]

c) Adult:

1) In a 1-year continuation study, [citalopram](#) 20 to 60 mg daily remained effective and was superior to placebo for treating [panic disorder](#); however, [citalopram](#) 20 to 30 mg/day appeared to be the optimal dose. In this dose-finding, double-blind, randomized, placebo- and clomipramine-controlled trial (n=279), 179 patients completed 1 year of treatment. Lack of efficacy was the primary reason for discontinuation in the placebo group; whereas, improvement and adverse effects were the primary reasons in the active treatment groups. Regardless of treatment, most patients who remained in the study at 1 year were free of panic attacks based on the Clinical Anxiety Scale. The Physician's and Patient's Global Improvement Scales showed significant differences between the active and placebo groups throughout the 12-month period. [Citalopram](#) is an effective therapy for treating [panic disorder](#) with headache as a frequent adverse effect [29].

d) Pediatric:

1) Treatment with low-dose [citalopram](#), 20 mg daily for 8-15 months, alleviated panic attacks and [school phobia](#) in 3 school-aged patients with minimal, temporary adverse reaction (headache) [30].

4.5.A.13] [Postmenopausal flushing](#)

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:

[Citalopram](#) was more effective than placebo in reducing hot flash symptoms of postmenopausal women in a randomized, double-blind study (n=254) [1].

4.5.A.14] [Premenstrual dysphoric 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:

A meta-analysis of 3 randomized, double-blind, placebo-controlled studies of women with [premenstrual syndrome](#) (n=69) showed a significant reduction of symptoms with [citalopram](#) 5 to 20 mg (odds ratio, 0.18; 95% confidence interval, 0.06 to 0.51) [32] [33].

c) Adult:

1) Intermittent treatment with [citalopram](#) was more effective than placebo for treating women with premenstrual [dysphoria](#) syndrome (PDS) characterized primarily by irritability. After a 2-cycle run-in phase, patients were randomly assigned to receive placebo (n=20), [citalopram](#) continuous treatment (CC; dose - 20 mg/day; n=19), [citalopram](#) semi-intermittent treatment (CS; dose - 5 mg/day follicular phase, 30 mg/day luteal phase; n=20), or [citalopram](#) intermittent treatment (CI; dose - placebo follicular phase, 30 mg/day luteal phase; n=19); dose adjustment was allowed based on response and side effects. Efficacy was based on patient symptom-ratings with a visual analog scale (VAS; 100=worst symptoms) and global assessment where +3=enormously improved, 0=no change, and -3=enormously deteriorated. Based on global improvement, the CC and CI groups were superior to PL (p=0.002 and p=0.02). Using the VAS, the CI group revealed significant improvement for all treatment cycles compared to PL (p=0.0004), for the last 2 cycles compared to CC (p=0.002), and for the last cycle compared to CS (p=0.005). Nine patients withdrew from treatment of whom 5 withdrew during the luteal phase of the first treatment [33].

4.6] Comparative Efficacy / Evaluation With Other Therapies

4.6.A] [Amitriptyline](#)

4.6.A.1] Depression

a) [Citalopram](#) 20 to 60 mg daily has generally been comparable in efficacy to [amitriptyline](#) (75 to 225 milligrams daily) in the treatment of depression in short-term studies (inpatients and outpatients) [404] [405] [406]. However, [amitriptyline](#) has been superior to [citalopram](#) in improving sleep disturbances [404] [406].

b) Anticholinergic adverse effects have tended to occur less frequently with [citalopram](#) compared to [amitriptyline](#) in some studies [406] [405], although a similar number of patients receiving each agent developed dry mouth in another study [404]. Comparative studies against low-anticholinergic tricyclic antidepressants (eg, [desipramine](#)) would provide useful information here.

4.6.A.2] Headache

a) [Amitriptyline](#) significantly reduced headache duration (P=0.01), frequency (P=0.01), and intake of analgesics (P=0.02), as compared to [citalopram](#) and placebo, but had no effect on headache intensity (P=0.12). In a 32 week, double-blind, placebo controlled, three-way crossover study, 40-non-depressed patients with [chronic tension type headache](#), were given 8 weeks of [amitriptyline](#) (titrated up to 75 milligrams(mg)), [citalopram](#) (20 mg) and placebo separated by 2 week wash-out periods. [Citalopram](#) had no significant effect on headache. [Amitriptyline](#) did induce more side effects than both [citalopram](#) and

placebo (P less than 0.001). This suggests that analgesic effect of [amitriptyline](#) may not be related to the inhibition of serotonin reuptake [407].

4.6.B] [Clomipramine](#)

4.6.B.1] Depression

a) [ClomiPRAMINE](#) (a tricyclic antidepressant with potent 5-HT reuptake inhibiting properties) 150 milligrams once daily was statistically superior to [citalopram](#) 40 milligrams once daily in the treatment of endogenously depressed patients in a 5-week double-blind study (n=75). [ClomiPRAMINE](#) appeared to have a faster onset and was particularly more effective in improving sleep disturbances, although other depressive symptoms were also improved to a greater degree with this agent compared to [citalopram](#). In the subgroup of patients with nonendogenous depression in this study (n=27), a similar trend was observed in favor of [clomiPRAMINE](#); however, the number of patients treated was too small to enable an effective comparison. Orthostatic symptoms, dry mouth, and perspiration were seen only with [clomiPRAMINE](#), whereas nausea, vomiting, and headache were more common with [citalopram](#) [408]. Flaws in this study were that fixed doses of each agent were employed and the duration of 5 weeks may have been too short. The onset of full antidepressant effects of [citalopram](#) may take 5 to 6 weeks. Titrating the dose of each agent based on clinical response would enable a more effective comparison in that optimal doses for specific patients could be achieved. A further comparison of these agents with flexible dosing regimens is warranted.

4.6.B.2) Efficacy

a) A small, 5-week, double-blind study reported significant orthostatic hypotensive effects (systolic pressure) in depressed patients treated with [clomiPRAMINE](#) 150 milligrams once daily but not [citalopram](#) 40 milligrams once daily. Diastolic blood pressure was also significantly reduced, although to a lesser extent, with [clomiPRAMINE](#), whereas this change did not occur in citalopram-treated patients [409].

b) Similar findings were reported in a clinical efficacy comparison of [clomiPRAMINE](#) and [citalopram](#) [408], and these results are consistent with other clinical data suggesting the lower propensity of [citalopram](#) to induce cardiovascular effects compared to tricyclic antidepressants [410].

4.6.C] [Escitalopram](#)

4.6.C.1] Depression

a) Direct placebo-controlled comparisons of escitalopram 10 or 20 mg daily and [citalopram](#) 20 or 40 mg daily in patients with [major depression](#) have revealed a trend toward the superiority of escitalopram in improving symptoms, although this did not reach statistical significance [416] [417] [414]. In all studies, improvements from baseline with escitalopram versus placebo tended to be greater than [citalopram](#) versus placebo, leading the investigators to indicate greater efficacy of escitalopram; however, the statistical superiority of escitalopram versus [citalopram](#) for baseline improvements was not demonstrated. Using placebo-effect versus baseline comparisons, the onset of action of escitalopram was judged faster than that of [citalopram](#); statistical analysis between escitalopram and [citalopram](#) were not applied.

b) In pooled data from three 8-week, placebo-controlled studies comparing [citalopram](#) 20 to 40 mg daily and escitalopram 10 to 20 mg daily in patients with [major depressive disorder](#), improvement of Montgomery Asberg Depression Rating Scale (MADRS) scores was significantly greater with escitalopram versus placebo after one week, whereas borderline significance (p=0.068) versus placebo was seen for [citalopram](#) at week 4. Similar trends were reported for Clinical Global Impressions (CGI) scale scores. In patients completing 8 weeks of treatment, MADRS scores had improved by at least 50% in 59%,

53%, and 41% of patients receiving escitalopram, [citalopram](#), and placebo, respectively; MADRS response rates for both escitalopram and [citalopram](#) were significantly greater compared to placebo, although there was no significant difference between active drug groups [416].

4.6.C.2] Mixed anxiety and [depressive disorder](#)

a) In unpublished, 8-week placebo-controlled studies, escitalopram 10 or 20 mg daily was comparable in efficacy to [citalopram](#) 20 or 40 mg daily in treating both anxiety and depression in outpatients with [major depression](#) [415]. A trend toward faster improvement of anxiety symptoms was seen with escitalopram, although this was not statistically significant. Adverse-effect data was provided only for escitalopram.

4.6.C.3] [Panic disorder](#)

a) Escitalopram achieved statistical significance in reduction of panic attack frequency, but [citalopram](#) did not when both were compared with placebo in a 10-week study. In a randomized, double-blind, placebo-controlled, flexible-dose, multicenter study, patients with [panic disorder](#) with or without [agoraphobia](#) received escitalopram (n=128; mean dose, 10.8 mg/day), [citalopram](#) (n=119; mean dose, 21.3 mg/day), or placebo (n=119). Panic attack frequency in escitalopram-treated patients was significantly reduced from baseline to endpoint as compared with patients who received placebo (-1.61 vs -0.32, respectively; p=0.04). Additionally, the percentage of patients in the escitalopram group with zero panic attacks at endpoint as compared with placebo approached statistical significance (50% vs 38%, respectively p=0.051). The [citalopram](#) group was not statistically different from placebo on either of these measures. However, patients in both the escitalopram and [citalopram](#) groups did show significant improvements in numerous other efficacy measures relative to placebo including, Panic and [Agoraphobia](#) Scale total score, Clinical Global Impression-Improvement (CGI-I) and -Severity of Illness (CGI-S) scores, CGI-Phobia Avoidance score, Patient Global Evaluation score, and Quality of Life Enjoyment and Satisfaction Questionnaire score (p less than or equal to 0.05, all values). The most commonly reported adverse events included headache, dry mouth, nausea, insomnia, fatigue, dizziness, and somnolence. The rate of discontinuation due to adverse effects with escitalopram, [citalopram](#), and placebo were 6.3%, 8.4%, and 7.6%, respectively [418].

4.6.C.4] Adverse Effects

a) In one large study (N=491) adverse effects occurred in 71%, 79%, 86%, and 86% of patients treated with placebo, escitalopram 10 mg daily, escitalopram 20 mg daily, and [citalopram](#) 40 mg daily, respectively; corresponding incidences of therapy discontinuation due to adverse effects were 2.5%, 4.2%, 10.4%, and 8.8%. There was no significant statistical difference in the number of adverse effects between placebo and escitalopram 10 mg daily. There was also no significant statistical difference in the number of adverse effects reported for escitalopram 20 mg daily and [citalopram](#) 40 mg daily, but both groups had statistically (p less than 0.01) higher rates of treatment-emergent adverse effects than placebo or escitalopram 10 mg daily [414].

4.6.D] [Imipramine](#)

4.6.D.1] [Depression](#)

a) Unpublished studies involving small numbers of patients suggest the comparable efficacy of [imipramine](#) and [citalopram](#) in depression, although [imipramine](#) has tended to be more effective in improving sleep disturbances [420]. Further well-controlled comparisons of these agents are needed.

4.6.E] [Maprotiline](#)

4.6.E.1] Depression

a) SUMMARY: Controlled studies of 4 to 6 weeks duration have demonstrated that [citalopram](#) 40 to 60 milligrams daily is comparable in efficacy to [maprotiline](#) (tetracyclic [norepinephrine](#) uptake inhibitor) 75 to 150 milligrams daily in the treatment of endogenous or nonendogenous depression [402] [403].

b) [Citalopram](#) in doses of 40 or 60 milligrams once daily was as effective as [maprotiline](#) 75 or 150 milligrams once daily in the treatment of depression in a controlled study involving 96 patients [402]. Both drugs were similarly effective in reducing MADRS (Montgomery-Asberg Depression Rating Scale) total scores and CGI scores, either for the group as a whole or when patients were subgrouped into endogenously/non-endogenously depressed or melancholic/non-melancholic patients. Adverse effects occurred to a similar degree with either agent, with [citalopram](#) producing a higher incidence of sweating, headache, and nausea. [Maprotiline](#) was associated with more anticholinergic adverse effects.

4.6.F] Mianserin

4.6.F.1] Depression

a) [Citalopram](#) and mianserin showed equal efficacy for treating depression in elderly patients participating in a large, multicenter, randomized, double-blind study. Patients 65 years of age or older and with [major depression](#) (DSM-III-R) and/or [dysthymic disorder](#) received either [citalopram](#) (n=140) or mianserin (n=149) for 12 weeks. For the first 4 weeks, doses were 20 milligrams (mg) of [citalopram](#) per day and 30 mg of mianserin per day. During weeks 5 to 12, the doses could be increased at the investigator's discretion to [citalopram](#) 40 mg/day or mianserin 60 mg/day. At the end of 12 weeks, the average reduction in score on the Montgomery-Asberg Depression Rating Scale (MADRS) was 16 points for [citalopram](#) and 18 points for mianserin. The response rate (a final MADRS score of less than 12) was 57% for [citalopram](#) and 65% for mianserin (not significantly different). For both treatments, patients with [dementia](#) responded less well than those without [dementia](#) (p less than 0.04). The incidence of fatigue and somnolence was greater for mianserin than for [citalopram](#) (p less than 0.01 and p less than 0.03, respectively), whereas insomnia was more frequent with [citalopram](#) than with mianserin (p less than 0.01) [399].

b) [Citalopram](#) 40 to 80 milligrams once daily has been at least as effective as the tetracyclic antidepressant mianserin (60 to 120 milligrams once daily) in patients with [endogenous depression](#) in small double-blind studies of 4 to 6 weeks duration. However, onset of antidepressant effects was more rapid with [citalopram](#) [400] [401]. In one study, [citalopram](#) was more effective than mianserin in a subgroup of patients with nonendogenous depression [401].

c) The incidence of adverse effects was similar with these agents in one study [401] but tended to be greater with [citalopram](#) in the other (eg, dry mouth, increased sweating, headache) [400]. The small numbers of patients evaluated in these studies precludes an adequate comparison of efficacy.

4.6.G] Mirtazapine

4.6.G.1] Depression

a) In a multicenter, double-blind, 8-week study, [mirtazapine](#) was as effective as [citalopram](#), with [mirtazapine](#) possibly having a faster onset of action [419]. Patients with a [major depressive episode](#) were randomized to receive [mirtazapine](#) titrated up to 60 milligrams (mg) daily (n=136) or [citalopram](#) titrated up to 60 mg daily (n=133). Lower doses were allowed if adverse effects occurred. Both groups had significant changes from baseline scores on the Montgomery-Asberg Depression Rating Scale. The magnitude of change from baseline was significantly higher in the [mirtazapine](#) group at day 14 (p=0.002) suggesting a faster onset of action for [mirtazapine](#) than [citalopram](#). At the end of the study both groups had a high percentage of responders: 85% for [mirtazapine](#) and 88% for [citalopram](#). Both treatments also resulted

in improved anxiety as measured by the Hamilton Anxiety Scale. Again at day 14, mirtazapine-treated patients had significantly greater improvements in their anxiety scores as compared to the [citalopram](#) group ($p=0.033$). Both treatments were well-tolerated with only 3.6% of the [mirtazapine](#) group and 3% of the [citalopram](#) group terminating the study due to adverse events. Citalopram-treated patients had more complaints of nausea and sweating. [Mirtazapine](#) patients had more complaints of increased appetite and weight gain. Sedation was similar in both groups 8% for [mirtazapine](#) and 6% for [citalopram](#).

4.6.H] Moclobemide

4.6.H.1] Depression

a) [Citalopram](#) and moclobemide were both effective for [major depression](#) in a randomized, open, 6-week study [413]. [Citalopram](#) 20 milligrams (mg) ($n=20$) was given initially and increased to 40 to 60 mg as needed. Moclobemide 300 mg ($n=20$) was given initially and increased to 450 to 600 mg. The Hamilton Depression Rating Scale scores were significantly decreased during weeks 2 through 6 for the [citalopram](#) group (p less than 0.001) and for the moclobemide group (p less than 0.001). The [citalopram](#) actually had significantly lower scores than the moclobemide group during weeks 4 (p less than 0.02) and 6 (p less than 0.04). Overall side effects were low in both groups.

4.6.I] Paroxetine

4.6.I.1] Late ejaculation

a) [Paroxetine](#) significantly increased the latency time of ejaculation in men with life-long [premature ejaculation](#), whereas [citalopram](#) had very little effect. Thirty men with intravaginal ejaculation times (IELT) of less than 1 minute were given either [paroxetine](#) 20 milligrams (mg) per day or [citalopram](#) 20 mg/day for 5 weeks after receiving half-doses for a week. The geometric mean of IELT increased from 20 to 170 seconds in the [paroxetine](#) group and from 20 to 44 seconds in the [citalopram](#) group (p less than 0.001 for group differences; p less than 0.001 for change from baseline for [paroxetine](#); and $p=0.07$ for change from baseline for [citalopram](#)). Neither drug had clinically relevant effects on sexual desire, arousal, [erectile dysfunction](#), or penile rigidity, although 3 patients in the [paroxetine](#) group reported a slight decrease in sexual desire and penile rigidity. The authors suggested that [paroxetine](#) may be useful for treating [premature ejaculation](#) and that [citalopram](#) may be useful for treating patients in need of a selective serotonin reuptake inhibitor who do not want ejaculation delay [412].

4.6.J] Reboxetine

4.6.J.1] Panic disorder

a) Reboxetine and [citalopram](#) therapies were similarly effective in reducing panic attack severity in patients with [panic disorder](#). In a randomized, single-blind, crossover study, patients with [panic disorder](#) with or without [agoraphobia](#) received reboxetine 4 to 10 milligrams (mg) daily (mean dose, 6.3 mg/day) or [citalopram](#) 20 to 60 mg daily (mean dose, 31.7 mg/day) for 8 weeks and then switched to the other treatment arm for 8 weeks following a 2-week washout period. Response was defined as a score of "very much improved" or "much improved" on the Clinical Global Impression Scale. The response rate was similar between groups, with 82% of patients in the [citalopram](#) group and 54% of reboxetine-treated patients responding at endpoint. Both treatments produced a significant improvement in panic attack severity as measured by the [Panic Disorder Severity Scale](#) (PDSS). Mean PDSS scores improved from 14.5 at baseline to 6.4 at endpoint (p less than 0.001) with no significant between-drug differences being found ($p=NS$). Additionally, there were no significant between-drug differences found in endpoint scores on the Sheehan Patient Rated Anxiety Scale ($p=NS$). However, [citalopram](#) treatment produced greater improvements in depressive symptoms as compared to reboxetine as measured by the Montgomery-Asberg Depression

Rating Scale (MADRS) (mean MADRS score at endpoint, 7.4 for [citalopram](#) vs 11.5 for reboxetine; $p=0.042$). Both medications were well tolerated with dry mouth being the most frequently reported adverse event for both [citalopram](#) (58%) and reboxetine (46%) [421].

4.6.K] Risperidone

4.6.K.1] Dementia - Psychotic disorder

a) [Citalopram](#) reduced agitation and [psychosis](#) scores in hospitalized patients with [dementia](#), while [risperiDONE](#) reduced [psychosis](#) scores but not agitation. In a 12-week, randomized, double-blind study, 103 patients with [dementia](#) of varying etiology were enrolled upon admission to an inpatient geropsychiatric unit for agitation and/or psychotic symptoms. Patients were randomized to receive either [citalopram](#) ($n=53$, titrated to a mean dose of 31.1 mg/day) or [risperiDONE](#) ($n=50$, titrated to a mean dose of 1.35 mg/day). Primary outcomes were symptoms measured with the Neurobehavioral Rating Scale (NBRS) for agitation, and for NBRS for [psychosis](#). Significantly more females were randomized to [risperiDONE](#) ($n=38$) than to [citalopram](#) ($n=25$; $p=0.003$). The [citalopram](#) group had higher total NBRS scores at baseline than the [risperiDONE](#) group (60.3 vs 52.6; $p=0.044$), but baseline NBRS-agitation and NBRS-psychosis scores were not significantly different. In the [citalopram](#) arm, the mean NBRS-agitation scores improved by -1.26 points (95% confidence intervals (CI), -2.527 to -0.001, $p=0.05$) and the mean NBRS-psychosis scores improved by -1.9 points (95% CI, -3.165 to -0.639; p less than 0.004). In the [risperiDONE](#) group, the reduction in mean NBRS-agitation score was not significant (-0.73 points; 95% CI -2.145 to 0.676, $p=0.3$) but the mean NBRS-psychosis score decreased by -2.16 points (95% CI, -3.56 to -0.751; p less than 0.004). There were no significant differences in NBRS score changes between the two groups. The overall dropout rate was 56.3%, with 47.2% of the [citalopram](#) patients and 40% of the [risperiDONE](#) patients completing the trial. The primary reasons for dropouts were similar between the two groups, with psychiatric worsening being most common (28 patients), followed by adverse events (13), and other concomitant medical illness (11). Adverse events were measured with the Udvalg for Kuriske Undersogelser (UKU) side effect scale. At the end of the study, the mean UKU score increased in the [risperiDONE](#) group (2.33; 95% CI, 0.588 to 4.065; p less than 0.01), primarily due to sedation. In the [citalopram](#) group, the mean UKU score did not differ significantly from baseline, and was significantly lower compared with the [risperiDONE](#) group (-2.61, 95% CI; -4.957 to -0.677; p less than 0.011). The study was not designed with a placebo arm due to ethical concerns [411].

6.0] References

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