

DRUGDEX-EV 2193

MICROMEDEX

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DULOXETINE

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0.0] Overview

1] Class

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

Antianxiety
Antidepressant
Central Nervous System Agent
Neuropathic Pain Agent

2] Dosing Information

a) [Duloxetine](#) Hydrochloride

1] Adult

a) Avoid abrupt discontinuation; taper dose gradually; if intolerable symptoms, resume previous dose followed by smaller decreases [1]

1] Diabetic peripheral neuropathy - Pain

a) 60 mg orally once daily; MAX 60 mg orally once daily [4]

2] Fibromyalgia

a) Initial, 30 mg orally once daily for 1 week; increase to usual dosage of 60 mg once daily based on tolerability; MAX 60 mg once daily [4]

3] Generalized anxiety disorder

a) Initial, 60 mg orally once daily; may start at 30 mg orally once daily for 1 week and then increase to 60 mg orally once daily; may increase further by increments of 30 mg once daily; MAX 120 mg orally once daily [1]

4)) Major depressive disorder

a)) Initial, 20 mg orally twice daily up to 60 mg/day (once daily or 30 mg twice daily); maintenance, 60 mg orally once daily; may increase by increments of 30 mg once daily to MAX 120 mg orally once daily [4]

5)) Musculoskeletal pain, Chronic

a)) Initial, 30 mg orally once daily for 1 week; maintenance, 60 mg orally once daily; MAX 60 mg/day [4]

6)) Pain, Chemotherapy-induced - Peripheral nerve disease

a)) 30 mg orally once daily for 1 week, then 60 mg orally once daily (off-label dosage) [26]

7)) Urinary incontinence

a)) 40 mg orally twice daily (off-label dosage) [27][28][29][30]

2)) Pediatric**a)) Generalized anxiety disorder**

1)) (7 years or older) Initial, 30 mg orally once daily for 2 weeks, and may then increase to 60 mg orally once daily; may increase further by increments of 30 mg once daily; MAX 120 mg once daily [1]

3)) Contraindications**a)) Duloxetine Hydrochloride**

1)) Concomitant use with an MAOI, including [linezolid](#) or IV methylene blue, or within 14 days of discontinuing an MAOI; at least 5 days should elapse after discontinuation of [duloxetine](#) before MAOI initiation due to risk of [serotonin syndrome](#) [37]

4)) Serious Adverse Effects**a)) Duloxetine Hydrochloride****1)) Gastrointestinal hemorrhage****2)) Hemorrhage, Abnormal****3)) Hypertensive crisis****4)) Liver failure**

- 5j) [Myocardial infarction](#)
- 6j) Orthostatic hypotension
- 7j) [Serotonin syndrome](#)
- 8j) [Stevens-Johnson syndrome](#)
- 9j) Suicidal thoughts
- 10j) Withdrawal sign or symptom

5j) Clinical Applications

a) [Duloxetine](#) Hydrochloride

1j) FDA Approved Indications

- a) [Diabetic peripheral neuropathy](#) - Pain
- b) [Fibromyalgia](#)
- c) [Generalized anxiety disorder](#)
- d) [Major depressive disorder](#)
- e) Musculoskeletal pain, Chronic

2j) Non-FDA Approved Indications

- a) Pain, Chemotherapy-induced - Peripheral nerve disease
- b) [Urinary incontinence](#)

1.0j Dosing Information

[Drug Properties](#)

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1.1j Drug Properties

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

B) Synonyms

[Duloxetine](#)

[Duloxetine HCl](#)

[Duloxetine Hydrochloride](#)

C) Physicochemical Properties

1j) [Duloxetine](#) Hydrochloride

a)) Molecular Weight**1))** 333.88 [51]**b)) Solubility****1))** Slightly soluble in water [51].**1.2] Storage and Stability****A)) Duloxetine Hydrochloride****1)) Preparation****a)) Nasogastric route****1))** Following NG administration, apple juice may be used to flush tube without compromising the potency of duloxetine from opened capsules [36].**b)) Oral route****1))** Capsules should be swallowed whole and not chewed, crushed, or opened to be sprinkled on food or mixed with liquids [35].**2))** For patients with difficulty swallowing, capsules may be opened and the pellet contents mixed with 30 mL of applesauce or apple juice without compromising the potency of duloxetine when administered within 2 hours; do not mix in chocolate pudding. Do not crush or chew the pellets [36].**3))** May be given with food or on an empty stomach [35].**B)) Duloxetine Hydrochloride****1)) Oral route****a)) Capsule, Delayed Release****1))** Store at controlled room temperature, 25 degrees Celsius (77 degrees Fahrenheit), with excursions permitted between 15 and 30 degrees Celsius (59 and 86 degrees Fahrenheit) [51].**1.3] Adult Dosage****1.3.1] Normal Dosage****1.3.1.A] Important Note****j)** Duloxetine should not be used concomitantly with MAOIs intended to treat psychiatric disorders or with linezolid or IV methylene blue. Do not initiate duloxetine within 14 days of MAOI discontinuation. Do not initiate an MAOI within 5 days of discontinuing duloxetine. Do

not initiate duloxetine in patients being treated with linezolid or IV methylene blue; duloxetine may be resumed 24 hours after the last linezolid or IV methylene blue dose [1].

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

1.3.1.B] Duloxetine Hydrochloride

1.3.1.B.1] Oral route

1.3.1.B.1.a] Diabetic peripheral neuropathy - Pain

1) Usual dosage: 60 mg orally once daily. A lower starting dose may be considered for patients in whom tolerability is a concern [4].

2) Maximum dosage: 60 mg once daily. There is no evidence that higher doses provide additional significant benefit [4].

3) Duration of use: Efficacy beyond 12 weeks of treatment has not been evaluated in placebo-controlled trials [4].

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

1.3.1.B.1.b] Fibromyalgia

1) Usual dosage: 60 mg orally once daily; doses above 60 mg/day do not offer additional clinical benefit and are associated with a higher rate of adverse events [23]

2) Titration: Begin with 30 mg once daily for 1 week and increase to 60 mg/day based on tolerability [23].

3) Duration of use: Base duration of maintenance therapy on clinical response; efficacy was demonstrated for up to 3 months in clinical trials [23]. In one clinical trial, efficacy onset occurred at 3 months and was maintained for 6 months of therapy [34].

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

1.3.1.B.1.c] Generalized anxiety disorder

1) Usual dosage: 60 mg orally once daily without regard to meals [1]

2) Titration: If tolerability is a concern, begin with 30 mg once daily for 1 week and then increase to 60 mg once daily. Dose may be increased further by increments of 30 mg once daily. There is no evidence that doses greater than 60 mg/day provide additional benefit [1].

3) Maximum dose: 120 mg once daily [1]

4) Duration of use: Periodically reassess for appropriate dose and need for continued maintenance treatment [1]

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

1.3.1.B.1.d] Major depressive disorder

1) Initial dosage: 40 mg orally (taken as 20 mg twice daily) to 60 mg/day taken once daily or 30 mg twice daily. Alternatively, if tolerability is a concern, begin with 30 mg once daily for 1 week, then increase to 60 mg once daily [4].

2) Titration: May increase by increments of 30 mg once daily to up to maximum dosage [4].

3) Maintenance dosage: 60 mg orally once daily [4]

4)) Maximum dosage: 120 mg orally once daily; however, there is no evidence that doses greater than 60 mg/day confer any added benefits [4].

5)) Duration of use: Reassess dosage and need for maintenance therapy in patients periodically [23].

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

1.3.1.B.1.e) Musculoskeletal pain, Chronic

1)) Initial dosage: 30 mg orally once daily for 1 week [4]

2)) Titration: May increase to 60 mg orally once daily. Even if patients are not responding to treatment, doses higher than 60 mg/day do not afford additional benefit and are associated with a higher frequency of adverse events [4].

3)) Duration of use: Efficacy beyond 13 weeks has not been established [4].

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

1.3.1.B.1.f) Pain, Chemotherapy-induced - Peripheral nerve disease

1)) Off-label dosage: 30 mg orally once daily for 1 week, then 60 mg orally once daily for 4 weeks [26].

1.3.1.B.1.g) [Urinary incontinence](#)

1)) Off-label dosage: 40 mg orally twice daily [27][28][29][30]

1.3.1.B.1.h) Withdrawal of Therapy

1)) Abrupt discontinuation of [duloxetine](#) has lead to symptoms such as dizziness, nausea, headache, paresthesia, vomiting, irritability, and anxiety. Gradual reduction of the dose, rather than abrupt discontinuation, is recommended. If intolerable symptoms occur following a decrease in dose, consider resuming the previous dose and using smaller decreases [1].

1.3.2] Dosage in [Renal Failure](#)

A) [Duloxetine](#) Hydrochloride

1)) Severe impairment (CrCl less than 30 mL/min): Avoid use [1]

1.3.3] Dosage in [Hepatic Insufficiency](#)

A) [Duloxetine](#) Hydrochloride

1)) [Chronic liver disease](#) or [cirrhosis](#): Avoid use [1]

1.3.4] Dosage in Geriatric Patients

A) [Duloxetine](#) Hydrochloride

1)) [Generalized Anxiety Disorder](#)

a)) Begin with 30 mg orally once daily for 2 weeks and then increase to target dose 60 mg orally once daily. Increase further, if needed, by increments of 30 mg once daily to maximum 120 mg once daily [1].

1.3.6] Dosage in Other Disease States

A) [Duloxetine](#) Hydrochloride

- 1) No adjustment is necessary on the basis of gender [1].
- 2) No adjustment is necessary in smokers [1].

1.4] Pediatric Dosage

1.4.1] Normal Dosage

1.4.1.A] Important Note

j) Duloxetine should not be used concomitantly with MAOIs intended to treat psychiatric disorders or with linezolid or IV methylene blue. Do not initiate duloxetine within 14 days of MAOI discontinuation. Do not initiate an MAOI within 5 days of discontinuing duloxetine. Do not initiate duloxetine in patients being treated with linezolid or IV methylene blue; duloxetine may be resumed 24 hours after the last linezolid or IV methylene blue dose [1].

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

1.4.1.B] [Duloxetine](#) Hydrochloride

1.4.1.B.1] [Generalized anxiety disorder](#)

- a) Usual dosage: 30 to 60 mg orally once daily [1]
 - b) Titration: Begin with 30 mg orally once daily for 2 weeks; may increase to 60 mg once daily; may increase further by 30-mg increments once daily [1]
 - c) Maximum dose: 120 mg once daily [1]
- See Drug Consult reference: Class Comparison: SSRIs and Serotonin [Norepinephrine](#) Reuptake Inhibitors (SNRIs) (Selected)

2.0] Pharmacokinetics

[Onset and Duration](#)

[Drug Concentration Levels](#)

[ADME](#)

2.1] Onset and Duration

A) Onset

1) [Duloxetine](#) Hydrochloride

a) Initial Response

- 1) Depression, oral: within 2 weeks [156].

a) Patients treated with duloxetine experienced significant improvements in the 17-item Hamilton Depression Rating Scale (HAM-D-17) compared to placebo-treated patients by the second week of treatment ($p < 0.05$). In a pooled analysis of two 9-week trials, which compared duloxetine 60 mg orally once daily ($n = 251$) with placebo ($n = 261$) in the treatment of major depressive disorder, rapid improvements

in the individual symptoms of depressed mood, guilt, suicidal ideation, work/activities, and psychic anxiety were demonstrated by the end of the first week with duloxetine treatment [156].

b)) Peak Response

1)) Platelet serotonin uptake inhibition, oral: 4 to 6 hours [157][158].

a)) Represents time to maximal or near-maximal inhibition in platelets from healthy subjects treated with 20 mg daily. This pharmacodynamic parameter may correlate with CNS activity [159][157], although its usefulness for clinical monitoring has not been determined.

B)) Duration

1)) Duloxetine Hydrochloride

a)) Multiple Dose

1)) Platelet serotonin uptake inhibition, oral: at least 7 days [157][158].

a)) Represents duration of inhibition after the last dose of a regimen of 20 mg daily for one week. Effects persisted after plasma levels of duloxetine were no longer detectable.

2.2) Drug Concentration Levels

A)) Duloxetine Hydrochloride

1)) Therapeutic Drug Concentration

a)) Pediatrics steady-state concentrations: 30% lower compared with adults [1]

1)) Average steady state concentrations of duloxetine observed in children and adolescents were about 30% lower than that observed for adults. However, overall steady state concentrations were comparable among children, adolescents and adults, and average steady state concentrations in children and adolescents did not exceed and were within the concentration range observed for adults [1].

2)) Peak Concentration

a)) Oral: 13 nanograms/mL (ng/mL; 44 nanomol/L (nmol/L); 20-mg dose) [160].

1)) Following single oral doses of 20 mg, a mean peak duloxetine plasma level of 13 ng/mL (44 nmol/L) was reported; plasma levels of the desmethyl metabolite (active) were less than 2 ng/mL [160].

3) Time to Peak Concentration**a) Oral: 6 to 10 hours [51][161][160].**

1) Maximal plasma concentrations (C_{max}) of duloxetine occur 6 hours post dose, but are delayed from 6 to 10 hours if taken in the presence of food [51].

2) Values represent times to peak levels over the range of 10 to 40 mg once daily, with a tendency toward prolonged times with higher doses. Duloxetine exhibits linear pharmacokinetics [162].

3) Steady-State: Steady-state has been reached in 3 to 5 days with 20 to 40 mg twice-daily, and after 7 days with 20 mg once daily in healthy subjects; with the latter regimen, the mean peak plasma level at steady-state was 21 nanograms/mL (ng/mL; 71 nanomol/L (nmol/L); 15 to 32 ng/mL (50 to 110 nmol/L)) [161].

4) During oral administration of 20 and 30 mg twice daily in healthy subjects, mean steady-state trough plasma levels were approximately 15 ng/mL (50 nmol/L) and 20 ng/mL (70 nmol/L), respectively, in one study [162].

4) Area Under the Curve**a) Renal Impairment**

1) After a single 60-milligram dose of duloxetine, patients with end stage renal disease receiving chronic intermittent hemodialysis had C_{max} and AUC values approximately 100% greater than those of patients with normal renal function. The AUCs of 4-hydroxy duloxetine glucuronide and 5-hydroxy, 6-methoxy duloxetine sulfate, the major circulating metabolites, which are largely excreted in urine, were approximately 7- to 9-fold higher and would be expected to increase further with multiple dosing [51].

b) Hepatic Impairment

1) After a single 20-milligram dose of duloxetine, 6 cirrhotic patients with moderate liver impairment (Child-Pugh Class B) showed a 5-fold increase in AUC compared to non-cirrhotic patients [51].

c) Geriatric

1) After a single 40 mg dose of duloxetine, AUC values were approximately 25% higher among elderly women (65 to 77 years) compared younger women (32 to 50 years), but there was no difference observed for C_{max} [1].

2.3] ADME**2.3.1] Absorption****A) Duloxetine Hydrochloride**

1) Bioavailability

a) Oral: 30% to 80% [163].

1) The absolute oral bioavailability of a 60-mg dose averaged 50%, but ranged from 30% to 80% [163].

b) There is a median 2-hour lag until absorption begins [51].

c) With an evening dose, there is a 3-hour delay in absorption and a 30% increase in apparent clearance, compared to a morning dose [51].

2) Effects of Food

a) slows absorption

b) Food does not affect C_{max} but delays time to peak concentration from 6 to 10 hours and reduces extent of absorption by 10% [51].

2.3.2] Distribution**A) Distribution Sites****1) Duloxetine Hydrochloride**

a) Protein Binding

1) greater than 90%, primarily to albumin and alpha-1-acid glycoprotein [51].

b) Other Distribution Sites

1) Saliva, 0% [160].

B) Distribution Kinetics**1) Duloxetine Hydrochloride**

a) Volume of Distribution

1) 1640 L [51].

2.3.3] Metabolism**A) Metabolism Sites and Kinetics****1) Duloxetine Hydrochloride**

a) LIVER, extensive [162][161].

1)) The major metabolic pathways involve oxidation of the naphthyl ring followed by conjugation and further oxidation involving 2 cytochrome P450 (CYP) isozymes, CYP1A2 and CYP2D6 [51].

B)) Metabolites

1)) Duloxetine Hydrochloride

a)) 4-hydroxy duloxetine glucuronide (inactive) [51][163][164].

1)) Approximately 47% of a given dose is conjugated to 4-hydroxy duloxetine glucuronide, which lacks pharmacologic activity since the inhibition constant (K_i) values for serotonin and norepinephrine uptake inhibition are much higher than the parent compound duloxetine [163].

b)) 5-hydroxy-6-methoxy duloxetine sulfate (inactive) [51][163][164].

1)) Approximately 22% of a given dose is conjugated to 5-hydroxy-6-methoxy duloxetine sulfate, which lacks pharmacologic activity since the inhibition constant (K_i) values for serotonin and norepinephrine uptake inhibition are much higher than the parent compound duloxetine [163].

2.3.4] Excretion

A)) Kidney

1)) Duloxetine Hydrochloride

a)) Renal Excretion (%)

1)) 70% [51].

a)) Excreted mainly as metabolites; only trace amounts (less than 1% of the dose) as unchanged drug [51].

B)) Feces

1)) Duloxetine Hydrochloride

a)) 20% [51].

1)) Approximately 20% of duloxetine is excreted in the feces [51]. It is unclear from available data if this represents unabsorbed drug or biliary excretion.

C)) Total Body Clearance

1)) Duloxetine Hydrochloride

a)) 114 L/hr [162].

- 1)) Total clearance was 114 L/hr after oral doses in healthy subjects [162].
- 2)) Cirrhotic (Child-Pugh Class B) patients (n=6) had a clearance of 15% that of age- and gender-matched healthy subjects after a 20-milligram dose of duloxetine [1][165].
- 3)) Based on a population pharmacokinetic analysis, it is predicted that clearance decreases by 1% for each year of age between 25 and 75 years [1].

2.3.5] Elimination Half-life

A)) Parent Compound

1)) Duloxetine Hydrochloride

a)) 12 hours (range: 8 to 17 hours) [1]

- 1)) Duloxetine pharmacokinetics are dose proportional over the therapeutic range and the elimination half-life is 12 hours (range: 8 to 17 hours) [1].
- 2)) The elimination half-life of duloxetine in 6 cirrhotic patients with moderate liver impairment (Child-Pugh class B) showed a significantly longer half-life (47.8 hours vs 13.5 hours, $p < 0.05$) compared to healthy subjects [165].
- 3)) After a single 40 mg dose of duloxetine, the elimination half-life was approximately 4 hour longer among elderly women (65 to 77 years) compared with younger women (32 to 50 years) [1].

3.0] Cautions

[Contraindications](#)

[Precautions](#)

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

[Drug Interactions](#)

3.0.A] Black Box WARNING

Duloxetine Hydrochloride

Oral (Capsule, Delayed Release)

Antidepressants increased the risk of suicidal thinking and behavior in children, adolescents, and young adults in short-term studies. These studies did not show an increase in the risk of suicidal thoughts and behavior with antidepressant use in patients over age 24; there was a reduction in risk with antidepressant use in patients aged 65 or older. In patients of all ages who are started on antidepressant therapy monitor closely for worsening, and for emergence of suicidal thoughts and behaviors. Advise families and caregivers of the need for close observation and communication with the prescriber [20].

3.1] Contraindications

A) Duloxetine Hydrochloride

1J) Concomitant use with an MAOI, including [linezolid](#) or IV methylene blue, or within 14 days of discontinuing an MAOI; at least 5 days should elapse after discontinuation of [duloxetine](#) before MAOI initiation due to risk of [serotonin syndrome](#) [37]

3.2] Precautions

A) Duloxetine Hydrochloride

1J) Black Box Warning: Increased risk of suicidal thinking and behavior in children, adolescents, and young adults with major depressive and other psychiatric disorders; especially during first few months of therapy or following changes in dosage; monitoring recommended [37]

2J) Beers Criteria: Avoid use in older adults with a history of falls or fractures (unless safer alternatives are not available) as ataxia and impaired psychomotor function may occur. If prescribed in older adults, use caution as SIADH or [hyponatremia](#) may occur or be exacerbated. Monitor sodium levels when starting or changing doses [2].

3J) Cardiovascular: Orthostatic hypotension and syncope have been reported, especially in first week of therapy, after dose increases, with concomitant use of antihypertensives or potent CYP1A2 inhibitors, and with [duloxetine](#) doses above 60 mg/day; dose reduction or discontinuation may be necessary [20]

4J) Cardiovascular: Blood pressure increases have been reported; monitoring recommended [37]

5J) Dermatologic: Severe skin reactions, including [Stevens-Johnson syndrome](#) and [erythema multiforme](#), may occur; discontinue if signs of hypersensitivity occur and no other etiology has been identified [37]

6J) Discontinuation: Abrupt discontinuation may increase risk of serious discontinuation symptoms; gradual dose reduction recommended[37]

7J) Endocrine and Metabolic: [Hyponatremia](#), in many case due to SIADH, has been reported with other SSRI and serotonin [norepinephrine](#) reuptake inhibitors (SNRI), especially in volume-depleted patients, elderly, or with concomitant use of diuretics; discontinue if symptoms develop [37]

8J) Endocrine and Metabolic: Use caution in patients with [diabetes](#) as glycemic control may worsen [37]

9J) Falls: Falls with serious consequences including bone fractures and hospitalizations have been reported, with an increased risk in presence of orthostatic hypotension and in elderly patients, with use of multiple medications, medical comorbidities, and gait disturbances; dose reduction or discontinuation may be necessary [20]

10J) Gastrointestinal: Conditions that slow gastric emptying may affect stability of enteric coating [37]

11J) Hematologic: Bleeding events, including life-threatening hemorrhages, have been reported with SSRIs and serotonin [norepinephrine](#) reuptake inhibitors; increased risk possible with concomitant use of NSAIDs, [aspirin](#), [warfarin](#), and other anticoagulants [37]

12J) Hepatic: [Hepatotoxicity](#), including [hepatitis](#), [jaundice](#), elevated transaminase levels, and fatal [liver failure](#), has been reported; discontinue if patient develops [jaundice](#) or other evidence of [liver dysfunction](#) and resume only if no other etiology has been identified [37]

- 13)) Hepatic: Avoid use in patients with [chronic liver disease](#) or [cirrhosis](#) [37]
- 14)) Neurologic: Use caution in patients with history of seizures [37]
- 15)) Ophthalmic: Pupillary dilation that occurs with antidepressants may cause an angle closure attack in patients with anatomically narrow angles without a patent [iridectomy](#) [37]
- 16)) Psychiatric: [Hypomania](#) or mixed or [manic episode](#) may occur in patients at risk for [bipolar disorder](#); baseline screening recommended [37]
- 17)) Renal: Avoid use in patients with severe [renal impairment](#) (CrCl less than 30 mL/min) [37]
- 18)) Renal: Urinary retention, including cases that required hospitalization and/or [catheterization](#), has been reported [37]
- 19)) [Serotonin syndrome](#): [Serotonin syndrome](#) has been reported, especially with concomitant use of other serotonergic drugs (eg, triptans, tricyclic antidepressants, [fentanyl](#), [lithium](#), [tramadol](#), tryptophan, [buspirone](#), [amphetamines](#), St. John's wort), MAOIs (eg, [linezolid](#), IV methylene blue), or other drugs that interfere with metabolism of serotonin; monitoring recommended [38]
- 20)) Concomitant use: Avoid heavy alcohol intake; risk of severe [liver injury](#) [37]
- 21)) Concomitant use: Avoid concomitant use of [thioridazine](#) [37]
- 22)) Concomitant use: Avoid potent CYP1A2 inhibitors, including [fluvoxamine](#), [cimetidine](#), and quinolone antimicrobials such as [ciprofloxacin](#) and [enoxacin](#) [37]

3.3] Adverse Reactions

3.3.1] Cardiovascular Effects

3.3.1.A] [Duloxetine Hydrochloride](#)

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

a)) Incidence: 2% [20]

b)) Adult Clinical Trials

- 1)) Diabetic peripheral nerve pain, [fibromyalgia](#), or chronic musculoskeletal pain (oral route): 2% vs 1% with placebo [20]

3.3.1.A.2] [Hypertensive crisis](#)

a)) [Hypertensive crisis](#) has been reported with [duloxetine](#) during postmarketing experience [40].

3.3.1.A.3] [Increased blood pressure](#)

- a)) In clinical trials of all indications, [duloxetine](#) hydrochloride treatment led to a mean blood pressure increase of 0.5 mmHg in systolic and 0.8 mmHg in diastolic blood pressures compared with mean decreases of 0.6 mmHg in systolic and 0.4 mmHg in diastolic pressure in patients treated with placebo. Blood pressure should be monitored prior to therapy initiation and periodically during treatment [40].
- b)) Small increases in systolic/diastolic blood pressure and decreases in heart rate compared with placebo have been observed with twice-daily dosing in recumbent healthy subjects; no significant effects on blood pressure or heart rate were seen in the standing position [41].

3.3.1.A.4] Increased heart rate

- a) Incidence: Pediatric, up to 2% [1]
- b) Pediatric Clinical Trials

- 1) Major depressive disorder or generalized anxiety disorder (oral route): less than 2%[1]

3.3.1.A.5] Myocardial infarction

- a) Incidence: 0.01% to 0.001%[40]
- b) Myocardial infarction was reported in 0.01% to 0.001% of patients during the premarketing and postmarketing clinical trial evaluation of duloxetine [40]

3.3.1.A.6] Orthostatic hypotension

- a) General Information

- 1) Usually occurs within the first week of therapy [40].

- 2) Risk of blood pressure decrease is especially seen in patients taking duloxetine at doses above 60 mg daily or who are on concomitant medications that induce orthostatic hypotension (eg, antihypertensives) or are potent CYP1A2 inhibitors (eg, fluvoxamine, cimetidine, or quinolone antimicrobials [eg, ciprofloxacin, enoxacin]) [40].

- 3) Risk of falling increases steadily with age and seems to be related to degree of orthostatic decrease in blood pressure as well as other underlying risks [20].

- b) Prevention and Management

- 1) If patient experiences orthostatic hypotension, falls, or syncope, consider dose reduction or therapy discontinuation [20].

- c) Adult Clinical Trials

- 1) Orthostatic hypotension, falls, and syncope have been reported; no incidence given [20]

3.3.1.A.7] Palpitations

- a) Incidence: Up to 2% [20][1]
- b) Adult Clinical Trials

- 1) Major depressive disorder or generalized anxiety disorder (oral route): 2% vs 1% with placebo [20]

- c) Pediatric Clinical Trials

- 1) Major depressive disorder or generalized anxiety disorder (oral route): Less than 2%[1]

3.3.1.A.8] Supraventricular arrhythmia

- a) Supraventricular arrhythmias have been reported with duloxetine during postmarketing experience [40].

3.3.1.A.9] Syncope

- a) General Information

1) Usually occurs within the first week of therapy [40].

2) Risk of blood pressure decrease is especially seen in patients taking [duloxetine](#) at doses above 60 mg daily or who are on concomitant medications that induce orthostatic hypotension (eg, antihypertensives) or are potent CYP1A2 inhibitors (eg, [fluvoxamine](#), [cimetidine](#), or quinolone antimicrobials [eg, [ciprofloxacin](#), [enoxacin](#)]) [40].

3) Risk of falling increases steadily with age and seems to be related to degree of orthostatic decrease in blood pressure as well as other underlying risks [20].

b) Adult Clinical Trials

1) Orthostatic hypotension, falls, and syncope have been reported; no incidence given [20]

3.3.2] Dermatologic Effects

3.3.2.A] [Duloxetine Hydrochloride](#)

3.3.2.A.1] Diaphoresis

a) Incidence: Up to 6% [20][1]

b) General Information

1) Dose-related effect [20]

c) Adult Clinical Trials

1) All indications (oral route): 6% vs 1% with placebo [20]

2) [Diabetic peripheral neuropathy](#), [fibromyalgia](#), or chronic musculoskeletal pain (oral route): 6% vs 1% with placebo [20]

3) [Major depressive disorder](#) or [generalized anxiety disorder](#) (oral route): 6% vs 2% with placebo [20]

d) Pediatric Clinical Trials

1) [Major depressive disorder](#) or [generalized anxiety disorder](#) (oral route): Less than 2% [1]

3.3.2.A.2] Flushing

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

b) Adult Clinical Trials

1) [Diabetic peripheral neuropathy](#), [fibromyalgia](#), or chronic musculoskeletal pain (oral route): 3% vs 1% with placebo [40]

c) Pediatric Clinical Trials

1) [Major depressive disorder](#) or [generalized anxiety disorder](#) (oral route): Less than 2% [1]

3.3.2.A.3] [Stevens-Johnson syndrome](#)

a) Severe skin reactions, including [Stevens-Johnson syndrome](#), may occur with [duloxetine](#) therapy. The incidence of [Stevens-Johnson syndrome](#) associated with [duloxetine](#) therapy exceeds the general population background incidence rate (1 to 2 cases per million person years). Discontinue treatment

with duloxetine if blisters, peeling rash, mucosal erosions, or other signs of hypersensitivity with no other identifiable etiology emerge [40].

3.3.3] Endocrine/Metabolic Effects

3.3.3.A] Duloxetine Hydrochloride

3.3.3.A.1] Decrease in height

a) General Information

1) A mean decrease of 1% in height percentile (2% in children 7 to 11 years old and 0.3% in adolescents age 12 to 17 old) has been reported [1].

b) Prevention and Management

1) Monitor height and weight regularly in children and adolescents [1].

3.3.3.A.2] High glucose level in blood

a) There was an increase in mean fasting blood glucose of 12 mg/dL (0.67 mmol/L) in duloxetine-treated patients compared with a decrease of 11.5 mg/dL (0.638 mmol/L) in patients receiving only routine care, according to a 52-week clinical trial of patients with neuropathic pain associated with diabetic peripheral neuropathy [4].

b) Based on pooled data from three 12-week, double-blind, randomized, placebo-controlled trials (n=1024), each followed by a 52-week, open-label extension phase (n=867), duloxetine therapy was associated with modest increases in fasting plasma glucose (FPG) among patients treated for diabetic peripheral neuropathy (DPN) pain. During the 12-week acute phase, patients were randomized to receive placebo (n=339) or duloxetine 60 mg once or twice daily (n=685). Upon completion of the 12-week treatment, patients were then re-randomized in a 2:1 ratio during the extension phase to either duloxetine 60 mg twice daily (n=580) or investigator-driven routine care (n=287), such as gabapentin, venlafaxine, or amitriptyline. The study population had about 4 years history of DPN, and more than 88% had type 2 diabetes mellitus. The baseline FPG and HbA1C was 181 mg/dL (10.1 mmol/L) and 7.8%, respectively. Duloxetine therapy was associated with increases in FPG compared with placebo during the acute phase (9 mg/dL (0.5 mmol/L) vs -2 mg/dL (-0.11 mmol/L); p=0.064), as well as increases relative to routine care during the extension phase (12 mg/dL (0.67 mmol/L) vs -11.5 mg/dL (-0.64 mmol/L); p less than 0.001). However, the changes in HbA1C associated with duloxetine was significantly different from routine care only during the extension phase (0.52% vs 0.19%; p less than 0.001) [44].

3.3.3.A.3] Hyponatremia

a) Summary

1) Hyponatremia has been associated with duloxetine therapy. Serum sodium levels lower than 110 mmol/L have been reported and were reversible upon duloxetine discontinuation. In many cases hyponatremia has been the result of the syndrome of inappropriate antidiuretic hormone secretion (SIADH). The elderly, patients taking diuretics, or volume depleted patients are at greater risk of hyponatremia. Discontinuation of duloxetine therapy should be considered in patients exhibiting symptomatic hyponatremia [4].

b) Hyponatremia developed in 5 depressed patients after approximately 1 week of a dose increase to 90 mg/day or 120 mg/day of duloxetine. The 5 patients (35 to 70 years old) had a history of recurrent major depressive episodes and were in treatment for a severe acute episode. Duloxetine was initiated

at 30 mg/day followed by dose increases to 60 mg/day after 3 to 5 days. The dose was subsequently increased to 90 mg/day or 120 mg/day, after 3 to 4 weeks, due to lack of response or partial response. Other medications were [lorazepam](#) and zopiclone. Serum osmolality, and sodium and potassium levels were normal on admission. One week after the dose increase, patients developed fatigue, lethargy, and headache, and laboratory analyses revealed [hyponatremia](#) in all patients. [Duloxetine](#) was discontinued in 4 patients and the dose reduced to 60 mg/day in 1 patient. Patients were also placed on water restriction (less than 1200 mL/day), and the intake of [sodium chloride](#) was increased by dietary measures in 1 patient and salt tablets in 2 patients. Symptoms of [hyponatremia](#) and serum sodium concentrations resolved within 2 weeks. Other causes for [hyponatremia](#) such as advanced age, thiazide diuretics, [polypharmacy](#), or other disease states ([renal insufficiency](#), [adrenal insufficiency](#), [hypothyroidism](#), tumors, respiratory disease, or acute [central nervous system diseases](#)) were ruled out [45].

c) In a case report, a 48-year-old woman developed syndrome of [inappropriate antidiuretic hormone secretion](#) (SIADH) with [hyponatremia](#) and seizures when administered [duloxetine](#). The patient was admitted to the hospital for acute severe headache, and upon psychiatric evaluation was diagnosed with minor depression and administered [duloxetine](#) 30 mg twice daily. Two days later, she developed 2 generalized seizures, was afebrile, comatose, and her pupils were dilated and sluggishly reactive. Blood analysis revealed serum sodium level of 103 mEq/L (103 mmol/L), and a BUN of 6 mg/dL (2 mmol/L). [Duloxetine](#) was discontinued and the patient was diagnosed with SIADH (urinary sodium 118 mEq/L (118 mmol/L), serum osmolality 215 milliosmoles/kilogram (mOsm/kg) H₂O, and [urine osmolality](#) 450 mOsm/kg H₂O). The patient was inadvertently rechallenged with [duloxetine](#) on days 3 and 4, which reproduced her [hyponatremia](#) (serum sodium levels 120 mEq/L (120 mmol/L) on day 3, and 98 mEq/L (98 mmol/L) on day 4) and she had 1 additional seizure. [Duloxetine](#) was again discontinued and within 2 days the patient regained consciousness and was uneventfully discharged 7 days later [43].

3.3.3.A.4] Syndrome of [inappropriate antidiuretic hormone secretion](#)

a) [Hyponatremia](#) has been associated with [duloxetine](#) therapy. Serum sodium levels lower than 110 mmol/L have been reported and were reversible upon [duloxetine](#) discontinuation. In many cases, [hyponatremia](#) has been the result of the syndrome of [inappropriate antidiuretic hormone secretion](#) (SIADH). Patients who are elderly, are taking diuretics, or are volume-depleted are at greater risk of [hyponatremia](#). Discontinuation of [duloxetine](#) therapy should be considered in patients exhibiting symptomatic [hyponatremia](#) [4].

b) In a case report, a 48-year-old woman developed syndrome of [inappropriate antidiuretic hormone secretion](#) (SIADH) with [hyponatremia](#) and seizures when administered [duloxetine](#). The patient was admitted to the hospital for acute severe headache, and upon psychiatric evaluation was diagnosed with minor depression and administered [duloxetine](#) 30 mg twice daily. Two days later, she developed 2 generalized seizures, was afebrile, comatose, and her pupils were dilated and sluggishly reactive. Blood analysis revealed serum sodium level of 103 mEq/L (103 mmol/L), and a BUN of 6 mg/dL (2 mmol/L). [Duloxetine](#) was discontinued, and the patient was diagnosed with SIADH (urinary sodium 118 mEq/L (118 mmol/L), serum osmolality 215 milliosmoles/kilogram (mOsm/kg) H₂O, and [urine osmolality](#) 450 mOsm/kg H₂O). The patient was inadvertently rechallenged with [duloxetine](#) on days 3 and 4, which reproduced her [hyponatremia](#) (serum sodium levels 120 mEq/L (120 mmol/L) on day 3, and 98 mEq/L (98 mmol/L) on day 4) and she had 1 additional seizure. [Duloxetine](#) was again discontinued and within 2 days the patient regained consciousness and was uneventfully discharged 7 days later [43].

3.3.3.A.5] Weight loss

a) Incidence: Adult, 2% [1]; pediatric, 14% [4]

b) General Information

1) Weight loss with [duloxetine](#) in adults averaged 0.5 to 0.6 kg compared with a weight gain of 0.2 kg in placebo-treated patients [4].

2) In pediatric clinical trials, the average weight loss over 10 weeks was 0.1 kg compared to a 0.9 kg weight gain with placebo [1].

c) Prevention and Management

1) Monitor weight and height regularly in children and adolescents [1].

d) Adult Clinical Trials

1) [Major depressive disorder](#) and [generalized anxiety disorder](#) (oral route): 2% vs less than 1% with placebo [4]

e) Pediatric Clinical Trials

1) [Major depressive disorder](#) or [generalized anxiety disorder](#) (oral route): at least 3.5% weight loss, 14% vs 6% with placebo [1]

3.3.4] Gastrointestinal Effects

3.3.4.A] [Duloxetine Hydrochloride](#)

3.3.4.A.1] Abdominal pain

a) Incidence: 5% [20] to 13% [1]

b) General Information

1) Included abdominal pain, abdominal discomfort, abdominal pain lower, abdominal pain upper, abdominal tenderness, or gastrointestinal pain [20]

c) Adult Clinical Trials

1) All indications (oral route): 5% vs 4% with placebo [20]

2) [Diabetic peripheral neuropathy](#), [fibromyalgia](#), or chronic musculoskeletal pain (oral route): 5% vs 4% with placebo [20]

3) [Major depressive disorder](#) or [generalized anxiety disorder](#) (oral route): 5% vs 4% with placebo [20]

d) Pediatric Clinical Trials

1) [Major depressive disorder](#) or [generalized anxiety disorder](#) (oral route): 13% vs 10% with placebo [1]

3.3.4.A.2] Constipation

a) Incidence: 9% to 10% [20]

b) General Information

1) Dose-related effect [20]

c) Adult Clinical Trials

1) All indications (oral route): 9% vs 4% with placebo [20]

2) [Diabetic peripheral neuropathy](#), [fibromyalgia](#), or chronic musculoskeletal pain (oral route): 10% vs 3% with placebo [20]

3) [Major depressive disorder](#) or [generalized anxiety disorder](#) (oral route): 9% vs 4% with placebo [20]

3.3.4.A.3] Decrease in appetite

a) Incidence: 6% [20] to 10% [1]

b) General Information

1) Dose-related effect [20]

c) Adult Clinical Trials

1) All indications (oral route): 7% vs 2% with placebo [20]

2) [Diabetic peripheral neuropathy](#), [fibromyalgia](#), or chronic musculoskeletal pain (oral route): 8% vs 1% with placebo [20]

3) [Major depressive disorder](#) or [generalized anxiety disorder](#) (oral route): 6% vs 2% with placebo [20]

d) Pediatric Clinical Trials

1) [Major depressive disorder](#) or [generalized anxiety disorder](#) (oral route): 10% vs 5% with placebo [1]

3.3.4.A.4] Diarrhea

a) Incidence: 6% [1] to 9% [20]

b) Adult Clinical Trials

1) All indications (oral route): 9% vs 6% with placebo [40]

2) [Diabetic peripheral neuropathy](#), [fibromyalgia](#), or chronic musculoskeletal pain (oral route): 9% vs 5% with placebo [20]

3) [Major depressive disorder](#) or [generalized anxiety disorder](#) (oral route): 9% vs 6% with placebo [20]

c) Pediatric Clinical Trials

1) [Major depressive disorder](#) or [generalized anxiety disorder](#) (oral route): 6% vs 3% with placebo [1]

3.3.4.A.5] [Gastrointestinal hemorrhage](#)

a) Case reports and epidemiological studies have shown that drugs which interfere with serotonin reuptake (eg, SSRIs, serotonin [norepinephrine](#) reuptake inhibitors [SNRIs]) have been associated with an increased incidence of [gastrointestinal bleeding](#). Bleeding events, including ecchymoses, [hematomas](#), epistaxes, [petechiae](#), [gastrointestinal bleeding](#), and life-threatening hemorrhages have been reported with SSRI and SNRI use. Rare cases of hematochezia and melena have been reported in patients treated with [duloxetine](#) in clinical trials [40].

3.3.4.A.6] Lymphocytic-plasmacytic colitis

a) A 50-year-old woman developed lymphocytic colitis 6 weeks after duloxetine initiation for the management of chronic depression that later resolved within 2 weeks of duloxetine discontinuation. Concurrent medications included gabapentin, levothyroxine, calcium carbonate, vitamins D and E, and folic acid. Antidepressant treatment with sertraline was switched to duloxetine, and 6 weeks later she presented for treatment of mild abdominal pain, bloating, and 6 to 8 episodes of watery diarrhea daily with occasional nocturnal diarrhea. Physical examination, lab tests, and colonoscopy were normal; however, fecal culture was positive for lymphocytes, and a colon biopsy revealed markedly increased intraepithelial lymphocytes, a typical feature of lymphocytic colitis. Upon discontinuation of duloxetine, symptoms disappeared within 2 weeks and resolution was sustained at a 6-week follow-up. The Beaugerie and Pardi scoring system for drug microscopic colitis was applied and reported duloxetine to have an intermediate likelihood of causing lymphocytic colitis. The authors recommend discontinuing duloxetine in patients with suspected lymphocytic colitis [47].

3.3.4.A.7] Melena

a) Rare cases of hematochezia and melena have been reported in patients treated with duloxetine in clinical trials. Case reports and epidemiological studies have shown that drugs which interfere with serotonin reuptake (eg, SSRIs, serotonin norepinephrine reuptake inhibitors (SNRIs)) have been associated with an increased incidence of gastrointestinal bleeding. Bleeding events, including ecchymoses, hematomas, epistaxes, petechiae, gastrointestinal bleeding, and life-threatening hemorrhages have been reported with SSRI and SNRI use [40].

3.3.4.A.8] Nausea

a) Incidence: 18% [1] to 23% [20]

b) General Information

1) Dose-related effect [20]

c) Adult Clinical Trials

1) All indications (oral route): 23% vs 8% with placebo [20]

2) Diabetic peripheral nerve pain, fibromyalgia, or chronic musculoskeletal pain (oral route): 23% vs 7% with placebo [20]

3) Major depressive disorder or generalized anxiety disorder (oral route): 23% vs 8% with placebo [20]

d) Pediatric Clinical Trials

1) Major depressive disorder or generalized anxiety disorder (oral route): 18% vs 8% with placebo [1]

3.3.4.A.9] Pain in throat

a) Incidence: Pediatric, 4% [1]

b) Pediatric Clinical Trials

1) Major depressive disorder or generalized anxiety disorder (oral route): Oropharyngeal pain, 4% vs 2% with placebo [1]

3.3.4.A.10] Pancreatitis, acute**a) General Information**

1) Temporally related to duloxetine hydrochloride [46]

b) Postmarketing

1) Has been reported [46].

3.3.4.A.11] Taste sense altered

a) Dysgeusia was a frequently reported adverse event, occurring in at least 0.01% of patients, during premarketing and postmarketing clinical trial evaluation of duloxetine [40].

3.3.4.A.12] Vomiting

a) Incidence: 3% [20] to 9% [1]

b) Adult Clinical Trials

1) Diabetic peripheral neuropathy, fibromyalgia, or chronic musculoskeletal pain (oral route): 3% vs 2% with placebo [40]

2) Major depressive disorder or generalized anxiety disorder (oral route): 4% vs 2% with placebo [20]

c) Pediatric Clinical Trials

1) Major depressive disorder or generalized anxiety disorder (oral route): 9% vs 4% with placebo [1]

3.3.4.A.13] Xerostomia

a) Incidence: Adult, 11% to 14% [20]; pediatric, 2% [1]

b) Adult Clinical Trials

1) All indications (oral route): 13% vs 5% with placebo [1]

2) Diabetic peripheral neuropathy, fibromyalgia, or chronic musculoskeletal pain (oral route): 11% vs 3% with placebo [20]

3) Major depressive disorder or generalized anxiety disorder (oral route): 14% vs 6% with placebo [20]

c) Pediatric Clinical Trials

1) Major depressive disorder or generalized anxiety disorder (oral route): 2% vs 1% with placebo [1]

3.3.5] Hematologic Effects**3.3.5.A] Duloxetine Hydrochloride****3.3.5.A.1] Hemorrhage, Abnormal****a) General Information**

- 1) Increased risk of [gastrointestinal bleeding](#) due to interference with serotonin reuptake [4].
- 2) Bleeding events include ecchymoses, [hematomas](#), [epistaxis](#), [petechiae](#), [gastrointestinal bleeding](#), and life-threatening hemorrhages [4].
- 3) Risk may be increased by the concomitant use of drugs that affect coagulation (eg, NSAIDs, [aspirin](#), [warfarin](#)) [4].

b) Prevention and Management

- 1) Use caution when coadministering drugs that affect coagulation with [duloxetine](#) [4].
- 2) Monitor patients receiving concurrent [warfarin](#) therapy when [duloxetine](#) is started or discontinued [4].
- 3) Consider discontinuation of [duloxetine](#) 2 weeks prior to surgery (particularly, breast or orthopedic surgery) in patients in a stable phase of depression that are at a high risk of bleeding. Gradual tapering of treatment is recommended to minimize discontinuation syndrome. Restart therapy as soon as possible when there is no longer perioperative bleeding risk [39].
- 4) Use of an antidepressant agent that is less likely to or does not increase the clinical risk of bleeding (eg, [bupropion](#), [mirtazapine](#)) may be considered [39].
- 5) Take into account the type of surgery, type of antidepressant, risk of suicide, severity of depression, risk factors for bleeding, and potential for discontinuation syndrome when determining management plan [39]

c) Adult Clinical Trials

- 1) [Facelift surgery](#), [CABG](#) surgery (oral route): No significant relationship between serotonergic antidepressant use and a risk of perioperative bleeding in 4 studies (review article) [39]
- 2) Orthopedic, spinal, breast, or [CABG](#) surgery (oral route): Some increased risk of bleeding associated with serotonergic antidepressant use in 6 studies; clinical significance unclear (review article) [39]

3.3.6] Hepatic Effects

3.3.6.A] [Duloxetine Hydrochloride](#)

3.3.6.A.1] [Cholestatic jaundice syndrome](#)

- a) [Cholestatic jaundice](#) with minimal serum transaminase elevations have been reported with therapeutic use of [duloxetine](#) [40].

3.3.6.A.2] [Increased liver enzymes](#)

- a) Elevated transaminase, [bilirubin](#), and [alkaline phosphatase](#) have been reported with [duloxetine](#) in patients with [chronic liver disease](#) or [cirrhosis](#) [40].
- b) The risk for elevated serum transaminase levels increases with the use of [duloxetine](#). Median time to detection of elevated transaminase levels has been approximately 2 months and has resulted in discontinuation of [duloxetine](#) therapy in 0.3% (89 of 29,435) of patients. In the cohort of controlled trials in any indication, alanine transaminase ([ALT](#)) elevations greater than 3 times the upper limit

of normal were observed in 1.37% (132 of 9611) of patients receiving [duloxetine](#) as compared to 0.49% (35 of 7182) of patients in the placebo group. During placebo-controlled, fixed-dose trials, dose response relationships for [aspartate aminotransferase](#) (AST) elevations greater than 5 times the upper limit of normal and [ALT](#) elevations greater than 3 times the upper limit of normal were observed [40].

c) [Hepatic failure](#), sometimes fatal, has been reported with therapeutic use of [duloxetine](#). Reported cases presented as [hepatitis](#) with abdominal pain, hepatomegaly, and transaminase elevation to more than 20 times the upper limit of normal with or without [jaundice](#). [Duloxetine](#) should not be used in patients with evidence of [chronic liver disease](#) and should be discontinued if [jaundice](#) or other signs of clinically significant liver disease develop and should not be resumed unless another cause has been established [40].

3.3.6.A.3] [Liver failure](#)

a) [Hepatic failure](#), sometimes fatal, has been reported with therapeutic use of [duloxetine](#). Reported cases presented as [hepatitis](#) with abdominal pain, hepatomegaly, and transaminase elevation to more than 20 times the upper limit of normal with or without [jaundice](#). [Duloxetine](#) should not be used in patients with evidence of [chronic liver disease](#) and should be discontinued if [jaundice](#) or other signs of clinically significant liver disease develop [40].

3.3.8] Musculoskeletal Effects

3.3.8.A] [Duloxetine](#) Hydrochloride

3.3.8.A.1] Musculoskeletal pain

a) Musculoskeletal pain was a frequently reported adverse event, occurring in at least 0.01% of patients, during premarketing and postmarketing clinical trial evaluation of [duloxetine](#) [40].

3.3.9] Neurologic Effects

3.3.9.A] [Duloxetine](#) Hydrochloride

3.3.9.A.1] [Asthenia](#)

a) General Information

1) Dose-related effect [20]

b) Adult Clinical Trials

1) All indications (oral route): Fatigue or asthenia, 9% vs 5% with placebo [20]

2) Diabetic peripheral nerve pain, [fibromyalgia](#), or chronic musculoskeletal pain (oral route): 11% vs 5% with placebo [20]

3) [Major depressive disorder](#) or [generalized anxiety disorder](#) (oral route): Fatigue or asthenia, 9% vs 5% with placebo [20]

c) Pediatric Clinical Trials

1) [Major depressive disorder](#) or [generalized anxiety disorder](#) (oral route): Fatigue or asthenia, 7% vs 5% with placebo [1]

3.3.9.A.2] [Dizziness](#)

a) Incidence: 8% [1] to 9% [20]

b) Adult Clinical Trials

1) All indications (oral route): 9% vs 5% with placebo [20]

2) [Diabetic peripheral neuropathy](#), [fibromyalgia](#), or chronic musculoskeletal pain (oral route): 9% vs 5% with placebo [20]

3) [Major depressive disorder](#) or [generalized anxiety disorder](#) (oral route): 9% vs 5% with placebo [20]

c) Pediatric Clinical Trials

1) [Major depressive disorder](#) or [generalized anxiety disorder](#) (oral route): 8% vs 4% with placebo [1]

3.3.9.A.3] Extrapyramidal disease

a) [Extrapyramidal disorder](#) has been reported with [duloxetine](#) during postmarketing experience [40].

3.3.9.A.4] Headache

a) Incidence: 13% [20] to 18% [1]

b) Adult Clinical Trials

1) All indications (oral route): 14% vs 12% with placebo [20]

2) [Diabetic peripheral neuropathy](#), [fibromyalgia](#), or chronic musculoskeletal pain (oral route): 13% vs 8% with placebo [20]

3) [Major depressive disorder](#) or [generalized anxiety disorder](#) (oral route): 14% vs 14% with placebo [20]

c) Pediatric Clinical Trials

1) [Major depressive disorder](#) or [generalized anxiety disorder](#) (oral route): 18% vs 13% with placebo [1]

3.3.9.A.5] Hypersomnia**a) Adult Clinical Trials**

1) All indications (oral route): Somnolence, hypersomnia, or sedation, 10% vs 3% with placebo [40]

2) [Diabetic peripheral neuropathy](#), [fibromyalgia](#), or chronic musculoskeletal pain (oral route): Somnolence, hypersomnia, or sedation, 11% vs 3% with placebo [20]

3) [Major depressive disorder](#) or [generalized anxiety disorder](#) (oral route): Somnolence, hypersomnia, or sedation, 9% vs 3% with placebo [20]

b) Pediatric Clinical Trials

1) [Major depressive disorder](#) or [generalized anxiety disorder](#) (oral route): Somnolence, hypersomnia, or sedation, 11% vs 6% with placebo [1]

3.3.9.A.6] Insomnia

a) Incidence: 7% [1] to 10% [20]

b) Adult Clinical Trials

- 1) All indications (oral route): [Initial](#) or [middle insomnia](#) or early morning awakening, 9% vs 5% with placebo [20]
- 2) [Diabetic peripheral neuropathy](#), [fibromyalgia](#), or chronic musculoskeletal pain (oral route): Initial, middle, or terminal insomnia, 10% vs 5% with placebo [20]
- 3) [Major depressive disorder](#) or [generalized anxiety disorder](#) (oral route): Initial, middle, or terminal insomnia, 9% vs 5% with placebo [20]

c) Pediatric Clinical Trials

- 1) [Major depressive disorder](#) or [generalized anxiety disorder](#) (oral route): Initial, middle, or terminal insomnia, 7% vs 4% with placebo [1]

3.3.9.A.7] Restless legs syndrome

a) In a prospective, naturalistic study of patients (median age, 46 years; range, 18 to 87 years) treated with antidepressants, 24 of 271 (9%) subjects experienced new-onset [restless leg syndrome](#) (RLS) or worsening of preexisting RLS as a side effect related to treatment. Antidepressants included [fluoxetine](#), [paroxetine](#), [citalopram](#), [sertraline](#), escitalopram, [venlafaxine](#), [duloxetine](#), reboxetine, and [mirtazapine](#). [Mirtazapine](#) led to a marked decline of RLS in 28% of subjects compared with reboxetine, which had none. The other antidepressants showed RLS symptoms (newly occurred or deteriorated) at the rate of 5% to 10%. Subjects stated symptoms occurred early in treatment (median of 2.5 days, range 1 to 23 days) [42].

3.3.9.A.8] Sedated**a) Adult Clinical Trials**

- 1) All indications (oral route): Somnolence, hypersomnia, or sedation, 10% vs 3% with placebo [40]
- 2) [Diabetic peripheral neuropathy](#), [fibromyalgia](#), or chronic musculoskeletal pain (oral route): Somnolence, hypersomnia, or sedation, 11% vs 3% with placebo [20]
- 3) [Major depressive disorder](#) or [generalized anxiety disorder](#) (oral route): Somnolence, hypersomnia, or sedation, 9% vs 3% with placebo [20]

b) Pediatric Clinical Trials

- 1) [Major depressive disorder](#) or [generalized anxiety disorder](#) (oral route): Somnolence, hypersomnia, or sedation, 11% vs 6% with placebo [1]

3.3.9.A.9] Seizure

a) Incidence: 0.03% [40]

b) In placebo-controlled clinical trials, seizures occurred in 0.03% (3 of 10,524) of patients following administration of [duloxetine](#) hydrochloride compared with 0.01% (1 of 7699) of patients receiving placebo. Seizures, following discontinuation of [duloxetine](#) hydrochloride, have also been reported in postmarketing surveillance reports [40].

c) In a case report, a 48-year-old woman developed syndrome of [inappropriate antidiuretic hormone secretion](#) (SIADH) with [hyponatremia](#) and seizures when administered [duloxetine](#). The patient was admitted to the hospital for acute severe headache, and upon psychiatric evaluation was diagnosed

with minor depression and administered [duloxetine](#) 30 mg twice daily. Two days later, she developed 2 generalized seizures, was afebrile, comatose, and her pupils were dilated and sluggishly reactive. Blood analysis revealed serum sodium level of 103 mEq/L (103 mmol/L), and a BUN of 6 mg/dL (2 mmol/L). [Duloxetine](#) was discontinued and the patient was diagnosed with SIADH (urinary sodium 118 mEq/L (118 mmol/L), serum osmolality 215 milliosmoles/kilogram (mOsm/kg) H₂O, and [urine osmolality](#) 450 mOsm/kg H₂O). The patient was inadvertently rechallenged with [duloxetine](#) on days 3 and 4, which reproduced her [hyponatremia](#) (serum sodium levels 120 mEq/L (120 mmol/L) on day 3, and 98 mEq/L (98 mmol/L) on day 4), and she had 1 additional seizure. [Duloxetine](#) was again discontinued; within 2 days, the patient regained consciousness and was uneventfully discharged 7 days later [43].

3.3.9.A.10] Somnolence

a) Adult Clinical Trials

- 1) All indications (oral route): Somnolence, hypersomnia, or sedation, 10% vs 3% with placebo [40]
- 2) [Diabetic peripheral neuropathy](#), [fibromyalgia](#), or chronic musculoskeletal pain (oral route): Somnolence, hypersomnia, or sedation, 11% vs 3% with placebo [20]
- 3) [Major depressive disorder](#) or [generalized anxiety disorder](#) (oral route): Somnolence, hypersomnia, or sedation, 9% vs 3% with placebo [20]

b) Pediatric Clinical Trials

- 1) [Major depressive disorder](#) or [generalized anxiety disorder](#) (oral route): Somnolence, hypersomnia, or sedation, 11% vs 6% with placebo [1]

3.3.9.A.11] Tremor

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

b) Adult Clinical Trials

- 1) [Diabetic peripheral neuropathy](#), [fibromyalgia](#), or chronic musculoskeletal pain (oral route): 2% vs less than 1% with placebo [40]
- 2) [Major depressive disorder](#) or [generalized anxiety disorder](#) (oral route): 3% vs 1% with placebo [40]

c) Pediatric Clinical Trials

- 1) [Major depressive disorder](#) or [generalized anxiety disorder](#) (oral route): Less than 2% [1]

3.3.9.A.12] Vertigo

a) Vertigo was a frequently reported adverse event, occurring in at least 0.01% of patients, during premarketing and postmarketing clinical trial evaluation of [duloxetine](#) [40].

3.3.9.A.13] Yawning

a) Incidence: 2% [40]

b) In [major depressive disorder](#) and [generalized anxiety disorder](#) placebo-controlled trials, yawning occurred in 2% of patients receiving [duloxetine](#) hydrochloride (n=2995) compared with less than 1% of patients receiving placebo (n=1955). Yawning was also a frequently reported adverse event, occurring

in at least 0.01% of patients, during premarketing and postmarketing clinical trial evaluation of [duloxetine](#) [40].

3.3.10] Ophthalmic Effects

3.3.10.A] [Duloxetine](#) Hydrochloride

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

a) General Information

1) Pupillary dilation that occurs with antidepressants may cause an angle closure attack in patients with anatomically narrow angles without a patent [iridectomy](#) [37].

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 [37].

3.3.10.A.2] Blurred vision

a) Incidence: 3% [20]

b) Adult Clinical Trials

1) [Major depressive disorder](#) and [generalized anxiety disorder](#) (oral route): 3% vs 1% with placebo [20]

3.3.12] Psychiatric Effects

3.3.12.A] [Duloxetine](#) Hydrochloride

3.3.12.A.1] Aggressive behavior

a) Pediatric Clinical Trials

1) Various indications (Off-label usages; oral route): Significantly increased risk of aggressive behavior by 179% with antidepressant use ([duloxetine](#), [fluoxetine](#), [paroxetine](#), [sertraline](#), or [venlafaxine](#)) in a systematic review and meta-analysis of clinical study reports (11 trials in 1231 children and adolescents) [49].

3.3.12.A.2] Agitation

a) Incidence: 3% to 4% [40]

b) General Information

1) Included agitation, feeling jittery, nervousness, restlessness, tension, and psychomotor hyperactivity [20]

c) Adult Clinical Trials

1) [Diabetic peripheral neuropathy](#), [fibromyalgia](#), or chronic musculoskeletal pain (oral route): 3% vs 1% with placebo [20]

2) [Major depressive disorder](#) or [generalized anxiety disorder](#) (oral route): 4% vs 2% with placebo [20]

3.3.12.A.3] Anxiety

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

b) Adult Clinical Trials

1) Major depressive disorder or generalized anxiety disorder (oral route): 3% vs 2% with placebo [40]

c) Pediatric Clinical Trials

1) Major depressive disorder or generalized anxiety disorder (oral route): less than 2%[1]

3.3.12.A.4] Bipolar disorder, Rapid cycling induction

a) A 17-year-old female (weight 45 kg) with bipolar disorder experienced ultrarapid cycling of depression and mania within 2 days after starting duloxetine. Significant medical history included a depressive episode followed 2 manic episodes, each 1 year apart. Her oral medications were sodium valproate 400 mg/day and olanzapine 10 mg/day. A month prior to her current presentation, she became depressed without a precipitating reason, with signs of sadness, frequent crying, anorexia, reduced sleep, and social withdrawal. Duloxetine 20 mg twice daily was initiated and after 2 days, her sleep further reduced, she spoke excessively, was euphoric, had assertions of high intelligence and ability to perform any assignment, and exhibited frequent aggressive and abusive behavior. It was subsequently noticed that about every fourth day she would cycle through periods of euphoria and depression. Duloxetine was stopped, sodium valproate was increased to 1000 mg/day, and olanzapine was maintained. Manic symptoms resolved and she had sub-syndromal depressive symptoms within 4 weeks [48].

3.3.12.A.5] Dream disorder

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

b) Adult Clinical Trials

1) Major depressive disorder or generalized anxiety disorder (oral route): 2% vs 1% with placebo [40]

c) Pediatric Clinical Trials

1) Major depressive disorder or generalized anxiety disorder (oral route): less than 2% [1]

3.3.12.A.6] Posttraumatic stress disorder, Exacerbation of symptoms

a) In a case report, a 53-year-old Vietnam veteran with posttraumatic stress disorder (PTSD) taking duloxetine for moderate depression experienced severe exacerbation of PTSD symptoms. The patient's PTSD was previously controlled with valproic acid, propranolol, and risperidone. Within 1 week of beginning duloxetine 60 mg per day, the patient experienced daily flashbacks of Vietnam, nightmares, emotional numbing, increased startle response, extreme hypervigilance, and daily suicidal thoughts. Decreasing his duloxetine dose to 30 mg per day lessened the PTSD symptoms, but only upon discontinuation of duloxetine therapy did the symptoms return to baseline [50].

3.3.12.A.7] Suicidal thoughts

a) General Information

1j) Antidepressants have been shown to increase the risk of suicidal thinking and behavior in children, adolescents and young adults (18 to 24 years of age) with [major depressive disorder](#) and other psychiatric disorders. Adult and pediatric patients being treated with antidepressants for [major depressive disorder](#) who experience symptoms of anxiety, agitation, panic attacks, insomnia, irritability, hostility (aggressiveness), impulsivity, [akathisia](#) (psychomotor restlessness), [hypomania](#), or mania may be at risk of [suicidal ideation](#) and behavior (suicidality). This same concern applies to treating patients with other psychiatric and nonpsychiatric disorders [40].

b) Prevention and Management

1j) 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].

c) Pediatric Clinical Trials

1j) Various indications (Off-label usages; oral route): Significantly increased risk of suicidality by 139% and suicide events by 124% with antidepressant use ([duloxetine](#), [fluoxetine](#), [paroxetine](#), [sertraline](#), or [venlafaxine](#)) in a systematic review and meta-analysis of clinical study reports (11 trials in 1231 children and adolescents) [49].

3.3.13] Renal Effects

3.3.13.A] [Duloxetine](#) Hydrochloride

3.3.13.A.1] Delay when starting to pass urine

a) Urinary hesitation has been associated with the use of selective serotonin and [norepinephrine](#) reuptake inhibitors (SNRIs) [4].

3.3.13.A.2] Urinary retention

a) Urethral retention has been associated with the use of selective serotonin and [norepinephrine](#) reuptake inhibitors (SNRIs). During postmarketing surveillance of [duloxetine](#), cases of urinary retention requiring hospitalization and/or [catheterization](#) has been reported [4].

3.3.14] Reproductive Effects

3.3.14.A] [Duloxetine](#) Hydrochloride

3.3.14.A.1] Abnormal ejaculation

a) Adult Clinical Trials

1j) [Diabetic peripheral neuropathy](#), [fibromyalgia](#), or chronic musculoskeletal pain (oral route): [Ejaculation disorder](#) (including ejaculation failure), 2% vs less than 1% with placebo [51]

3.3.14.A.2] Absence of ejaculation

a) Adult Clinical Trials

1)) [Diabetic peripheral neuropathy](#), [fibromyalgia](#), or chronic musculoskeletal pain (oral route): [Ejaculation disorder](#) (including ejaculation failure), 2% vs less than 1% with placebo [51]

3.3.14.A.3] [Erectile dysfunction](#)

a)) Incidence: 4% [1]

b)) Adult Clinical Trials

1)) [Diabetic peripheral neuropathy](#), [fibromyalgia](#), or chronic musculoskeletal pain (oral route): 4% vs less than 1% with placebo [1]

2)) [Major depressive disorder](#) or [generalized anxiety disorder](#) (oral route): 4% v 1% with placebo [1]

3.3.14.A.4] [Late ejaculation](#)

a)) Incidence: 2% [20]

b)) General Information

1)) Dose-related effect [20]

c)) Adult Clinical Trials

1)) [Major depressive disorder](#) or [generalized anxiety disorder](#) (oral route): 2% vs 1% with placebo [20]

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

a)) In [major depressive disorder](#) and [generalized anxiety disorder](#) placebo-controlled trials, [abnormal orgasm](#), including [anorgasmia](#), occurred in 3% of patients receiving [duloxetine](#) hydrochloride (n=2995) compared with less than 1% of patients receiving placebo (n=1955) and was also a frequently reported adverse event, occurring in at least 1 in 100 patients, during the premarketing and postmarketing clinical trial evaluation of [duloxetine](#) [40].

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

a)) Adult Clinical Trials

1)) [Major depressive disorder](#) or [generalized anxiety disorder](#) (oral route): [Abnormal orgasm](#) or [anorgasmia](#), 2% vs less than 1% with placebo [20]

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

a)) Adult Clinical Trials

1)) [Major depressive disorder](#) or [generalized anxiety disorder](#) (oral route): Reduced or loss of libido, 3% vs 1% with placebo [20]

3.3.15] [Respiratory Effects](#)

3.3.15.A] [Duloxetine Hydrochloride](#)

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

- a) Incidence: 3% [40]
- b) Pediatric Clinical Trials

1) Major depressive disorder or generalized anxiety disorder (oral route): 3% vs 1% with placebo [1]

3.3.16] Other

3.3.16.A] Duloxetine Hydrochloride

3.3.16.A.1] Falls

- a) General Information

1) Syncope and orthostasis usually occur within the first week of therapy [40].

2) Risk of falling increases steadily with age and seems to be related to degree of orthostatic decrease in blood pressure as well as other underlying risks [20].

3) Risk of blood pressure decrease is especially seen in patients taking duloxetine at doses above 60 mg daily or who are on concomitant medications that induce orthostatic hypotension (eg, antihypertensives) or are potent CYP1A2 inhibitors (eg, fluvoxamine, cimetidine, or quinolone antimicrobials [eg, ciprofloxacin, enoxacin]) [40].

- b) Prevention and Management

1) If patient experiences orthostatic hypotension, falls, or syncope, consider dose reduction or therapy discontinuation [20].

- c) Adult Clinical Trials

1) Orthostatic hypotension, falls, and syncope have been reported; no incidence given [20]

3.3.16.A.2] Fatigue

- a) General Information

1) Dose-related effect [20]

- b) Adult Clinical Trials

1) All indications (oral route): Fatigue or asthenia, 9% vs 5% with placebo [20]

2) Diabetic peripheral nerve pain, fibromyalgia, or chronic musculoskeletal pain (oral route): 11% vs 5% with placebo [20]

3) Major depressive disorder or generalized anxiety disorder (oral route): Fatigue or asthenia, 9% vs 5% with placebo [20]

- c) Pediatric Clinical Trials

1) Major depressive disorder or generalized anxiety disorder (oral route): Fatigue or asthenia, 7% vs 5% with placebo [1]

3.3.16.A.3] Influenza

- a) Incidence: 3% [40]

b) Influenza occurred in 3% of patients receiving duloxetine hydrochloride (n=2621) compared with 2% of patients receiving of placebo (n=1672) in controlled trials of patients with diabetic peripheral neuropathic pain, fibromyalgia, osteoarthritis, and chronic low back pain [40]

3.3.16.A.4] Serotonin syndrome

a) Serotonin syndrome, including life-threatening cases, or neuroleptic malignant syndrome (NMS)-like reactions have been reported with the use of duloxetine 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].

3.3.16.A.5] Withdrawal sign or symptom

a) Incidence: 1% or greater [40]

b) In clinical trials, abrupt discontinuation of duloxetine resulted in 1% or greater incidence of withdrawal symptoms including dizziness, nausea, headache, fatigue, paresthesia, vomiting, irritability, nightmares, insomnia, diarrhea, anxiety, hyperhidrosis, and vertigo compared with patients discontinuing placebo. During marketing of other SSRIs and serotonin and norepinephrine inhibitors (SNRIs), reports of dysphoric mood, irritability, agitation, dizziness, sensory disturbances (paresthesias), anxiety, confusion, headache, lethargy, emotional lability, insomnia, hypomania, tinnitus, and seizures have been reported. Most events have been self-limiting, however some have been severe. All patients should be monitored closely during discontinuation of therapy and the dose should be gradually tapered. If intolerable symptoms occur, treatment should be temporarily restored to the previous dose before instituting a more gradual decrease in dose [40].

c) In a pooled analysis of 9 clinical trials divided into three categories: 6 short-term placebo-controlled trials (8 to 9 weeks; duloxetine n=490, placebo n=380), 2 long-term placebo-controlled (34 weeks; duloxetine n=242, placebo n=101), and 1 long-term open-label study (52 weeks; duloxetine n=553), discontinuation-emergent adverse events (DEAEs) occurred when duloxetine therapy was abruptly stopped. Patients experiencing at least one DEAE in each of the 3 categories of studies was 44.3% (vs 22.9% placebo), 9.1% (vs 2% placebo) and 50% (open-label), respectively. Comparing the 3 categories of studies, the most common DEAE was dizziness reported in 12.4% (vs 0.8% placebo), 3.3% (vs 1% placebo), and 19.2% (open-label) of patients, respectively, followed by nausea (5.9% [vs 0.3% placebo], 0.8% [vs 0% placebo], and 9.8% [open-label]), and headache (5.3% [vs 0.8% placebo], 0.8% [vs 0% placebo], and 7.2% [open-label]). Patients who experienced DEAEs categorized them as mild to moderate in severity, and incidence and severity was not affected by duration of therapy beyond 8 or 9 weeks. Overall, 45.1% of DEAEs resolved by study end with 68.2%, 47.1% and 63.7% resolving within 7 days in the short-term placebo-controlled, long-term placebo-controlled, and long-term open-label studies, respectively. The authors recommend a gradual reduction of dose, over not less than 2 weeks prior to discontinuation of duloxetine therapy [52].

d) Small increases in heart rate and sleep disturbances (insomnia, abnormal dreams) have occurred following abrupt discontinuation of multiple-dose administration in healthy subjects. However, doses in this study were relatively high (20 to 40 mg twice daily). Withdrawal data following once-daily doses of 20 mg in healthy subjects or depressed patients are unavailable [41].

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: B3

a) Drugs which have been taken by only a limited number of pregnant women and women of childbearing age, without an increase in the frequency of malformation or other direct or indirect harmful effects on the human fetus having been observed. Studies in animals have shown evidence of an increased occurrence of fetal damage, the significance of which is considered uncertain in humans.

See Drug Consult reference: PREGNANCY RISK CATEGORIES

3) Crosses Placenta: Unknown

4) Clinical Management

a) Due to the lack of adequate, well-controlled studies in pregnant women, it is recommended that [duloxetine](#) be used during pregnancy only if the potential benefit outweighs the potential [risk to the fetus](#). Because adverse serotonergic-like effects have been reported in SSRI- and SNRI-exposed neonates late in the third trimester, the potential risks and benefits of [duloxetine](#) therapy during this time should be taken into account. The manufacturer has established a pregnancy registry to evaluate safety outcomes of women who become pregnant while receiving [duloxetine](#). Healthcare providers are encouraged to register their patients by contacting the registry at 1-866-814-6975 or by visiting www.cymbaltapregnancyregistry.com [1].

5) Literature Reports

a) In a prospective, observational, multicenter, cohort study (n=624), the rate of major malformations among duloxetine-exposed offspring was similar to that of women in 2 control groups with no [duloxetine](#) exposure during pregnancy (p=0.992). The incidence of major malformations (ie, [clubfoot](#), [kidney agenesis](#), [hydronephrosis](#)) was 1.8% among 165 duloxetine-exposed infants. Most women (99%) received [duloxetine](#) before pregnancy and continued treatment through early pregnancy (n=206), with 74.5% of women discontinuing [duloxetine](#) treatment by the end of the first trimester (n=155); 24.5% of women continued [duloxetine](#) therapy throughout pregnancy (n=51); and 1% of women only received [duloxetine](#) during the second or third trimester (n=2) [152].

b) A full-term infant developed [neonatal withdrawal syndrome](#) following prenatal exposure to [duloxetine](#) 90 mg/day, [lamotrigine](#) 100 mg/day, and [quetiapine](#) 200 mg 4 times daily throughout the pregnancy. Jitteriness and uncoordinated suckling and swallowing during bottle-feeding manifested within 36 hours of birth. Blood glucose levels and CBCs were normal; a [toxicology screen](#) was negative. The infant also received 24 hours of [phototherapy](#) for [unconjugated hyperbilirubinemia](#)

at 2 days of age. Neonatal withdrawal scores ranged from 5 to 7 up to age 5 days as symptoms progressed to tremors, hyperreflexia, spasticity, tachypnea, and irritability, accompanied by a 17% loss of birth weight. Feeding difficulties gradually resolved following 2 weeks of care in the neonatal intensive care unit, and she was discharged at 23 days of age. Growth and development were normal at followup at age 3 [153].

c) Neonates exposed to serotonin and [norepinephrine](#) reuptake inhibitors (SNRIs) or SSRIs late in the third trimester have developed complications necessitating extended hospitalization, respiratory support, and tube feeding. These complications can occur immediately upon delivery. Respiratory distress, cyanosis, [apnea](#), seizures, temperature instability, feeding difficulty, vomiting, [hypoglycemia](#), hypotonia, hyperreflexia, tremor, jitteriness, irritability, and constant crying have been reported. These clinical findings could be the result of a toxic effect of the drug or a drug discontinuation syndrome. In some cases, clinical findings have been consistent with [serotonin syndrome](#) [154].

d) There are no adequate and well-controlled studies with [duloxetine](#) in pregnant women. There was no evidence of [teratogenicity](#) in studies of rats and rabbits treated with oral [duloxetine](#) up to 45 mg/kg/day during organogenesis (4 times and 7 times the maximum recommended human dose [MRHD; 120 mg/day] on a mg/m(2) basis for rats and rabbits, respectively), although fetal weights were decreased. When pregnant rats were treated with [duloxetine](#) 30 mg/kg/day (2 times the MRHD) throughout gestation and lactation, pup weights decreased, and the incidence of stillborn pups and pup mortality increased. Maternal exposure to 30 mg/kg/day also increased rat pup reactivity (increased startle response to noise and decreased habituation of locomotor activity) [1].

B) Breastfeeding

1) Micromedex Lactation Rating: Infant risk cannot be ruled out.

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

2) Clinical Management

a) [Duloxetine](#) is excreted in human breast milk at approximately 0.14% of the maternal dose on a mg/kg basis. Exercise caution when administering this drug to a nursing woman [1]. However, if the potential benefits to the mother outweigh the potential risk to the infant and [duloxetine](#) is administered to a nursing woman, the nursing infant should be monitored closely for adverse effects [155]

3) Literature Reports

a) [Duloxetine](#) was found in human breast milk during a study of 6 lactating women (ranging in age from 22 to 35 years old; at least 12 weeks postpartum) who received [duloxetine](#) 40 mg twice daily for 3.5 days. [Duloxetine](#) levels in breast milk were approximately 7 mcg/day [1] (range, 4 to 15 mcg/day). The estimated daily infant dose was 2 mcg/kg/day (range, 0.6 to 3 mcg/kg/day), which was approximately 0.14% (maximum 0.25%) of the maternal dose. The mean steady-state milk-to-plasma exposure ratio for [duloxetine](#) was 0.25 (95% CI, 0.18 to 0.35). Excretion of [duloxetine](#) metabolites into breast milk was not evaluated [155].

3.5] Drug Interactions

3.5.1] Drug-Drug Combinations

3.5.1.A] **Abciximab**

- 1) Interaction Effect: an increased risk of bleeding
- 2) Summary: The release of serotonin by **platelets** is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of selective serotonin and **norepinephrine** reuptake inhibitors (such as **duloxetine**) 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[51].
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: probable
- 6) Clinical Management: When **duloxetine** and an antiplatelet agent are given concurrently, monitor patient for signs of increased bleeding[51].
- 7) Probable Mechanism: unknown

3.5.1.B] **Abiraterone**

- 1) Interaction Effect: increased plasma concentrations of CYP2D6 substrate
- 2) Summary: Coadministration of abiraterone (a CYP2D6 inhibitor) with a CYP2D6 substrate may result in increased plasma concentrations of the CYP2D6 substrate. When abiraterone (1000 mg/day) and **prednisone** (5 mg twice daily) were coadministered with the CYP2D6 substrate **dextromethorphan** (30 mg), the **dextromethorphan** C_{max} and AUC were increased 2.8-fold and 2.9-fold, respectively. If an alternative to the CYP2D6 substrate cannot be used, use caution and consider reducing the dose of the CYP2D6 substrate as necessary during coadministration[77].
- 3) Severity: moderate
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: The concomitant use of abiraterone, a CYP2D6 inhibitor, with a CYP2D6 substrate may increase the exposure of the CYP2D6 substrate. If an alternative to the CYP2D6 substrate cannot be used, use caution and consider a dose reduction of the CYP2D6 substrate as indicated during coadministration[77].
- 7) Probable Mechanism: inhibition of CYP2D6-mediated metabolism by abiraterone

3.5.1.C] **Aceclofenac**

- 1) Interaction Effect: an increased risk of bleeding
- 2) Summary: Use caution when coadministering NSAIDs and serotonin **norepinephrine** reuptake inhibitors (SNRI) as this may cause an increased risk of bleeding[106]. During clinical trials, concomitant use of NSAIDs and antidepressants, including tricyclic antidepressants, SSRIs, selective serotonin-norepinephrine reuptake inhibitors, and MOAIs, resulted in an increased risk of **intracranial hemorrhage** within 30 days of concomitant use compared with antidepressant use alone [107]. When NSAIDs and SNRIs are given concurrently, monitor the patient for signs of increased bleeding.
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: established

6) Clinical Management: Serotonin [norepinephrine](#) reuptake inhibitors (SNRI) increase bleeding risk, especially with concomitant use of NSAIDs[106]. When NSAIDs and SNRIs are given concurrently, monitor the patient for signs of increased bleeding.

7) Probable Mechanism: unknown

8) Literature Reports

a) Concomitant use of NSAIDs and antidepressants, including tricyclic antidepressants, SSRIs, serotonin-norepinephrine reuptake inhibitors, and MAOIs, resulted in an increased risk of [intracranial hemorrhage](#) within 30 days of concomitant use compared with antidepressant use alone. There was no significant difference between the antidepressant drug classes and the increased risk; however, there was an increased risk associated with male patients compared with female patients [107].

3.5.1.D) Acemetacin

1) Interaction Effect: an increased risk of bleeding

2) Summary: Use caution when coadministering NSAIDs and serotonin [norepinephrine](#) reuptake inhibitors (SNRI) as this may cause an increased risk of bleeding[106]. During clinical trials, concomitant use of NSAIDs and antidepressants, including tricyclic antidepressants, SSRIs, selective serotonin-norepinephrine reuptake inhibitors, and MOAIs, resulted in an increased risk of [intracranial hemorrhage](#) within 30 days of concomitant use compared with antidepressant use alone [107]. When NSAIDs and SNRIs are given concurrently, monitor the patient for signs of increased bleeding.

3) Severity: major

4) Onset: unspecified

5) Substantiation: established

6) Clinical Management: Serotonin [norepinephrine](#) reuptake inhibitors (SNRI) increase bleeding risk, especially with concomitant use of NSAIDs[106]. When NSAIDs and SNRIs are given concurrently, monitor the patient for signs of increased bleeding.

7) Probable Mechanism: unknown

8) Literature Reports

a) Concomitant use of NSAIDs and antidepressants, including tricyclic antidepressants, SSRIs, serotonin-norepinephrine reuptake inhibitors, and MAOIs, resulted in an increased risk of [intracranial hemorrhage](#) within 30 days of concomitant use compared with antidepressant use alone. There was no significant difference between the antidepressant drug classes and the increased risk; however, there was an increased risk associated with male patients compared with female patients [107].

3.5.1.E) Acenocoumarol

1) Interaction Effect: altered [anticoagulation](#) effects, including increased risk of bleeding

2) Summary: Coadministration of acenocoumarol and [duloxetine](#) may result in altered [anticoagulation](#) effects, including increased risk of bleeding. The release of serotonin by [platelets](#) is involved in hemostasis[53]. A population-based, case-controlled study of new coumarin users (acenocoumarol and phenprocoumon) receiving concomitant SSRIs suggested an increased risk of hospitalization due to nongastrointestinal bleeding; however, the risk of [gastrointestinal bleeding](#) was not significantly different [54]. In contrast, a case report described persistent decrease in INR values and events of headache and [hypertension](#) requiring hospitalization and acenocoumarol dosage increase after addition of [duloxetine](#) to longstanding stable acenocoumarol therapy [59]. If concomitant use is of acenocoumarol and [duloxetine](#) is required, closely monitor [anticoagulation](#) effects during initiation or discontinuation of [duloxetine](#) [53].

3) Severity: moderate

- 4) Onset: unspecified
- 5) Substantiation: established
- 6) Clinical Management: Concomitant use of acenocoumarol and [duloxetine](#) may result in altered [anticoagulation](#) effects, including increased risk of bleeding. Carefully monitor [anticoagulation](#) effects during [duloxetine](#) initiation or discontinuation[53].
- 7) Probable Mechanism: unknown
- 8) Literature Reports

a) A population-based, case-controlled study of new coumarin users (acenocoumarol and phenprocoumon) receiving 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 [54].

b) A 63-year-old woman successfully maintained on acenocoumarol 9 mg/wk (range, 8 to 10 mg/wk) for 8 years following a mechanical, [prosthetic mitral-valve](#) substitution experienced a persistent decrease in INR following a single dose of [duloxetine](#) 60 mg/day. Ten hours after taking [duloxetine](#), the patient was taken to the hospital for a severe headache, where tests revealed her [blood pressure had increased](#) to 190/110 mmHg and her INR had dramatically decreased to 1.49. [Labetalol](#) 20 mg was administered intravenously for the headache and [hypertension](#), [duloxetine](#) was discontinued, and acenocoumarol was gradually titrated to 12 mg/wk. Twenty-one days later, the INR returned to baseline and the dosage was reduced to the previous 9 mg/wk. Follow-up examinations on days 28, 56, 84, 168, and 252 revealed stable INR values and no return of [hypertension](#). Pill counts and family interviews discounted the possibility of acenocoumarol self-intoxication; however, [duloxetine](#) plasma levels were not measured and [genotyping](#) for CYP2D6 or CYP1A2 was not performed. The drug-drug interaction between acenocoumarol and [duloxetine](#) was deemed as probable based on the Naranjo Adverse Drug Reactions Probability Scale [59].

3.5.1.F] Acetophenazine

- 1) Interaction Effect: increased phenothiazine serum concentrations and potential toxicity (sedation, confusion, [cardiac arrhythmias](#), orthostatic hypotension, [hyperthermia](#), extrapyramidal effects)
- 2) Summary: [Duloxetine](#) is a moderately potent inhibitor of CYP2D6; therefore, the coadministration of [duloxetine](#) with a phenothiazine is likely to increase bioavailability of the phenothiazine agent, increasing the risk of serious adverse events[51].
- 3) Severity: moderate
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Use caution when prescribing [duloxetine](#) to patients who take phenothiazines as concomitant use may cause elevated phenothiazine plasma concentrations. Monitor for increased phenothiazine side effects[51].
- 7) Probable Mechanism: [duloxetine](#) inhibition of CYP2D6-mediated phenothiazine metabolism

3.5.1.G] Almotriptan

- 1) Interaction Effect: increased risk of [serotonin syndrome](#) ([hypertension](#), [hyperthermia](#), myoclonus, mental status changes)
- 2) Summary: Both [duloxetine](#) (a serotonin/[norepinephrine](#) reuptake inhibitor)[103], and [almotriptan](#) (a serotonin receptor agonist) [108], affect the serotonergic neurotransmitter systems and may result in an increased risk of [serotonin syndrome](#). If coadministration of [almotriptan](#) and [duloxetine](#) is warranted, monitor for signs and symptoms of [serotonin syndrome](#), especially during treatment and at dosage increases is recommended. [108]. 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 [63].
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: probable
- 6) Clinical Management: The concomitant use of [almotriptan](#) (a triptan) and [duloxetine](#) (a serotonin/[norepinephrine](#) reuptake inhibitor (SNRI)) may result in [serotonin syndrome](#), which may be life threatening. . If coadministration of [almotriptan](#) and [duloxetine](#) is warranted monitor closely for symptoms of [serotonin syndrome](#), such as mental status changes, autonomic instability, neuromuscular abnormalities, and/or gastrointestinal symptoms, , especially during treatment initiation and dose increases[103][108].
- 7) Probable Mechanism: additive pharmacologic effects resulting in excessive serotonergic stimulation

3.5.1.H] Amineptine

- 1) Interaction Effect: increased tricyclic antidepressant serum concentrations and potential toxicity (eg, anticholinergic effects, sedation, confusion, [cardiac arrhythmias](#))
- 2) Summary: The coadministration of [duloxetine](#) with a tricyclic antidepressant is likely to increase bioavailability of the tricyclic agent, increasing the risk of adverse events. [Duloxetine](#) is a moderately potent inhibitor of CYP2D6. When a single dose of the CYP2D6 substrate [desipramine](#) 50 mg and [duloxetine](#) 60 mg twice daily were coadministered, the [desipramine](#) AUC increased 3-fold over baseline[51].
- 3) Severity: moderate
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Use caution with the combined use of [duloxetine](#) with tricyclic antidepressants (TCAs). If concomitant therapy with [duloxetine](#) and a TCA is unavoidable, plasma concentrations of the tricyclic should be closely monitored and dose adjustments made accordingly[51]. Also, monitor patients for signs and symptoms of TCA toxicity (eg, anticholinergic effects, sedation, confusion, and [cardiac arrhythmias](#)).
- 7) Probable Mechanism: [duloxetine](#) inhibition of CYP2D6-mediated tricyclic agent metabolism

3.5.1.I] Amitriptyline

- 1) Interaction Effect: increased exposure of [amitriptyline](#)
- 2) Summary: Concomitant use of [amitriptyline](#) (a CYP2D6 substrate) with a CYP2D6 inhibitor may increase the exposure of [amitriptyline](#). Poor metabolizers are especially at risk. If concomitant administration is required, use caution and monitor the patient closely. Additionally, measure plasma levels of [amitriptyline](#) and adjust the dose, if needed. If the CYP2D6 inhibitor is discontinued, an increase in the [amitriptyline](#) dose may be required[130].
- 3) Severity: moderate

- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: The concomitant use of [amitriptyline](#) (a CYP2D6 substrate) with a CYP2D6 inhibitor may increase the exposure of [amitriptyline](#), especially in poor metabolizers. If concomitant administration is required, use caution and monitor the patient closely. Additionally, measure plasma levels of [amitriptyline](#) and reduce the dose, if needed. If the CYP2D6 inhibitor is discontinued, an increase in the [amitriptyline](#) dose may be required[130].
- 7) Probable Mechanism: inhibition of CYP2D6-mediated metabolism of [amitriptyline](#)

3.5.1.J] Amitriptylinoxide

- 1) Interaction Effect: increased tricyclic antidepressant serum concentrations and potential toxicity (eg, anticholinergic effects, sedation, confusion, [cardiac arrhythmias](#))
- 2) Summary: The coadministration of [duloxetine](#) with a tricyclic antidepressant is likely to increase bioavailability of the tricyclic agent, increasing the risk of adverse events. [Duloxetine](#) is a moderately potent inhibitor of CYP2D6. When a single dose of the CYP2D6 substrate [desipramine](#) 50 mg and [duloxetine](#) 60 mg twice daily were coadministered, the [desipramine](#) AUC increased 3-fold over baseline[51].
- 3) Severity: moderate
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Use caution with the combined use of [duloxetine](#) with tricyclic antidepressants (TCAs). If concomitant therapy with [duloxetine](#) and a TCA is unavoidable, plasma concentrations of the tricyclic should be closely monitored and dose adjustments made accordingly[51]. Also, monitor patients for signs and symptoms of TCA toxicity (eg, anticholinergic effects, sedation, confusion, and [cardiac arrhythmias](#)).
- 7) Probable Mechanism: [duloxetine](#) inhibition of CYP2D6-mediated tricyclic agent metabolism

3.5.1.K] Amoxapine

- 1) Interaction Effect: increased tricyclic antidepressant serum concentrations and potential toxicity (eg, anticholinergic effects, sedation, confusion, [cardiac arrhythmias](#))
- 2) Summary: The coadministration of [duloxetine](#) with a tricyclic antidepressant is likely to increase bioavailability of the tricyclic agent, increasing the risk of adverse events. [Duloxetine](#) is a moderately potent inhibitor of CYP2D6. When a single dose of the CYP2D6 substrate [desipramine](#) 50 mg and [duloxetine](#) 60 mg twice daily were coadministered, the [desipramine](#) AUC increased 3-fold over baseline[51].
- 3) Severity: moderate
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Use caution with the combined use of [duloxetine](#) with tricyclic antidepressants (TCAs). If concomitant therapy with [duloxetine](#) and a TCA is unavoidable, plasma concentrations of the tricyclic should be closely monitored and dose adjustments made accordingly[51]. Also, monitor patients for signs and symptoms of TCA toxicity (eg, anticholinergic effects, sedation, confusion, and [cardiac arrhythmias](#)).
- 7) Probable Mechanism: [duloxetine](#) inhibition of CYP2D6-mediated tricyclic agent metabolism

3.5.1.L] Amphetamine

- 1) Interaction Effect: increased [amphetamine](#) exposure and increased risk of [serotonin syndrome](#)
- 2) Summary: Coadministration of an [amphetamine](#) and a serotonergic agent that inhibits CYP2D6 may result in increased [amphetamine](#) exposure and additional risk for [serotonin syndrome](#). If concomitant use of an [amphetamine](#) and such an agent is clinically required, initiate with lower doses and monitor

patients carefully, especially during treatment initiation and dosage adjustment. Discontinue both drugs if [serotonin syndrome](#) is suspected[120].

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Coadministration of an [amphetamine](#) and another serotonergic agent may result in [serotonin syndrome](#), because both drugs affect the serotonergic neurotransmitter system. Additionally, coadministration of an [amphetamine](#) with a CYP2D6 inhibitor may increase [amphetamine](#) exposure, because [amphetamines](#) and their derivatives are metabolized to some degree by CYP2D6. An increase in [amphetamine](#) exposure may further increase risk of [serotonin syndrome](#). If concomitant use of an [amphetamine](#) and a serotonergic agent that inhibits CYP2D6 is clinically required, initiate with lower doses and monitor patients carefully, especially during treatment initiation and dosage adjustment. Discontinue both drugs if [serotonin syndrome](#) is suspected[120].

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

3.5.1.M] Amtolmetin Guacil

1) Interaction Effect: an increased risk of bleeding

2) Summary: Use caution when coadministering NSAIDs and serotonin [norepinephrine](#) reuptake inhibitors (SNRI) as this may cause an increased risk of bleeding[106]. During clinical trials, concomitant use of NSAIDs and antidepressants, including tricyclic antidepressants, SSRIs, selective serotonin-norepinephrine reuptake inhibitors, and MOAIs, resulted in an increased risk of [intracranial hemorrhage](#) within 30 days of concomitant use compared with antidepressant use alone [107]. When NSAIDs and SNRIs are given concurrently, monitor the patient for signs of increased bleeding.

3) Severity: major

4) Onset: unspecified

5) Substantiation: established

6) Clinical Management: Serotonin [norepinephrine](#) reuptake inhibitors (SNRI) increase bleeding risk, especially with concomitant use of NSAIDs[106]. When NSAIDs and SNRIs are given concurrently, monitor the patient for signs of increased bleeding.

7) Probable Mechanism: unknown

8) Literature Reports

a) Concomitant use of NSAIDs and antidepressants, including tricyclic antidepressants, SSRIs, serotonin-norepinephrine reuptake inhibitors, and MAOIs, resulted in an increased risk of [intracranial hemorrhage](#) within 30 days of concomitant use compared with antidepressant use alone. There was no significant difference between the antidepressant drug classes and the increased risk; however, there was an increased risk associated with male patients compared with female patients [107].

3.5.1.N] Anagrelide

1) Interaction Effect: an increased risk of bleeding

2) Summary: The release of serotonin by [platelets](#) is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of selective serotonin and [norepinephrine](#) reuptake inhibitors (such as [duloxetine](#)) 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[51].

3) Severity: major

4) Onset: unspecified

- 5) Substantiation: probable
- 6) Clinical Management: When [duloxetine](#) and an antiplatelet agent are given concurrently, monitor patient for signs of increased bleeding[51].
- 7) Probable Mechanism: unknown

3.5.1.O] Apixaban

- 1) Interaction Effect: an increased risk of bleeding
- 2) Summary: Coadministration of apixaban, a factor Xa inhibitor, and drugs that also affect hemostasis, such as a serotonin [norepinephrine](#) reuptake inhibitor (SNRI), increases the risk of bleeding. There is no established reversal therapy or antidote for apixaban-induced bleeding, and its [anticoagulation](#) effects usually persist until 24 hours after the last dose. Discontinue apixaban if active pathological bleeding occurs[110]. If concomitant apixaban and SNRI therapy is necessary, monitor the patient closely and use with caution.
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Concomitant apixaban therapy with drugs that also affect hemostasis, such as a serotonin [norepinephrine](#) reuptake inhibitor (SNRI), 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 until 24 hours after the last dose[110]. If concomitant apixaban and SNRI therapy is necessary, monitor the patient closely and use with caution.
- 7) Probable Mechanism: additive effects on hemostasis

3.5.1.P] Argatroban

- 1) Interaction Effect: altered [anticoagulation](#) effects, including increased risk of bleeding
- 2) Summary: Concomitant administration of an anticoagulant, such as argatroban and [duloxetine](#) may result in altered [anticoagulation](#) effects. Coadministration of the anticoagulant [warfarin](#) and SSRIs or serotonin [norepinephrine](#) reuptake inhibitors has resulted in altered [anticoagulation](#) effects, including increased bleeding. The release of serotonin by [platelets](#) is involved in hemostasis[53]. A population-based, case-controlled study of new coumarin users (acenocoumarol and phenprocoumon) receiving concomitant SSRIs suggested an increased risk of hospitalization due to nongastrointestinal bleeding; however, the risk of [gastrointestinal bleeding](#) was not significantly different [54] If concomitant use of an anticoagulant and [duloxetine](#) is required, closely monitor [anticoagulation](#) effects during initiation or discontinuation of [duloxetine](#) [53].
- 3) Severity: moderate
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Concomitant use of an anticoagulant, such as argatroban and [duloxetine](#) may increase the risk of bleeding. If concomitant use is required, carefully monitor [anticoagulation](#) effects during [duloxetine](#) initiation or discontinuation[53].
- 7) Probable Mechanism: unknown
- 8) Literature Reports

a) A population-based, case-controlled study of new coumarin users (acenocoumarol and phenprocoumon) receiving 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 [54].

3.5.1.Q] Asenapine

- 1) Interaction Effect: increased exposure of drug that is both a CYP2D6 substrate and inhibitor
- 2) Summary: Concomitant use of asenapine (a mild CYP2D6 inhibitor) and a drug that is both a CYP2D6 substrate and inhibitor may result in an increase in exposure of the CYP2D6 substrate and inhibitor. In a study of coadministration with [paroxetine](#) (a CYP2D6 substrate inhibitor), there was a 2-fold increase in [paroxetine](#) exposure[60]. Dose reductions of the CYP2D6 substrate and inhibitor may be necessary.
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Concomitant use of asenapine (a mild CYP2D6 inhibitor) and a drug that is both a CYP2D6 substrate and inhibitor may result in an increase in exposure of the CYP2D6 substrate and inhibitor[60]. Dose reductions of the CYP2D6 substrate and inhibitor may be necessary.
- 7) Probable Mechanism: inhibition of CYP2D6-mediated metabolism by asenapine
- 8) Literature Reports

a) In a study of coadministration with [paroxetine](#) (a CYP2D6 substrate and inhibitor), there was a 2-fold increase in [paroxetine](#) exposure [60].

3.5.1.R] Aspirin

- 1) Interaction Effect: an increased risk of bleeding
- 2) Summary: The release of serotonin by [platelets](#) is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of selective serotonin and [norepinephrine](#) reuptake inhibitors (such as [duloxetine](#)) 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[51].
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: probable
- 6) Clinical Management: When [duloxetine](#) and an antiplatelet agent are given concurrently, monitor patient for signs of increased bleeding[51].
- 7) Probable Mechanism: unknown

3.5.1.S] Bemiparin

- 1) Interaction Effect: altered [anticoagulation](#) effects, including increased risk of bleeding
- 2) Summary: Concomitant administration of [duloxetine](#) and an anticoagulant, such as bemiparin, may result in altered [anticoagulation](#) effects. Coadministration of the anticoagulant [warfarin](#) and SSRIs or serotonin [norepinephrine](#) reuptake inhibitors has resulted in altered [anticoagulation](#) effects, including increased bleeding. The release of serotonin by [platelets](#) is involved in hemostasis[53]. A population-based, case-controlled study of new coumarin users (acenocoumarol and phenprocoumon) receiving concomitant SSRIs suggested an increased risk of hospitalization due to nongastrointestinal bleeding; however, the risk of [gastrointestinal bleeding](#) was not significantly different [54]. If concomitant use of an anticoagulant and [duloxetine](#) is required, closely monitor [anticoagulation](#) effects during initiation or discontinuation of [duloxetine](#) [53].
- 3) Severity: moderate

- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Concomitant use of [duloxetine](#) and an anticoagulant, such as bempiparin, may increase the risk of bleeding. If concomitant use is required, carefully monitor [anticoagulation](#) effects during [duloxetine](#) initiation or discontinuation[53].
- 7) Probable Mechanism: unknown
- 8) Literature Reports

a) A population-based, case-controlled study of new coumarin users (acenocoumarol and phenprocoumon) receiving 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 [54].

3.5.1.T] [Benzphetamine](#)

- 1) Interaction Effect: increased [amphetamine](#) exposure and increased risk of [serotonin syndrome](#)
- 2) Summary: Coadministration of an [amphetamine](#) and a serotonergic agent that inhibits CYP2D6 may result in increased [amphetamine](#) exposure and additional risk for [serotonin syndrome](#). If concomitant use of an [amphetamine](#) and such an agent is clinically required, initiate with lower doses and monitor patients carefully, especially during treatment initiation and dosage adjustment. Discontinue both drugs if [serotonin syndrome](#) is suspected[120].
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Coadministration of an [amphetamine](#) and another serotonergic agent may result in [serotonin syndrome](#), because both drugs affect the serotonergic neurotransmitter system. Additionally, coadministration of an [amphetamine](#) with a CYP2D6 inhibitor may increase [amphetamine](#) exposure, because [amphetamines](#) and their derivatives are metabolized to some degree by CYP2D6. An increase in [amphetamine](#) exposure may further increase risk of [serotonin syndrome](#). If concomitant use of an [amphetamine](#) and a serotonergic agent that inhibits CYP2D6 is clinically required, initiate with lower doses and monitor patients carefully, especially during treatment initiation and dosage adjustment. Discontinue both drugs if [serotonin syndrome](#) is suspected[120].
- 7) Probable Mechanism: inhibition of CYP2D6-mediated metabolism of [amphetamine](#); additive serotonergic effects

3.5.1.U] [Bivalirudin](#)

- 1) Interaction Effect: altered [anticoagulation](#) effects, including increased risk of bleeding
- 2) Summary: Concomitant use of [bivalirudin](#) and [duloxetine](#) may result in altered [anticoagulation](#) effects. Coadministration of the anticoagulant [warfarin](#) and SSRIs or serotonin [norepinephrine](#) reuptake inhibitors has resulted in altered [anticoagulation](#) effects, including increased bleeding. The release of serotonin by [platelets](#) is involved in hemostasis[53]. A population-based, case-controlled study of new coumarin users (acenocoumarol and phenprocoumon) receiving concomitant SSRIs suggested an increased risk of hospitalization due to nongastrointestinal bleeding; however, the risk of [gastrointestinal bleeding](#) was not significantly different [54] If concomitant use of an anticoagulant and [duloxetine](#) is required, closely monitor [anticoagulation](#) effects during initiation or discontinuation of [duloxetine](#) [53].

- 3) Severity: moderate
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Concomitant use of [bivalirudin](#) and [duloxetine](#) may result in altered [anticoagulation](#) effects, including increased risk of bleeding. Carefully monitor [anticoagulation](#) effects during [duloxetine](#) initiation or discontinuation[53].
- 7) Probable Mechanism: unknown
- 8) Literature Reports

a) A population-based, case-controlled study of new coumarin users (acenocoumarol and phenprocoumon) receiving 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 [54].

3.5.1.V] Brexpiprazole

- 1) Interaction Effect: Increased brexpiprazole exposure
- 2) Summary: Concomitant use of brexpiprazole (a CYP3A4 and CYP2D6 substrate) with a moderate CYP2D6 inhibitor AND a strong or moderate CYP3A4 inhibitor should be undertaken with caution as this may increase brexpiprazole exposure and increase the risk of adverse effects. If coadministration of brexpiprazole with a moderate CYP2D6 inhibitor AND a strong or moderate CYP3A4 inhibitor, administer a quarter the usual brexpiprazole dose. If concurrent inhibitors are discontinued, adjust brexpiprazole to original dosage[58].
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Concomitant use of brexpiprazole (a CYP3A4 and CYP2D6 substrate) with a moderate CYP2D6 inhibitor AND a strong or moderate CYP3A4 inhibitor should be undertaken with caution as this may increase brexpiprazole exposure and increase the risk of adverse effects. If coadministration of brexpiprazole with a moderate CYP2D6 inhibitor AND a strong or moderate CYP3A4 inhibitor, administer a quarter the usual brexpiprazole dose. If concurrent inhibitors are discontinued, adjust brexpiprazole to original dosage[58].
- 7) Probable Mechanism: Inhibition of CYP2D6-mediated metabolism of brexpiprazole

3.5.1.W] [Bromfenac](#)

- 1) Interaction Effect: an increased risk of bleeding
- 2) Summary: Use caution when coadministering NSAIDs and serotonin [norepinephrine](#) reuptake inhibitors (SNRI) as this may cause an increased risk of bleeding[106]. During clinical trials, concomitant use of NSAIDs and antidepressants, including tricyclic antidepressants, SSRIs, selective serotonin-norepinephrine reuptake inhibitors, and MOAIs, resulted in an increased risk of [intracranial hemorrhage](#) within 30 days of concomitant use compared with antidepressant use alone [107]. When NSAIDs and SNRIs are given concurrently, monitor the patient for signs of increased bleeding.
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: established

6) Clinical Management: Serotonin [norepinephrine](#) reuptake inhibitors (SNRI) increase bleeding risk, especially with concomitant use of NSAIDs[106]. When NSAIDs and SNRIs are given concurrently, monitor the patient for signs of increased bleeding.

7) Probable Mechanism: unknown

8) Literature Reports

a) Concomitant use of NSAIDs and antidepressants, including tricyclic antidepressants, SSRIs, serotonin-norepinephrine reuptake inhibitors, and MAOIs, resulted in an increased risk of [intracranial hemorrhage](#) within 30 days of concomitant use compared with antidepressant use alone. There was no significant difference between the antidepressant drug classes and the increased risk; however, there was an increased risk associated with male patients compared with female patients [107].

3.5.1.X] Bromopride

1) Interaction Effect: increased risk of extrapyramidal reactions

2) Summary: Concomitant use of bromopride and other drugs that may cause extrapyramidal reactions is contraindicated[55].

3) Severity: contraindicated

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Concomitant use of bromopride and other drugs that may cause extrapyramidal reactions is contraindicated[55].

7) Probable Mechanism: additive extrapyramidal side effects

3.5.1.Y] Buprenorphine

1) Interaction Effect: an increased risk of bleeding

2) Summary: Use caution when coadministering NSAIDs and serotonin [norepinephrine](#) reuptake inhibitors (SNRI) as this may cause an increased risk of bleeding[106]. During clinical trials, concomitant use of NSAIDs and antidepressants, including tricyclic antidepressants, SSRIs, selective serotonin-norepinephrine reuptake inhibitors, and MAOIs, resulted in an increased risk of [intracranial hemorrhage](#) within 30 days of concomitant use compared with antidepressant use alone [107]. When NSAIDs and SNRIs are given concurrently, monitor the patient for signs of increased bleeding.

3) Severity: major

4) Onset: unspecified

5) Substantiation: established

6) Clinical Management: Serotonin [norepinephrine](#) reuptake inhibitors (SNRI) increase bleeding risk, especially with concomitant use of NSAIDs[106]. When NSAIDs and SNRIs are given concurrently, monitor the patient for signs of increased bleeding.

7) Probable Mechanism: unknown

8) Literature Reports

a) Concomitant use of NSAIDs and antidepressants, including tricyclic antidepressants, SSRIs, serotonin-norepinephrine reuptake inhibitors, and MAOIs, resulted in an increased risk of [intracranial hemorrhage](#) within 30 days of concomitant use compared with antidepressant use alone. There was no significant difference between the antidepressant drug classes and the increased risk; however, there was an increased risk associated with male patients compared with female patients [107].

3.5.1.Z] Buprenorphine

- 1) Interaction Effect: increased risk of [serotonin syndrome](#)
- 2) Summary: Exercise caution with the concomitant use of [buprenorphine](#) and other agents that affect the serotonergic neurotransmitter system due to the potential of [serotonin syndrome](#). If concurrent use is required, monitor for [serotonin syndrome](#), particularly during treatment initiation and with dosage adjustments[85]
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Concomitant use of [buprenorphine](#) with other agents that affect the serotonergic neurotransmitter system should be undertaken with caution due to the potential of [serotonin syndrome](#). If concurrent use is required, monitor for [serotonin syndrome](#), particularly during treatment initiation and with dosage adjustments[85]
- 7) Probable Mechanism: additive serotonergic effects

3.5.1.AA] Bupropion

- 1) Interaction Effect: increased exposure of CYP2D6 substrates; increased risk of seizure
- 2) Summary: Extreme caution is advised with concomitant use of [buPROPion](#) and other drugs that may lower the seizure threshold as this may increase the risk for seizures. Additionally, concurrent administration of [buPROPion](#) (a CYP2D6 inhibitor) and a CYP2D6 substrate may increase the exposure of the CYP2D6 substrate. The CYP2D6 substrate should be initiated at the lower end of the dose range and titrated gradually. If [buPROPion](#) is added to an existing regimen with a CYP2D6 substrate, consider decreasing the substrate dose, especially if it has a narrow therapeutic index. Use a low initial dose of [buPROPion](#) and titrate slowly to reduce the risk of seizures[74].
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Extreme caution is advised with concomitant use of [buPROPion](#) and other drugs that may lower the seizure threshold as this may increase the risk for seizures. Additionally, concurrent administration of [buPROPion](#) (a CYP2D6 inhibitor) and a CYP2D6 substrate may increase the exposure of the CYP2D6 substrate. The CYP2D6 substrate should be initiated at the lower end of the CYP2D6 substrate dose range and titrated gradually. If [buPROPion](#) is added to an existing regimen with a CYP2D6 substrate, consider decreasing the CYP2D6 substrate dose, especially if it has a narrow therapeutic index. Use a low initial dose of [buPROPion](#) and titrate slowly to reduce the risk of seizures[74].
- 7) Probable Mechanism: inhibition of CYP2D6-mediated metabolism of CYP2D6 substrates by [buPROPion](#); lowered seizure threshold
- 8) Literature Reports
 - a) The concomitant administration of [fluoxetine](#) and [buPROPion](#) was associated with a hyperactive libido in a patient receiving treatment for [major depression](#). The patient, a 35-year-old woman, initially received treatment with [fluoxetine](#) 40 mg daily after converting from [clomipramine](#) therapy due to suboptimal therapeutic effect. She experienced a diminished libido from the onset of [clomipramine](#) therapy which did not resolve after conversion to [fluoxetine](#). Three months after the conversion to [fluoxetine](#), [buPROPion](#) 100 mg/day was added to her treatment regimen as a potential antidote for the sexual dysfunction. Sexual function appeared to normalize 1 month after the start of [buPROPion](#) therapy. Approximately 5 months after beginning [buPROPion](#), the patient complained of having an exaggerated increase in libido, causing her to discontinue all medications. Her libido returned to normal within 2 months of stopping all

medication, accompanied by a recurrence of depressive symptoms. [Fluoxetine](#) was reintroduced within the same time period, producing another reduction in libido yet accompanied by a full remission from depressive symptoms [75].

b)) Coadministration of [buPROPion](#) 150 mg twice daily and a single dose of [desipramine](#) 50 mg (a CYP2D6 substrate) in healthy volunteers who were extensive CYP2D6 metabolizers (n=15) resulted in a 2-fold and 5-fold increase in [desipramine](#) C_{max} and AUC respectively. The effect persisted for 7 days following the last dose of [buPROPion](#) [76].

3.5.1.AB] [Celecoxib](#)

1)) Interaction Effect: an increased risk of bleeding

2)) Summary: Use caution when coadministering NSAIDs and serotonin [norepinephrine](#) reuptake inhibitors (SNRI) as this may cause an increased risk of bleeding[106]. During clinical trials, concomitant use of NSAIDs and antidepressants, including tricyclic antidepressants, SSRIs, selective serotonin-norepinephrine reuptake inhibitors, and MOAIs, resulted in an increased risk of [intracranial hemorrhage](#) within 30 days of concomitant use compared with antidepressant use alone [107]. When NSAIDs and SNRIs are given concurrently, monitor the patient for signs of increased bleeding.

3)) Severity: major

4)) Onset: unspecified

5)) Substantiation: established

6)) Clinical Management: Serotonin [norepinephrine](#) reuptake inhibitors (SNRI) increase bleeding risk, especially with concomitant use of NSAIDs[106]. When NSAIDs and SNRIs are given concurrently, monitor the patient for signs of increased bleeding.

7)) Probable Mechanism: unknown

8)) Literature Reports

a)) Concomitant use of NSAIDs and antidepressants, including tricyclic antidepressants, SSRIs, serotonin-norepinephrine reuptake inhibitors, and MAOIs, resulted in an increased risk of [intracranial hemorrhage](#) within 30 days of concomitant use compared with antidepressant use alone. There was no significant difference between the antidepressant drug classes and the increased risk; however, there was an increased risk associated with male patients compared with female patients [107].

3.5.1.AC] [Chlorpromazine](#)

1)) Interaction Effect: increased phenothiazine serum concentrations and potential toxicity (sedation, confusion, [cardiac arrhythmias](#), orthostatic hypotension, [hyperthermia](#), extrapyramidal effects)

2)) Summary: [Duloxetine](#) is a moderately potent inhibitor of CYP2D6; therefore, the coadministration of [duloxetine](#) with a phenothiazine is likely to increase bioavailability of the phenothiazine agent, increasing the risk of serious adverse events[51].

3)) Severity: moderate

4)) Onset: unspecified

5)) Substantiation: theoretical

6)) Clinical Management: Use caution when prescribing [duloxetine](#) to patients who take phenothiazines as concomitant use may cause elevated phenothiazine plasma concentrations. Monitor for increased phenothiazine side effects[51].

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

3.5.1.AD] [Choline Salicylate](#)

- 1) Interaction Effect: an increased risk of bleeding
- 2) Summary: Use caution when coadministering NSAIDs and serotonin [norepinephrine](#) reuptake inhibitors (SNRI) as this may cause an increased risk of bleeding[106]. During clinical trials, concomitant use of NSAIDs and antidepressants, including tricyclic antidepressants, SSRIs, selective serotonin-norepinephrine reuptake inhibitors, and MAOIs, resulted in an increased risk of [intracranial hemorrhage](#) within 30 days of concomitant use compared with antidepressant use alone [107]. When NSAIDs and SNRIs are given concurrently, monitor the patient for signs of increased bleeding.
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: established
- 6) Clinical Management: Serotonin [norepinephrine](#) reuptake inhibitors (SNRI) increase bleeding risk, especially with concomitant use of NSAIDs[106]. When NSAIDs and SNRIs are given concurrently, monitor the patient for signs of increased bleeding.
- 7) Probable Mechanism: unknown
- 8) Literature Reports

a) Concomitant use of NSAIDs and antidepressants, including tricyclic antidepressants, SSRIs, serotonin-norepinephrine reuptake inhibitors, and MAOIs, resulted in an increased risk of [intracranial hemorrhage](#) within 30 days of concomitant use compared with antidepressant use alone. There was no significant difference between the antidepressant drug classes and the increased risk; however, there was an increased risk associated with male patients compared with female patients [107].

3.5.1.AE] Cifenline

- 1) Interaction Effect: increased class IC antiarrhythmic serum concentrations and an increased risk of [cardiotoxicity](#) (QT prolongation, [torsades de pointes](#), [cardiac arrest](#))
- 2) Summary: [Duloxetine](#) is a moderately potent inhibitor of CYP2D6. Given the narrow therapeutic dosing index for the class IC antiarrhythmic agents as well as considering that they are CYP2D6 substrates, caution and close monitoring are recommended whenever [duloxetine](#) is coadministered with this class of antiarrhythmic agents[51].
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Use caution when prescribing [duloxetine](#) to patients who take a class IC antiarrhythmic agent as this may cause elevated plasma concentrations of the antiarrhythmic[51]. Monitor class IC antiarrhythmic serum concentrations and ECG for signs of potential [cardiotoxicity](#) (eg, bradycardia, [heart block](#), and hypotension); adjust dose accordingly. Alternatively, consider selecting another antidepressant that has less of a potential for altering the pharmacokinetics of class IC antiarrhythmic agents.
- 7) Probable Mechanism: inhibition of CYP2D6-mediated metabolism of class IC antiarrhythmic agents by [duloxetine](#)

3.5.1.AF] Cilostazol

- 1) Interaction Effect: an increased risk of bleeding
- 2) Summary: The release of serotonin by [platelets](#) is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of selective serotonin and [norepinephrine](#) reuptake inhibitors (such as [duloxetine](#)) 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[51].

- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: probable
- 6) Clinical Management: When [duloxetine](#) and an antiplatelet agent are given concurrently, monitor patient for signs of increased bleeding[51].
- 7) Probable Mechanism: unknown

3.5.1.AG] [Ciprofloxacin](#)

- 1) Interaction Effect: increased [duloxetine](#) bioavailability and risk of adverse effects
- 2) Summary: Since [duloxetine](#) is a substrate for cytochrome P450 isoforms CYP1A2 and CYP2D6, inhibition of [duloxetine](#) metabolism is expected to occur in the presence of coadministration with [ciprofloxacin](#), a CYP1A2 inhibitor. [Duloxetine](#) AUC and Cmax increased 6-fold and about 2.5-fold, respectively, when [duloxetine](#) was administered with [fluvoxamine](#), a potent CYP1A2 inhibitor[51].
- 3) Severity: moderate
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Use caution with the concomitant use of [ciprofloxacin](#) and [duloxetine](#) as it may result in increased [duloxetine](#) exposure and serum levels[51]. Monitor the patient for [duloxetine](#) adverse events and adjust [duloxetine](#) dose as necessary.
- 7) Probable Mechanism: inhibition of CYP1A2-mediated [duloxetine](#) metabolism

3.5.1.AH] [Citalopram](#)

- 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](#)[51].
- 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](#)[51].
- 7) Probable Mechanism: potentiation of serotonergic activity in the CNS by [duloxetine](#) and [citalopram](#)

3.5.1.AI] [Clobazam](#)

- 1) Interaction Effect: increased [duloxetine](#) plasma concentrations
- 2) Summary: The concomitant use of [duloxetine](#), a CYP2D6 substrate[40], and clobazam, a CYP2D6 inhibitor, may increase [duloxetine](#) plasma concentrations. Dose reduction of [duloxetine](#) may be required when coadministered with clobazam [105].
- 3) Severity: moderate
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: The concomitant use of clobazam with [duloxetine](#) may cause increased [duloxetine](#) plasma concentrations. If administered concomitantly, a dose reduction of [duloxetine](#) may be warranted[105].
- 7) Probable Mechanism: inhibition of CYP2D6-mediated [duloxetine](#) metabolism by clobazam

3.5.1.AJ] [Clomipramine](#)

- 1) Interaction Effect: increased tricyclic antidepressant serum concentrations and potential toxicity (eg, anticholinergic effects, sedation, confusion, [cardiac arrhythmias](#))
- 2) Summary: The coadministration of [duloxetine](#) with a tricyclic antidepressant is likely to increase bioavailability of the tricyclic agent, increasing the risk of adverse events. [Duloxetine](#) is a moderately potent inhibitor of CYP2D6. When a single dose of the CYP2D6 substrate [desipramine](#) 50 mg and [duloxetine](#) 60 mg twice daily were coadministered, the [desipramine](#) AUC increased 3-fold over baseline[51].
- 3) Severity: moderate
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Use caution with the combined use of [duloxetine](#) with tricyclic antidepressants (TCAs). If concomitant therapy with [duloxetine](#) and a TCA is unavoidable, plasma concentrations of the tricyclic should be closely monitored and dose adjustments made accordingly[51]. Also, monitor patients for signs and symptoms of TCA toxicity (eg, anticholinergic effects, sedation, confusion, and [cardiac arrhythmias](#)).
- 7) Probable Mechanism: [duloxetine](#) inhibition of CYP2D6-mediated tricyclic agent metabolism

3.5.1.AK] Clonixin

- 1) Interaction Effect: an increased risk of bleeding
- 2) Summary: Use caution when coadministering NSAIDs and serotonin [norepinephrine](#) reuptake inhibitors (SNRI) as this may cause an increased risk of bleeding[106]. During clinical trials, concomitant use of NSAIDs and antidepressants, including tricyclic antidepressants, SSRIs, selective serotonin-norepinephrine reuptake inhibitors, and MAOIs, resulted in an increased risk of [intracranial hemorrhage](#) within 30 days of concomitant use compared with antidepressant use alone [107]. When NSAIDs and SNRIs are given concurrently, monitor the patient for signs of increased bleeding.
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: established
- 6) Clinical Management: Serotonin [norepinephrine](#) reuptake inhibitors (SNRI) increase bleeding risk, especially with concomitant use of NSAIDs[106]. When NSAIDs and SNRIs are given concurrently, monitor the patient for signs of increased bleeding.
- 7) Probable Mechanism: unknown
- 8) Literature Reports

a) Concomitant use of NSAIDs and antidepressants, including tricyclic antidepressants, SSRIs, serotonin-norepinephrine reuptake inhibitors, and MAOIs, resulted in an increased risk of [intracranial hemorrhage](#) within 30 days of concomitant use compared with antidepressant use alone. There was no significant difference between the antidepressant drug classes and the increased risk; however, there was an increased risk associated with male patients compared with female patients [107].

3.5.1.AL] Clopidogrel

- 1) Interaction Effect: an increased risk of bleeding
- 2) Summary: The release of serotonin by [platelets](#) is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of selective serotonin and [norepinephrine](#) reuptake inhibitors (such as [duloxetine](#)) 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[51].
- 3) Severity: major
- 4) Onset: unspecified

- 5) Substantiation: probable
- 6) Clinical Management: When [duloxetine](#) and an antiplatelet agent are given concurrently, monitor patient for signs of increased bleeding[51].
- 7) Probable Mechanism: unknown

3.5.1.AM] [Clozapine](#)

- 1) Interaction Effect: increased plasma levels of [clozapine](#), other CYP2D6 substrates, or both
- 2) Summary: Concomitant use of [clozapine](#), a CYP2D6 substrate, with other drugs metabolized by CYP2D6 can increase plasma levels of one or both CYP2D6 substrates. Use caution with concomitant use of [clozapine](#) and other drugs metabolized by CYP2D6. Lower doses than usually prescribed for either [clozapine](#) or other CYP2D6 substrates may be required[65]. Monitor for increased CYP2D6-mediated adverse effects.
- 3) Severity: moderate
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Use caution with concomitant use of [clozapine](#) and other drugs metabolized by CYP2D6. Lower doses than usually prescribed for either [clozapine](#) or other CYP2D6 substrates may be required[65]. Monitor for increased CYP2D6-mediated adverse effects.
- 7) Probable Mechanism: competitive substrate inhibition
- 8) Literature Reports

a) [Paroxetine](#) had no significant effect on serum levels of [clozapine](#) in 14 patients with [schizophrenia](#). [Clozapine](#) 2.5 to 3 mg/kg/day was given for 14 days, then [paroxetine](#) 20 mg daily was added for 14 days. Serum concentrations of [clozapine](#) and 2 metabolites were measured on days 1, 7, and 14. Over the course of this study there was no significant difference in serum concentrations of [clozapine](#) or its metabolites [66].

b) Serum concentrations of [clozapine](#) and norclozapine, the major metabolite, were evaluated when given in combination with the SSRIs [fluoxetine](#), [paroxetine](#), and [sertraline](#). Eighty outpatients receiving [clozapine](#) all had been diagnosed with [schizophrenia](#) or major affective disorder, and 40 of these patients were receiving an SSRI in combination with [clozapine](#). Of these 40 patients, 14 were receiving [fluoxetine](#), 10 were receiving [sertraline](#), and 16 were receiving [paroxetine](#) therapy. Among the patients on SSRI therapy, serum concentrations of [clozapine](#) and norclozapine were 41.1% and 44.8% higher, respectively, than in matched patients who were not receiving an SSRI. The ratio of [clozapine](#) plus norclozapine concentration to dose was also 37.7% higher in patients receiving SSRIs, indicating [clozapine](#) impaired clearance. The differences between the 3 SSRIs were minor, and the study groups were too limited for an accurate statistical comparison between the individual SSRIs [67].

3.5.1.AN] [Cyclobenzaprine](#)

- 1) Interaction Effect: increased risk of [serotonin syndrome](#)
- 2) Summary: [Serotonin syndrome](#), a life-threatening condition, has occurred with coadministration of [cyclobenzaprine](#) and other drugs, such as serotonin [norepinephrine](#) reuptake inhibitors (SNRIs). 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[92][93].

- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Coadministration of [cyclobenzaprine](#) with a serotonin [norepinephrine](#) reuptake inhibitor (SNRI) may result in a life-threatening condition called [serotonin syndrome](#). If concurrent use is necessary, monitor patients closely for [serotonin syndrome](#), especially during treatment initiation and dose increases. Symptoms of [serotonin syndrome](#) include neuromuscular abnormalities (eg, hyperreflexia, tremor, and ataxia), autonomic instability (eg, [tachycardia](#), diaphoresis, and [hyperthermia](#)), gastrointestinal symptoms (eg, nausea, vomiting, diarrhea), or mental status changes (eg, agitation and confusion). Discontinue both drugs immediately if these symptoms occur and initiate supportive therapy[92][93].
- 7) Probable Mechanism: additive serotonergic effects

3.5.1.AO] Dabigatran Etxilate

- 1) Interaction Effect: altered [anticoagulation](#) effects, including increased risk of bleeding
- 2) Summary: Concomitant administration of an anticoagulant, such as dabigatran and [duloxetine](#) may result in altered [anticoagulation](#) effects. Coadministration of the anticoagulant [warfarin](#) and SSRIs or serotonin [norepinephrine](#) reuptake inhibitors has resulted in altered [anticoagulation](#) effects, including increased bleeding. The release of serotonin by [platelets](#) is involved in hemostasis[53]. A population-based, case-controlled study of new coumarin users (acenocoumarol and phenprocoumon) receiving concomitant SSRIs suggested an increased risk of hospitalization due to nongastrointestinal bleeding; however, the risk of [gastrointestinal bleeding](#) was not significantly different [54] If concomitant use of an anticoagulant and [duloxetine](#) is required, closely monitor [anticoagulation](#) effects during initiation or discontinuation of [duloxetine](#) [53].
- 3) Severity: moderate
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Concomitant use of an anticoagulant, such as dabigatran and [duloxetine](#) may increase the risk of bleeding. If concomitant use is required, carefully monitor [anticoagulation](#) effects during [duloxetine](#) initiation or discontinuation[53].
- 7) Probable Mechanism: unknown
- 8) Literature Reports

a) A population-based, case-controlled study of new coumarin users (acenocoumarol and phenprocoumon) receiving 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 [54].

3.5.1.AP] Dalteparin

- 1) Interaction Effect: altered [anticoagulation](#) effects, including increased risk of bleeding
- 2) Summary: Concomitant administration of an anticoagulant, such as [dalteparin](#) and [duloxetine](#) may result in altered [anticoagulation](#) effects. Coadministration of the anticoagulant [warfarin](#) and SSRIs or serotonin [norepinephrine](#) reuptake inhibitors has resulted in altered [anticoagulation](#) effects, including increased bleeding. The release of serotonin by [platelets](#) is involved in hemostasis[53]. A population-based,

case-controlled study of new coumarin users (acenocoumarol and phenprocoumon) receiving concomitant SSRIs suggested an increased risk of hospitalization due to nongastrointestinal bleeding; however, the risk of [gastrointestinal bleeding](#) was not significantly different [54] If concomitant use of an anticoagulant and [duloxetine](#) is required, closely monitor [anticoagulation](#) effects during initiation or discontinuation of [duloxetine](#) [53].

3) Severity: moderate

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Concomitant use of an anticoagulant, such as [dalteparin](#) and [duloxetine](#) may increase the risk of bleeding. If concomitant use is required, carefully monitor [anticoagulation](#) effects during [duloxetine](#) initiation or discontinuation[53].

7) Probable Mechanism: unknown

8) Literature Reports

a) A population-based, case-controlled study of new coumarin users (acenocoumarol and phenprocoumon) receiving 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 [54].

3.5.1.AQI [Danaparoid](#)

1) Interaction Effect: altered [anticoagulation](#) effects, including increased risk of bleeding

2) Summary: Concomitant administration of an anticoagulant, such as [danaparoid](#) and [duloxetine](#) may result in altered [anticoagulation](#) effects. Coadministration of the anticoagulant [warfarin](#) and SSRIs or serotonin [norepinephrine](#) reuptake inhibitors has resulted in altered [anticoagulation](#) effects, including increased bleeding. The release of serotonin by [platelets](#) is involved in hemostasis[53]. A population-based, case-controlled study of new coumarin users (acenocoumarol and phenprocoumon) receiving concomitant SSRIs suggested an increased risk of hospitalization due to nongastrointestinal bleeding; however, the risk of [gastrointestinal bleeding](#) was not significantly different [54] If concomitant use of an anticoagulant and [duloxetine](#) is required, closely monitor [anticoagulation](#) effects during initiation or discontinuation of [duloxetine](#) [53].

3) Severity: moderate

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Concomitant use of an anticoagulant, such as [danaparoid](#) and [duloxetine](#) may increase the risk of bleeding. If concomitant use is required, carefully monitor [anticoagulation](#) effects during [duloxetine](#) initiation or discontinuation[53].

7) Probable Mechanism: unknown

8) Literature Reports

a) A population-based, case-controlled study of new coumarin users (acenocoumarol and phenprocoumon) receiving 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 [54].

3.5.1.AR] [Darunavir](#)

- 1) Interaction Effect: increased CYP2D6 substrate exposure
- 2) Summary: Use caution with coadministration of [darunavir](#) (a CYP2D6 inhibitor) with CYP2D6 substrates. Coadministration may increase CYP2D6 substrate exposure and increase the risk of clinically significant reactions, including life-threatening or fatal effects. Monitor for adverse reactions associated with concomitant drugs if coadministered[128].
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Use caution with coadministration of [darunavir](#) (a CYP2D6 inhibitor) with CYP2D6 substrates. Coadministration may increase CYP2D6 substrate exposure and increase the risk of clinically significant reactions, including life-threatening or fatal effects. Monitor for adverse reactions associated with concomitant drugs if coadministered[128].
- 7) Probable Mechanism: inhibition of CYP2D6 substrate metabolism by [darunavir](#)

3.5.1.AS] [Deferasirox](#)

- 1) Interaction Effect: increased [duloxetine](#) exposure
- 2) Summary: Coadministration of [deferiasirox](#), a CYP1A2 inhibitor[102], with drugs that are metabolized by CYP1A2, such as [duloxetine](#), may lead to increased plasma concentrations of [duloxetine](#) [103]. Concomitant administration of [deferiasirox](#) with a single dose of [theophylline](#), a CYP1A2 substrate, resulted in an approximate doubling of the [theophylline](#) AUC and elimination half-life in healthy volunteers [102]. Additionally, concomitant use of [fluvoxamine](#), a CYP1A2 inhibitor, and [duloxetine](#) resulted in a 6-fold and 2.5-fold increase in [duloxetine](#) AUC and Cmax, respectively, during a drug interaction study. Avoid coadministration of [deferiasirox](#) and other potent CYP1A2 inhibitors, as similar increases in plasma concentration may be expected [103].
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Coadministration of [deferiasirox](#), a CYP1A2 inhibitor[102], with drugs that are metabolized by CYP1A2, such as [duloxetine](#), may lead to increased plasma concentrations of [duloxetine](#) and should be avoided [103].
- 7) Probable Mechanism: inhibition of CYP1A2-mediated [duloxetine](#) metabolism by [deferiasirox](#)

3.5.1.AT] [Desipramine](#)

- 1) Interaction Effect: increased tricyclic antidepressant serum concentrations and potential toxicity (eg, anticholinergic effects, sedation, confusion, [cardiac arrhythmias](#))
- 2) Summary: The coadministration of [duloxetine](#) with a tricyclic antidepressant is likely to increase bioavailability of the tricyclic agent, increasing the risk of adverse events. [Duloxetine](#) is a moderately potent inhibitor of CYP2D6. When a single dose of the CYP2D6 substrate [desipramine](#) 50 mg and [duloxetine](#) 60 mg twice daily were coadministered, the [desipramine](#) AUC increased 3-fold over baseline[51].
- 3) Severity: moderate
- 4) Onset: unspecified
- 5) Substantiation: theoretical

6J) Clinical Management: Use caution with the combined use of [duloxetine](#) with tricyclic antidepressants (TCAs). If concomitant therapy with [duloxetine](#) and a TCA is unavoidable, plasma concentrations of the tricyclic should be closely monitored and dose adjustments made accordingly[51]. Also, monitor patients for signs and symptoms of TCA toxicity (eg, anticholinergic effects, sedation, confusion, and [cardiac arrhythmias](#)).

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

3.5.1.AU] Desirudin

1J) Interaction Effect: altered [anticoagulation](#) effects, including increased risk of bleeding

2J) Summary: Concomitant use of an anticoagulant, such as desirudin and [duloxetine](#) may result in altered [anticoagulation](#) effects. Coadministration of the anticoagulant [warfarin](#) and SSRIs or serotonin [norepinephrine](#) reuptake inhibitors has resulted in altered [anticoagulation](#) effects, including increased bleeding. The release of serotonin by [platelets](#) is involved in hemostasis[53]. A population-based, case-controlled study of new coumarin users (acenocoumarol and phenprocoumon) receiving concomitant SSRIs suggested an increased risk of hospitalization due to nongastrointestinal bleeding; however, the risk of [gastrointestinal bleeding](#) was not significantly different [54] If concomitant use of an anticoagulant and [duloxetine](#) is required, closely monitor [anticoagulation](#) effects during initiation or discontinuation of [duloxetine](#) [53].

3J) Severity: moderate

4J) Onset: unspecified

5J) Substantiation: theoretical

6J) Clinical Management: Concomitant use of an anticoagulant, such as desirudin and [duloxetine](#) may result in altered [anticoagulation](#) effects, including an increased risk of bleeding. If concomitant use is required, carefully monitor [anticoagulation](#) effects during [duloxetine](#) initiation or discontinuation[53].

7J) Probable Mechanism: unknown

8J) Literature Reports

aJ) A population-based, case-controlled study of new coumarin users (acenocoumarol and phenprocoumon) receiving 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 [54].

3.5.1.AV] Desvenlafaxine

1J) Interaction Effect: increased CYP2D6 substrate exposure; increased risk of [serotonin syndrome](#) ([hypertension](#), [tachycardia](#), [hyperthermia](#), myoclonus, mental status changes)

2J) Summary: Coadministration of desvenlafaxine, a weak CYP2D6 inhibitor and serotonergic drug, with another serotonergic agent that is also a CYP2D6 substrate may result in increased drug exposure and increased risk of [serotonin syndrome](#). [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 gastrointestinal symptoms (eg, nausea, vomiting, diarrhea). If [serotonin syndrome](#) develops, discontinue both agents and initiate supportive symptomatic therapy. If concomitant use is required, no dose adjustment of the CYP2D6 substrate is needed with concurrent desvenlafaxine 100 mg/day or less. Reduce the CYP2D6 substrate dose by 50% if using concurrently with desvenlafaxine 400 mg/day (unapproved

dosing) and increase the CYP2D6 substrate to the original dose if concurrent desvenlafaxine 400 mg/day is discontinued. Monitor all patients closely for signs and symptoms of [serotonin syndrome](#), especially during treatment initiation and dose increases of either drug[89].

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Use extreme caution with coadministration of desvenlafaxine (a weak CYP2D6 inhibitor and serotonergic agent) with serotonergic drugs that are also CYP2D6 substrates. Coadministration may result in additive serotonergic effects and may increase CYP2D6 substrate exposure. If concurrent use is required, CYP2D6 substrates may be given at the recommended dose when coadministered with desvenlafaxine 100 mg/day or less. Reduce the CYP2D6 substrate dose by 50% if using concurrently with desvenlafaxine 400 mg/day (unapproved dosing); increase the CYP2D6 substrate to the original dose if concurrent desvenlafaxine 400 mg/day is discontinued. Careful monitoring for signs and symptoms of [serotonin syndrome](#) is recommended, especially during treatment initiation and dose increases. Drug discontinuation and supportive symptomatic treatment is recommended if [serotonin syndrome](#) develops[89].

7) Probable Mechanism: inhibition of CYP2D6-mediated metabolism by desvenlafaxine; additive serotonergic effect

8) Literature Reports

a) Coadministration of [desipramine](#) (a CYP2D6 substrate) 50 mg with desvenlafaxine 400 mg/day (unapproved dosing) in a clinical study resulted in an increase of approximately 50% for the C_{max} and 90% for the AUC of [desipramine](#). The differences in [desipramine](#) metabolism were not considered clinically relevant when the dose of desvenlafaxine was 100 mg/day (25% increase in C_{max} and 17% in AUC) [89].

3.5.1.AW] Dexibuprofen

1) Interaction Effect: an increased risk of bleeding

2) Summary: Use caution when coadministering NSAIDs and serotonin [norepinephrine](#) reuptake inhibitors (SNRI) as this may cause an increased risk of bleeding[106]. During clinical trials, concomitant use of NSAIDs and antidepressants, including tricyclic antidepressants, SSRIs, selective serotonin-norepinephrine reuptake inhibitors, and MAOIs, resulted in an increased risk of [intracranial hemorrhage](#) within 30 days of concomitant use compared with antidepressant use alone [107]. When NSAIDs and SNRIs are given concurrently, monitor the patient for signs of increased bleeding.

3) Severity: major

4) Onset: unspecified

5) Substantiation: established

6) Clinical Management: Serotonin [norepinephrine](#) reuptake inhibitors (SNRI) increase bleeding risk, especially with concomitant use of NSAIDs[106]. When NSAIDs and SNRIs are given concurrently, monitor the patient for signs of increased bleeding.

7) Probable Mechanism: unknown

8) Literature Reports

a) Concomitant use of NSAIDs and antidepressants, including tricyclic antidepressants, SSRIs, serotonin-norepinephrine reuptake inhibitors, and MAOIs, resulted in an increased risk of [intracranial hemorrhage](#) within 30 days of concomitant use compared with antidepressant use alone. There was no significant difference between the antidepressant drug classes and the increased risk; however, there was an increased risk associated with male patients compared with female patients [107].

3.5.1.AX] Dexketoprofen

- 1) Interaction Effect: an increased risk of bleeding
- 2) Summary: Use caution when coadministering NSAIDs and serotonin [norepinephrine](#) reuptake inhibitors (SNRI) as this may cause an increased risk of bleeding[106]. During clinical trials, concomitant use of NSAIDs and antidepressants, including tricyclic antidepressants, SSRIs, selective serotonin-norepinephrine reuptake inhibitors, and MAOIs, resulted in an increased risk of [intracranial hemorrhage](#) within 30 days of concomitant use compared with antidepressant use alone [107]. When NSAIDs and SNRIs are given concurrently, monitor the patient for signs of increased bleeding.
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: established
- 6) Clinical Management: Serotonin [norepinephrine](#) reuptake inhibitors (SNRI) increase bleeding risk, especially with concomitant use of NSAIDs[106]. When NSAIDs and SNRIs are given concurrently, monitor the patient for signs of increased bleeding.
- 7) Probable Mechanism: unknown
- 8) Literature Reports

a) Concomitant use of NSAIDs and antidepressants, including tricyclic antidepressants, SSRIs, serotonin-norepinephrine reuptake inhibitors, and MAOIs, resulted in an increased risk of [intracranial hemorrhage](#) within 30 days of concomitant use compared with antidepressant use alone. There was no significant difference between the antidepressant drug classes and the increased risk; however, there was an increased risk associated with male patients compared with female patients [107].

3.5.1.AY] Dextroamphetamine

- 1) Interaction Effect: increased [amphetamine](#) exposure and increased risk of [serotonin syndrome](#)
- 2) Summary: Coadministration of an [amphetamine](#) and a serotonergic agent that inhibits CYP2D6 may result in increased [amphetamine](#) exposure and additional risk for [serotonin syndrome](#). If concomitant use of an [amphetamine](#) and such an agent is clinically required, initiate with lower doses and monitor patients carefully, especially during treatment initiation and dosage adjustment. Discontinue both drugs if [serotonin syndrome](#) is suspected[120].
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Coadministration of an [amphetamine](#) and another serotonergic agent may result in [serotonin syndrome](#), because both drugs affect the serotonergic neurotransmitter system. Additionally, coadministration of an [amphetamine](#) with a CYP2D6 inhibitor may increase [amphetamine](#) exposure, because [amphetamines](#) and their derivatives are metabolized to some degree by CYP2D6. An increase in [amphetamine](#) exposure may further increase risk of [serotonin syndrome](#). If concomitant use of an [amphetamine](#) and a serotonergic agent that inhibits CYP2D6 is clinically required, initiate with lower doses and monitor patients carefully, especially during treatment initiation and dosage adjustment. Discontinue both drugs if [serotonin syndrome](#) is suspected[120].
- 7) Probable Mechanism: inhibition of CYP2D6-mediated metabolism of [amphetamine](#); additive serotonergic effects

3.5.1.AZ] Dextromethorphan

- 1) Interaction Effect: increased [dextromethorphan](#) plasma concentrations and increased risk of [serotonin syndrome](#)
- 2) Summary: [Duloxetine](#) is a moderate inhibitor of CYP2D6[23] and [dextromethorphan](#) is a CYP2D6 substrate. While not specifically studied with [duloxetine](#), the concomitant use of [paroxetine](#) (another SSRI) with the combination of [dextromethorphan/quinidine](#) in one study resulted in increased AUC and Cmax of [paroxetine](#), [dextromethorphan](#), and [quinidine](#). As the concomitant use of [dextromethorphan](#) with [duloxetine](#) may increase the risk of [serotonin syndrome](#), initial dose reductions of [dextromethorphan](#) may be warranted [131] 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 [duloxetine](#)), 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 [duloxetine](#)[131].
- 7) Probable Mechanism: inhibition of CYP2D6-mediated [dextromethorphan](#) metabolism by [duloxetine](#)
- 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) [131].

3.5.1.BA] Dibenzepin

- 1) Interaction Effect: increased tricyclic antidepressant serum concentrations and potential toxicity (eg, anticholinergic effects, sedation, confusion, [cardiac arrhythmias](#))
- 2) Summary: The coadministration of [duloxetine](#) with a tricyclic antidepressant is likely to increase bioavailability of the tricyclic agent, increasing the risk of adverse events. [Duloxetine](#) is a moderately potent inhibitor of CYP2D6. When a single dose of the CYP2D6 substrate [desipramine](#) 50 mg and [duloxetine](#) 60 mg twice daily were coadministered, the [desipramine](#) AUC increased 3-fold over baseline[51].
- 3) Severity: moderate
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Use caution with the combined use of [duloxetine](#) with tricyclic antidepressants (TCAs). If concomitant therapy with [duloxetine](#) and a TCA is unavoidable, plasma concentrations of the tricyclic should be closely monitored and dose adjustments made accordingly[51]. Also, monitor patients for signs and symptoms of TCA toxicity (eg, anticholinergic effects, sedation, confusion, and [cardiac arrhythmias](#)).
- 7) Probable Mechanism: [duloxetine](#) inhibition of CYP2D6-mediated tricyclic agent metabolism

3.5.1.BB| Diclofenac

- 1) Interaction Effect: an increased risk of bleeding
- 2) Summary: Use caution when coadministering NSAIDs and serotonin [norepinephrine](#) reuptake inhibitors (SNRI) as this may cause an increased risk of bleeding[106]. During clinical trials, concomitant use of NSAIDs and antidepressants, including tricyclic antidepressants, SSRIs, selective serotonin-norepinephrine reuptake inhibitors, and MAOIs, resulted in an increased risk of [intracranial hemorrhage](#) within 30 days of concomitant use compared with antidepressant use alone [107]. When NSAIDs and SNRIs are given concurrently, monitor the patient for signs of increased bleeding.
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: established
- 6) Clinical Management: Serotonin [norepinephrine](#) reuptake inhibitors (SNRI) increase bleeding risk, especially with concomitant use of NSAIDs[106]. When NSAIDs and SNRIs are given concurrently, monitor the patient for signs of increased bleeding.
- 7) Probable Mechanism: unknown
- 8) Literature Reports

a) Concomitant use of NSAIDs and antidepressants, including tricyclic antidepressants, SSRIs, serotonin-norepinephrine reuptake inhibitors, and MAOIs, resulted in an increased risk of [intracranial hemorrhage](#) within 30 days of concomitant use compared with antidepressant use alone. There was no significant difference between the antidepressant drug classes and the increased risk; however, there was an increased risk associated with male patients compared with female patients [107].

3.5.1.BC| Diflunisal

- 1) Interaction Effect: an increased risk of bleeding
- 2) Summary: Use caution when coadministering NSAIDs and serotonin [norepinephrine](#) reuptake inhibitors (SNRI) as this may cause an increased risk of bleeding[106]. During clinical trials, concomitant use of NSAIDs and antidepressants, including tricyclic antidepressants, SSRIs, selective serotonin-norepinephrine reuptake inhibitors, and MAOIs, resulted in an increased risk of [intracranial hemorrhage](#) within 30 days of concomitant use compared with antidepressant use alone [107]. When NSAIDs and SNRIs are given concurrently, monitor the patient for signs of increased bleeding.
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: established
- 6) Clinical Management: Serotonin [norepinephrine](#) reuptake inhibitors (SNRI) increase bleeding risk, especially with concomitant use of NSAIDs[106]. When NSAIDs and SNRIs are given concurrently, monitor the patient for signs of increased bleeding.
- 7) Probable Mechanism: unknown
- 8) Literature Reports

a) Concomitant use of NSAIDs and antidepressants, including tricyclic antidepressants, SSRIs, serotonin-norepinephrine reuptake inhibitors, and MAOIs, resulted in an increased risk of [intracranial hemorrhage](#) within 30 days of concomitant use compared with antidepressant use alone. There was no significant difference between the antidepressant drug classes and the increased risk; however, there was an increased risk associated with male patients compared with female patients [107].

3.5.1.BD] Dipyridamole

- 1) Interaction Effect: an increased risk of bleeding
- 2) Summary: The release of serotonin by [platelets](#) is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of selective serotonin and [norepinephrine](#) reuptake inhibitors (such as [duloxetine](#)) 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[51].
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: probable
- 6) Clinical Management: When [duloxetine](#) and an antiplatelet agent are given concurrently, monitor patient for signs of increased bleeding[51].
- 7) Probable Mechanism: unknown

3.5.1.BE] Dipyrrone

- 1) Interaction Effect: an increased risk of bleeding
- 2) Summary: Use caution when coadministering NSAIDs and serotonin [norepinephrine](#) reuptake inhibitors (SNRI) as this may cause an increased risk of bleeding[106]. During clinical trials, concomitant use of NSAIDs and antidepressants, including tricyclic antidepressants, SSRIs, selective serotonin-norepinephrine reuptake inhibitors, and MAOIs, resulted in an increased risk of [intracranial hemorrhage](#) within 30 days of concomitant use compared with antidepressant use alone [107]. When NSAIDs and SNRIs are given concurrently, monitor the patient for signs of increased bleeding.
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: established
- 6) Clinical Management: Serotonin [norepinephrine](#) reuptake inhibitors (SNRI) increase bleeding risk, especially with concomitant use of NSAIDs[106]. When NSAIDs and SNRIs are given concurrently, monitor the patient for signs of increased bleeding.
- 7) Probable Mechanism: unknown
- 8) Literature Reports

a) Concomitant use of NSAIDs and antidepressants, including tricyclic antidepressants, SSRIs, serotonin-norepinephrine reuptake inhibitors, and MAOIs, resulted in an increased risk of [intracranial hemorrhage](#) within 30 days of concomitant use compared with antidepressant use alone. There was no significant difference between the antidepressant drug classes and the increased risk; however, there was an increased risk associated with male patients compared with female patients [107].

3.5.1.BF] Dixyrazine

- 1) Interaction Effect: increased phenothiazine serum concentrations and potential toxicity (sedation, confusion, [cardiac arrhythmias](#), orthostatic hypotension, [hyperthermia](#), extrapyramidal effects)
- 2) Summary: [Duloxetine](#) is a moderately potent inhibitor of CYP2D6; therefore, the coadministration of [duloxetine](#) with a phenothiazine is likely to increase bioavailability of the phenothiazine agent, increasing the risk of serious adverse events[51].
- 3) Severity: moderate
- 4) Onset: unspecified
- 5) Substantiation: theoretical

- 6) Clinical Management: Use caution when prescribing [duloxetine](#) to patients who take phenothiazines as concomitant use may cause elevated phenothiazine plasma concentrations. Monitor for increased phenothiazine side effects[51].
- 7) Probable Mechanism: [duloxetine](#) inhibition of CYP2D6-mediated phenothiazine metabolism

3.5.1.BG] [Dolasetron](#)

- 1) Interaction Effect: increased risk of [serotonin syndrome](#)
- 2) Summary: Concomitant use of [dolasetron](#) with a serotonergic agent may increase the risk of [serotonin syndrome](#). Monitor for the emergence of [serotonin syndrome](#). Discontinue treatment with [dolasetron](#) and institute supportive therapy if symptoms of [serotonin syndrome](#) occur[71][72].
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Concomitant use of [dolasetron](#) with a serotonergic agent may increase the risk of [serotonin syndrome](#). Monitor for the emergence of [serotonin syndrome](#). Discontinue treatment with [dolasetron](#) and institute supportive therapy if symptoms of [serotonin syndrome](#) occur[71][72].
- 7) Probable Mechanism: unknown

3.5.1.BH] [Donepezil](#)

- 1) Interaction Effect: increased [donepezil](#) exposure and increased risk of seizure
- 2) Summary: Concomitant use of [donepezil](#) (a CYP2D6 substrate) with a CYP2D6 inhibitor may increase exposure of [donepezil](#). Additionally both drugs have been associated with lowering the seizure threshold[104]. If coadministered, monitor for donepezil-associated adverse events, including seizures.
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Concomitant use of [donepezil](#) (a CYP2D6 substrate) with a CYP2D6 inhibitor may increase exposure of [donepezil](#). Additionally both drugs have been associated with lowering the seizure threshold[104]. If coadministered, monitor for donepezil-associated adverse events, including seizures.
- 7) Probable Mechanism: inhibition of CYP2D6-mediated metabolism of [donepezil](#); additive seizure threshold lowering effects

3.5.1.BI] [Dothiepin](#)

- 1) Interaction Effect: increased tricyclic antidepressant serum concentrations and potential toxicity (eg, anticholinergic effects, sedation, confusion, [cardiac arrhythmias](#))
- 2) Summary: The coadministration of [duloxetine](#) with a tricyclic antidepressant is likely to increase bioavailability of the tricyclic agent, increasing the risk of adverse events. [Duloxetine](#) is a moderately potent inhibitor of CYP2D6. When a single dose of the CYP2D6 substrate [desipramine](#) 50 mg and [duloxetine](#) 60 mg twice daily were coadministered, the [desipramine](#) AUC increased 3-fold over baseline[51].
- 3) Severity: moderate
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Use caution with the combined use of [duloxetine](#) with tricyclic antidepressants (TCAs). If concomitant therapy with [duloxetine](#) and a TCA is unavoidable, plasma concentrations of the tricyclic should be closely monitored and dose adjustments made accordingly[51]. Also, monitor patients for signs and symptoms of TCA toxicity (eg, anticholinergic effects, sedation, confusion, and [cardiac arrhythmias](#)).

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

3.5.1.BJ] [Doxepin](#)

1J) Interaction Effect: increased tricyclic antidepressant serum concentrations and potential toxicity (eg, anticholinergic effects, sedation, confusion, [cardiac arrhythmias](#))

2J) Summary: The coadministration of [duloxetine](#) with a tricyclic antidepressant is likely to increase bioavailability of the tricyclic agent, increasing the risk of adverse events. [Duloxetine](#) is a moderately potent inhibitor of CYP2D6. When a single dose of the CYP2D6 substrate [desipramine](#) 50 mg and [duloxetine](#) 60 mg twice daily were coadministered, the [desipramine](#) AUC increased 3-fold over baseline[51].

3J) Severity: moderate

4J) Onset: unspecified

5J) Substantiation: theoretical

6J) Clinical Management: Use caution with the combined use of [duloxetine](#) with tricyclic antidepressants (TCAs). If concomitant therapy with [duloxetine](#) and a TCA is unavoidable, plasma concentrations of the tricyclic should be closely monitored and dose adjustments made accordingly[51]. Also, monitor patients for signs and symptoms of TCA toxicity (eg, anticholinergic effects, sedation, confusion, and [cardiac arrhythmias](#)).

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

3.5.1.BK] [Doxorubicin](#)

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

2J) Summary: Avoid concurrent use of [DOXOrubicin](#), a CYP2D6 substrate, with CYP2D6 inhibitors, as increased [DOXOrubicin](#) plasma concentrations may occur[79]. Although no formal drug interaction studies have been done with [DOXOrubicin hydrochloride liposome](#) injection, it may interact with drugs known to interact with the conventional formulation of [DOXOrubicin](#) [80].

3J) Severity: major

4J) Onset: unspecified

5J) Substantiation: theoretical

6J) Clinical Management: Avoid concurrent use of [DOXOrubicin](#) with CYP2D6 inhibitors, as increased [DOXOrubicin](#) plasma concentrations may result[79].

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

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

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

2J) Summary: Avoid concurrent use of [DOXOrubicin](#), a CYP2D6 substrate, with CYP2D6 inhibitors, as increased [DOXOrubicin](#) plasma concentrations may occur[79]. Although no formal drug interaction studies have been done with [DOXOrubicin hydrochloride liposome](#) injection, it may interact with drugs known to interact with the conventional formulation of [DOXOrubicin](#) [80].

3J) Severity: major

4J) Onset: unspecified

5J) Substantiation: theoretical

6J) Clinical Management: Avoid concurrent use of [DOXOrubicin](#) with CYP2D6 inhibitors, as increased [DOXOrubicin](#) plasma concentrations may result[79].

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

3.5.1.BM] [Drotrecogin Alfa](#)

1J) Interaction Effect: altered [anticoagulation](#) effects, including increased risk of bleeding

2) Summary: Concomitant administration of an anticoagulant, such as [drotrecogin alfa](#) and [duloxetine](#) may result in altered [anticoagulation](#) effects. Coadministration of the anticoagulant [warfarin](#) and SSRIs or serotonin [norepinephrine](#) reuptake inhibitors has resulted in altered [anticoagulation](#) effects, including increased bleeding. The release of serotonin by [platelets](#) is involved in hemostasis[53]. A population-based, case-controlled study of new coumarin users (acenocoumarol and phenprocoumon) receiving concomitant SSRIs suggested an increased risk of hospitalization due to nongastrointestinal bleeding; however, the risk of [gastrointestinal bleeding](#) was not significantly different [54] If concomitant use of an anticoagulant and [duloxetine](#) is required, closely monitor [anticoagulation](#) effects during initiation or discontinuation of [duloxetine](#) [53].

3) Severity: moderate

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Concomitant use of an anticoagulant, such as [drotrecogin alfa](#) and [duloxetine](#) may increase the risk of bleeding. If concomitant use is required, carefully monitor [anticoagulation](#) effects during [duloxetine](#) initiation or discontinuation[53].

7) Probable Mechanism: unknown

8) Literature Reports

a) A population-based, case-controlled study of new coumarin users (acenocoumarol and phenprocoumon) receiving 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 [54].

3.5.1.BN] Droxicam

1) Interaction Effect: an increased risk of bleeding

2) Summary: Use caution when coadministering NSAIDs and serotonin [norepinephrine](#) reuptake inhibitors (SNRI) as this may cause an increased risk of bleeding[106]. During clinical trials, concomitant use of NSAIDs and antidepressants, including tricyclic antidepressants, SSRIs, selective serotonin-norepinephrine reuptake inhibitors, and MAOIs, resulted in an increased risk of [intracranial hemorrhage](#) within 30 days of concomitant use compared with antidepressant use alone [107]. When NSAIDs and SNRIs are given concurrently, monitor the patient for signs of increased bleeding.

3) Severity: major

4) Onset: unspecified

5) Substantiation: established

6) Clinical Management: Serotonin [norepinephrine](#) reuptake inhibitors (SNRI) increase bleeding risk, especially with concomitant use of NSAIDs[106]. When NSAIDs and SNRIs are given concurrently, monitor the patient for signs of increased bleeding.

7) Probable Mechanism: unknown

8) Literature Reports

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

increased risk; however, there was an increased risk associated with male patients compared with female patients [107].

3.5.1.BO| Edoxaban

- 1) Interaction Effect: increased risk of bleeding
- 2) Summary: Concomitant use of edoxaban and serotonin [norepinephrine](#) reuptake inhibitors may increase the risk of bleeding. If coadministration is necessary, promptly evaluate any signs or symptoms of blood loss[134].
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Concomitant use of edoxaban and serotonin [norepinephrine](#) reuptake inhibitors may increase the risk of bleeding. If coadministration is necessary, promptly evaluate any signs or symptoms of blood loss[134].
- 7) Probable Mechanism: unknown

3.5.1.BP| [Eletriptan](#)

- 1) Interaction Effect: increased risk of [serotonin syndrome](#)
- 2) Summary: Concomitant use of [eletriptan](#) with a serotonin [norepinephrine](#) reuptake inhibitor (SNRI) may result in [serotonin syndrome](#) due to additive serotonergic effects. Cases of life-threatening [serotonin syndrome](#) have been reported following coadministration of triptans and SNRIs. If treatment with [eletriptan](#) and an SNRI is required, the patient should be monitored closely for signs and symptoms of [serotonin syndrome](#), particularly during treatment initiation and dose increases[61].
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Concomitant use of [eletriptan](#) and a serotonin [norepinephrine](#) reuptake inhibitor (SNRI) may result in [serotonin syndrome](#). Cases of life-threatening [serotonin syndrome](#) have been reported following coadministration of triptans and SNRIs. Symptoms may include agitation, hallucinations, coma, incoordination, [tachycardia](#), labile blood pressure, [hyperthermia](#), hyperreflexia, nausea, vomiting, and diarrhea. If concomitant use is warranted, closely observe the patient for signs and symptoms of [serotonin syndrome](#), especially during treatment initiation and dose increases[61].
- 7) Probable Mechanism: additive serotonergic effects

3.5.1.BQ| Eliglustat

- 1) Interaction Effect: increased eliglustat exposure and subsequent prolongation of the QT interval
- 2) Summary: Coadministration of eliglustat, a CYP2D6 and CYP3A4 substrate, with strong or moderate CYP2D6 inhibitors, can result in increased eliglustat exposure and may cause serious [cardiac arrhythmias](#), including QT-interval prolongation. Coadministration with strong or moderate CYP2D6 inhibitors led to increases in eliglustat Cmax and AUC among extensive CYP2D6 metabolizers with [Gaucher disease type 1](#) and similar increases are expected to occur in intermediate CYP2D6 metabolizers. If coadministration in extensive or intermediate CYP2D6 metabolizers with [Gaucher disease type 1](#) is clinically indicated, reduce the eliglustat dose to 84 mg/day. Do not administer eliglustat with strong or moderate CYP2D6 inhibitors plus strong or moderate CYP3A4 inhibitors, as concurrent use is contraindicated for all patients[70].
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical

6j) Clinical Management: Coadministration of eliglustat with strong or moderate CYP2D6 inhibitors may result in increased eliglustat exposure that can progress to serious [cardiac arrhythmias](#), including QT-interval prolongation. If coadministration in extensive or intermediate metabolizers with [Gaucher disease type 1](#) is clinically indicated, reduce the eliglustat dose to 84 mg/day. Do not administer eliglustat with strong or moderate CYP2D6 inhibitors plus strong or moderate CYP3A4 inhibitors, as concurrent use is contraindicated for all patients[70].

7j) Probable Mechanism: inhibition of CYP2D6-mediated eliglustat metabolism

8j) Literature Reports

a) Coadministration of eliglustat 84 mg twice daily with the strong CYP2D6 inhibitor, [paroxetine](#) (30 mg/day), led to 7-fold and 8.4-fold increases in eliglustat C_{max} and AUC, respectively, in extensive CYP2D6 metabolizers with [Gaucher disease type 1](#) (N=30). Intermediate CYP2D6 metabolizers were predicted to experience 2.1- and 2.3-fold increases in eliglustat C_{max} and AUC, respectively. Among extensive CYP2D6 metabolizers treated eliglustat and [terbinafine](#), a moderate CYP2D6 inhibitor, simulations suggested that coadministration would cause eliglustat C_{max} and AUC to rise 3.8-fold and 4.5-fold, respectively, and to increase 1.6-fold in intermediate CYP2D6 metabolizers [70]

b) Among extensive CYP2D6 metabolizers with [Gaucher disease type 1](#), simulations suggested that eliglustat C_{max} and AUC would increase 16.7- and 24.2-fold, respectively, with concomitant use of [paroxetine](#) (a strong CYP2D6 inhibitor) plus [ketoconazole](#) (a strong CYP3A4 inhibitor). Among intermediate CYP2D6 metabolizers, the predicted eliglustat C_{max} and AUC were 7.5- and 9.8-fold higher, respectively, with concurrent use of [paroxetine](#) plus [ketoconazole](#). Among extensive metabolizers, the predicted eliglustat C_{max} and AUC were 16.7- and 24.2-fold higher, respectively, with concurrent use of [paroxetine](#) plus [ketoconazole](#). Treatment with moderate CYP2D6 and CYP3A inhibitors would increase eliglustat C_{max} and AUC an estimated 10.2- and 13.6-fold, respectively, with concomitant use of [terbinafine](#) (a moderate CYP2D6 inhibitor) plus [fluconazole](#) (a moderate CYP3A inhibitor) among extensive CYP2D6 metabolizers, and would increase by 4.2- and 5-fold, respectively, among intermediate CYP2D6 metabolizers [70].

3.5.1.BR] [Encainide](#)

1j) Interaction Effect: increased class IC antiarrhythmic serum concentrations and an increased risk of [cardiotoxicity](#) (QT prolongation, [torsades de pointes](#), [cardiac arrest](#))

2j) Summary: [Duloxetine](#) is a moderately potent inhibitor of CYP2D6. Given the narrow therapeutic dosing index for the class IC antiarrhythmic agents as well as considering that they are CYP2D6 substrates, caution and close monitoring are recommended whenever [duloxetine](#) is coadministered with this class of antiarrhythmic agents[51].

3j) Severity: major

4j) Onset: unspecified

5j) Substantiation: theoretical

6j) Clinical Management: Use caution when prescribing [duloxetine](#) to patients who take a class IC antiarrhythmic agent as this may cause elevated plasma concentrations of the antiarrhythmic[51]. Monitor class IC antiarrhythmic serum concentrations and ECG for signs of potential [cardiotoxicity](#) (eg, bradycardia, [heart block](#), and hypotension); adjust dose accordingly. Alternatively, consider selecting another antidepressant that has less of a potential for altering the pharmacokinetics of class IC antiarrhythmic agents.

7j) Probable Mechanism: inhibition of CYP2D6-mediated metabolism of class IC antiarrhythmic agents by [duloxetine](#)

3.5.1.BS] Enoxacin

- 1) Interaction Effect: increased **duloxetine** bioavailability and risk of adverse effects
- 2) Summary: Since **duloxetine** is a substrate for cytochrome P450 isoforms CYP1A2 and CYP2D6, inhibition of **duloxetine** metabolism is expected to occur in the presence of coadministration with **enoxacin**, a CYP1A2 inhibitor. **Duloxetine** AUC and Cmax increased 6-fold and about 2.5-fold, respectively, when **duloxetine** was administered with **fluvoxamine**, a potent CYP1A2 inhibitor[51].
- 3) Severity: moderate
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Use caution with the concomitant use of **duloxetine** and **enoxacin** as it may result in increased **duloxetine** exposure and serum levels[51]. Monitor the patient for **duloxetine** adverse events and adjust **duloxetine** dose as necessary.
- 7) Probable Mechanism: inhibition of CYP1A2-mediated **duloxetine** metabolism

3.5.1.BT] Enoxaparin

- 1) Interaction Effect: altered **anticoagulation** effects, including increased risk of bleeding
- 2) Summary: Concomitant administration of **duloxetine** and an anticoagulant, such as **enoxaparin**, may result in altered **anticoagulation** effects. Coadministration of the anticoagulant **warfarin** and SSRIs or serotonin **norepinephrine** reuptake inhibitors has resulted in altered **anticoagulation** effects, including increased bleeding. The release of serotonin by **platelets** is involved in hemostasis[53]. A population-based, case-controlled study of new coumarin users (acenocoumarol and phenprocoumon) receiving concomitant SSRIs suggested an increased risk of hospitalization due to nongastrointestinal bleeding; however, the risk of **gastrointestinal bleeding** was not significantly different [54] If concomitant use of an anticoagulant and **duloxetine** is required, closely monitor **anticoagulation** effects during initiation or discontinuation of **duloxetine** [53].
- 3) Severity: moderate
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Concomitant use of **duloxetine** and an anticoagulant, such as **enoxaparin**, may increase the risk of bleeding. If concomitant use is required, carefully monitor **anticoagulation** effects during **duloxetine** initiation or discontinuation[53].
- 7) Probable Mechanism: unknown
- 8) Literature Reports

a) A population-based, case-controlled study of new coumarin users (acenocoumarol and phenprocoumon) receiving 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 [54].

3.5.1.BU] Epoprostenol

- 1) Interaction Effect: an increased risk of bleeding

2) Summary: The release of serotonin by [platelets](#) is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of selective serotonin and [norepinephrine](#) reuptake inhibitors (such as [duloxetine](#)) 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[51].

3) Severity: major

4) Onset: unspecified

5) Substantiation: probable

6) Clinical Management: When [duloxetine](#) and an antiplatelet agent are given concurrently, monitor patient for signs of increased bleeding[51].

7) Probable Mechanism: unknown

3.5.1.BV] [Eptifibatide](#)

1) Interaction Effect: an increased risk of bleeding

2) Summary: The release of serotonin by [platelets](#) is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of selective serotonin and [norepinephrine](#) reuptake inhibitors (such as [duloxetine](#)) 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[51].

3) Severity: major

4) Onset: unspecified

5) Substantiation: probable

6) Clinical Management: When [duloxetine](#) and an antiplatelet agent are given concurrently, monitor patient for signs of increased bleeding[51].

7) Probable Mechanism: unknown

3.5.1.BW] [Escitalopram](#)

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 escitalopram, a selective serotonin reuptake inhibitor, is not recommended due to the potential for [serotonin syndrome](#)[51].

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: The concomitant use of [duloxetine](#) and escitalopram is not recommended due to the potential for development of [serotonin syndrome](#)[51].

7) Probable Mechanism: additive serotonergic effects

3.5.1.BX] [Ethopropazine](#)

1) Interaction Effect: increased phenothiazine serum concentrations and potential toxicity (sedation, confusion, [cardiac arrhythmias](#), orthostatic hypotension, [hyperthermia](#), extrapyramidal effects)

2) Summary: [Duloxetine](#) is a moderately potent inhibitor of CYP2D6; therefore, the coadministration of [duloxetine](#) with a phenothiazine is likely to increase bioavailability of the phenothiazine agent, increasing the risk of serious adverse events[51].

3) Severity: moderate

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Use caution when prescribing [duloxetine](#) to patients who take phenothiazines as concomitant use may cause elevated phenothiazine plasma concentrations. Monitor for increased phenothiazine side effects[51].

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

3.5.1.BY] [Etodolac](#)

1) Interaction Effect: an increased risk of bleeding

2) Summary: Use caution when coadministering NSAIDs and serotonin [norepinephrine](#) reuptake inhibitors (SNRI) as this may cause an increased risk of bleeding[106]. During clinical trials, concomitant use of NSAIDs and antidepressants, including tricyclic antidepressants, SSRIs, selective serotonin-norepinephrine reuptake inhibitors, and MOAIs, resulted in an increased risk of [intracranial hemorrhage](#) within 30 days of concomitant use compared with antidepressant use alone [107]. When NSAIDs and SNRIs are given concurrently, monitor the patient for signs of increased bleeding.

3) Severity: major

4) Onset: unspecified

5) Substantiation: established

6) Clinical Management: Serotonin [norepinephrine](#) reuptake inhibitors (SNRI) increase bleeding risk, especially with concomitant use of NSAIDs[106]. When NSAIDs and SNRIs are given concurrently, monitor the patient for signs of increased bleeding.

7) Probable Mechanism: unknown

8) Literature Reports

a) Concomitant use of NSAIDs and antidepressants, including tricyclic antidepressants, SSRIs, serotonin-norepinephrine reuptake inhibitors, and MAOIs, resulted in an increased risk of [intracranial hemorrhage](#) within 30 days of concomitant use compared with antidepressant use alone. There was no significant difference between the antidepressant drug classes and the increased risk; however, there was an increased risk associated with male patients compared with female patients [107].

3.5.1.BZ] [Etofenamate](#)

1) Interaction Effect: an increased risk of bleeding

2) Summary: Use caution when coadministering NSAIDs and serotonin [norepinephrine](#) reuptake inhibitors (SNRI) as this may cause an increased risk of bleeding[106]. During clinical trials, concomitant use of NSAIDs and antidepressants, including tricyclic antidepressants, SSRIs, selective serotonin-norepinephrine reuptake inhibitors, and MOAIs, resulted in an increased risk of [intracranial hemorrhage](#) within 30 days of concomitant use compared with antidepressant use alone [107]. When NSAIDs and SNRIs are given concurrently, monitor the patient for signs of increased bleeding.

3) Severity: major

4) Onset: unspecified

5) Substantiation: established

6) Clinical Management: Serotonin [norepinephrine](#) reuptake inhibitors (SNRI) increase bleeding risk, especially with concomitant use of NSAIDs[106]. When NSAIDs and SNRIs are given concurrently, monitor the patient for signs of increased bleeding.

7) Probable Mechanism: unknown

8) Literature Reports

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

alone. There was no significant difference between the antidepressant drug classes and the increased risk; however, there was an increased risk associated with male patients compared with female patients [107].

3.5.1.CA] Etoricoxib

- 1) Interaction Effect: an increased risk of bleeding
- 2) Summary: Use caution when coadministering NSAIDs and serotonin [norepinephrine](#) reuptake inhibitors (SNRI) as this may cause an increased risk of bleeding[106]. During clinical trials, concomitant use of NSAIDs and antidepressants, including tricyclic antidepressants, SSRIs, selective serotonin-norepinephrine reuptake inhibitors, and MOAIs, resulted in an increased risk of [intracranial hemorrhage](#) within 30 days of concomitant use compared with antidepressant use alone [107]. When NSAIDs and SNRIs are given concurrently, monitor the patient for signs of increased bleeding.
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: established
- 6) Clinical Management: Serotonin [norepinephrine](#) reuptake inhibitors (SNRI) increase bleeding risk, especially with concomitant use of NSAIDs[106]. When NSAIDs and SNRIs are given concurrently, monitor the patient for signs of increased bleeding.
- 7) Probable Mechanism: unknown
- 8) Literature Reports

a) Concomitant use of NSAIDs and antidepressants, including tricyclic antidepressants, SSRIs, serotonin-norepinephrine reuptake inhibitors, and MAOIs, resulted in an increased risk of [intracranial hemorrhage](#) within 30 days of concomitant use compared with antidepressant use alone. There was no significant difference between the antidepressant drug classes and the increased risk; however, there was an increased risk associated with male patients compared with female patients [107].

3.5.1.CB] Felbinac

- 1) Interaction Effect: an increased risk of bleeding
- 2) Summary: Use caution when coadministering NSAIDs and serotonin [norepinephrine](#) reuptake inhibitors (SNRI) as this may cause an increased risk of bleeding[106]. During clinical trials, concomitant use of NSAIDs and antidepressants, including tricyclic antidepressants, SSRIs, selective serotonin-norepinephrine reuptake inhibitors, and MOAIs, resulted in an increased risk of [intracranial hemorrhage](#) within 30 days of concomitant use compared with antidepressant use alone [107]. When NSAIDs and SNRIs are given concurrently, monitor the patient for signs of increased bleeding.
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: established
- 6) Clinical Management: Serotonin [norepinephrine](#) reuptake inhibitors (SNRI) increase bleeding risk, especially with concomitant use of NSAIDs[106]. When NSAIDs and SNRIs are given concurrently, monitor the patient for signs of increased bleeding.
- 7) Probable Mechanism: unknown
- 8) Literature Reports

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

increased risk; however, there was an increased risk associated with male patients compared with female patients [107].

3.5.1.CC| Fenoprofen

- 1) Interaction Effect: an increased risk of bleeding
- 2) Summary: Use caution when coadministering NSAIDs and serotonin [norepinephrine](#) reuptake inhibitors (SNRI) as this may cause an increased risk of bleeding[106]. During clinical trials, concomitant use of NSAIDs and antidepressants, including tricyclic antidepressants, SSRIs, selective serotonin-norepinephrine reuptake inhibitors, and MAOIs, resulted in an increased risk of [intracranial hemorrhage](#) within 30 days of concomitant use compared with antidepressant use alone [107]. When NSAIDs and SNRIs are given concurrently, monitor the patient for signs of increased bleeding.
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: established
- 6) Clinical Management: Serotonin [norepinephrine](#) reuptake inhibitors (SNRI) increase bleeding risk, especially with concomitant use of NSAIDs[106]. When NSAIDs and SNRIs are given concurrently, monitor the patient for signs of increased bleeding.
- 7) Probable Mechanism: unknown
- 8) Literature Reports

a) Concomitant use of NSAIDs and antidepressants, including tricyclic antidepressants, SSRIs, serotonin-norepinephrine reuptake inhibitors, and MAOIs, resulted in an increased risk of [intracranial hemorrhage](#) within 30 days of concomitant use compared with antidepressant use alone. There was no significant difference between the antidepressant drug classes and the increased risk; however, there was an increased risk associated with male patients compared with female patients [107].

3.5.1.CD| 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[73], including SSRIs [122][121][123]. [Serotonin syndrome](#) may also result from concomitant use of [fentanyl](#) with serotonin-norepinephrine reuptake inhibitors, tricyclic antidepressants, or other synthetic piperidine opioids. If possible, consider replacing serotonergic opioids with non-serotonergic opioids [73]. Monitor patients for symptoms of [serotonin syndrome](#), including neuromuscular abnormalities, autonomic hyperactivity, and mental status changes. [Serotonin syndrome](#) can be life-threatening. If [serotonin syndrome](#) develops, discontinue the offending agents and provide supportive care and other therapy as necessary [63].
- 3) Severity: major
- 4) Onset: delayed
- 5) Substantiation: theoretical
- 6) Clinical Management: [Fentanyl](#) is a proserotonergic, synthetic piperidine opioid and has been associated with [serotonin syndrome](#) when coadministered with other serotonergic drugs. Therefore, use caution with coadministration of [fentanyl](#) and a serotonergic drug, such as an SSRI, serotonin-norepinephrine reuptake inhibitor, tricyclic antidepressant, or another synthetic piperidine opioid, as this may result in additive serotonergic effects and may increase the risk of [serotonin syndrome](#). If possible, consider replacing serotonergic opioids (eg, [fentanyl](#)) with non-serotonergic opioids (eg, [morphine](#)) [73]. Monitor patients for symptoms of [serotonin syndrome](#), including neuromuscular abnormalities (eg, hyperreflexia, tremor, muscle rigidity, clonus, peripheral hypertonicity, shivering), autonomic hyperactivity (eg, [tachycardia](#), mydriasis, diaphoresis, the presence of bowel sounds, diarrhea), and mental

status changes (eg, agitation, [delirium](#)). [Serotonin syndrome](#) can be life-threatening. If [serotonin syndrome](#) develops, discontinue the offending agents and provide supportive care and other therapy as necessary [63].

7J) Probable Mechanism: additive serotonergic effect

8J) Literature Reports

aJ) [Serotonin syndrome](#) associated with [fentanyl](#) use during an [esophagogastroduodenoscopy](#) was reported in a 39-year-old woman also taking [sertraline](#) 100 mg daily as an outpatient. The patient initially presented with [hematemesis](#) and a history of [alcoholic cirrhosis](#). Prior to the [esophagogastroduodenoscopy](#), an [octreotide](#) and [pantoprazole](#) drip was started, 2 doses of [fentanyl](#) 50 micrograms, and 2 doses of [midazolam](#) 1 mg were administered. The patient became somnolent and extremely rigid in all four extremities following the procedure, and vecuronium and [etomidate](#) were given for immediate intubation. The rigidity progressed with diffuse diaphoresis, horizontal [roving eye movements](#), and a fever of 105 degrees F. Due to the potential for seizure activity, [lorazepam](#) 2 mg IV was given with no improvement and a [propofol](#) drip was started for continued sedation during intubation. A CPK value of 2800 units/L and an ammonia level of 340 micromols/L indicated [rhabdomyolysis](#). An acute intracranial process was ruled out on a [CT scan](#) of the brain and the neurology team made the diagnosis of [serotonin syndrome](#) secondary to an interaction between [fentanyl](#) and [sertraline](#). [Propofol](#) was continued for sedation and the patient received supportive treatment with a cooling blanket and [cyproheptadine](#). After 3 days, the patient's temperature and CPK level normalized and she later extubated with no further complications [121].

bJ) [Serotonin syndrome](#) following the administration of IV [fentanyl](#) during surgical procedures was reported in 2 patients also taking SSRIs ([sertraline](#) and escitalopram). The first patient received IV [fentanyl](#) (50 micrograms), [midazolam](#) (2 mg), and 2 doses [propofol](#) (60 mg and 40 mg) in an [outpatient surgery](#) center prior to a [carpal tunnel release](#) procedure. Postoperatively the patient began shivering and became increasingly agitated for which she was transferred to the emergency department. On presentation the patient was combative, diaphoretic, confused, was unable to follow commands, tachycardic, hypertensive, had hyperreflexia, and ankle clonus. Baseline [creatinine](#) kinase rose to 613 units/L on day 2 of hospitalization. The toxicology service treated her with escalating doses of benzodiazepines with no improvement. The patient was subsequently intubated and sedated with a continuous [propofol](#) infusion. After 2 days the patient was extubated and by day 3 all symptoms had resolved and the patient was discharged home. The second patient was a 59-year-old woman admitted for an [omentectomy](#) for which she received IV [fentanyl](#) 250 micrograms, [etomidate](#), vecuronium, [morphine](#) and cephazolin. Following [extubation](#) the patient became hypoxic and acidotic and was reintubated and transferred to the ICU. On postoperative day 1 she was extubated and later became tachycardic and was unable to follow commands. On examination the patient was agitated and diaphoretic, had patellar hyperreflexia and a bilateral 3 to 4 beat ankle clonus. Laboratory evaluation was remarkable for a peak [creatinine kinase](#) of 1161 units/L on postoperative day 2. The patient was treated with [lorazepam](#) and [cyproheptadine](#) with resolution of symptoms after 3 days [122].

cJ) A case of postoperative [serotonin syndrome](#) following the administration of [fentanyl](#) for general [anesthesia](#) and post operative analgesia was reported in a 60-year-old woman also receiving [paroxetine](#). Outpatient medications included only [paroxetine](#) and thyroxine for a history of depression and [hypothyroidism](#). The patient was admitted for an extensive resection of a recurrent left chest wall [myxofibrosarcoma](#) and given [propofol](#) and 200 micrograms (mcg) of [fentanyl](#) for the [induction of anesthesia](#). The patient also received an additional 800 mcg of [fentanyl](#) (intermittent 50 mcg boluses) intraoperatively and a subsequent [fentanyl](#) infusion (100 to 200 mcg/hr) for postoperative sedation and analgesia (2545 mcg of [fentanyl](#) received over 36 hours). The [fentanyl](#)

infusion was continued 36 hours postoperatively, at which time intermittent agitation, bilateral hypertonia and hyperreflexia, and bilateral inducible ankle clonus were observed on neurological examination. Symptoms were more severe in the lower limbs and on the right side of the body. A CT scan of the brain was unremarkable and all other examination findings, including a thyroid function test, were within normal limits with the exception of elevated blood pressure (180/90 mmHg), which spontaneously resolved 24 hours after the procedure. Fentanyl was discontinued, and 24 hours later, there was marked improvement in neurological symptoms and complete recovery by postoperative day 4. The patient was ultimately discharged home with no further complications [123].

3.5.1.CE] Fepradinol

- 1) Interaction Effect: an increased risk of bleeding
- 2) Summary: Use caution when coadministering NSAIDs and serotonin norepinephrine reuptake inhibitors (SNRI) as this may cause an increased risk of bleeding[106]. During clinical trials, concomitant use of NSAIDs and antidepressants, including tricyclic antidepressants, SSRIs, selective serotonin-norepinephrine reuptake inhibitors, and MOAIs, resulted in an increased risk of intracranial hemorrhage within 30 days of concomitant use compared with antidepressant use alone [107]. When NSAIDs and SNRIs are given concurrently, monitor the patient for signs of increased bleeding.
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: established
- 6) Clinical Management: Serotonin norepinephrine reuptake inhibitors (SNRI) increase bleeding risk, especially with concomitant use of NSAIDs[106]. When NSAIDs and SNRIs are given concurrently, monitor the patient for signs of increased bleeding.
- 7) Probable Mechanism: unknown
- 8) Literature Reports

a) Concomitant use of NSAIDs and antidepressants, including tricyclic antidepressants, SSRIs, serotonin-norepinephrine reuptake inhibitors, and MAOIs, resulted in an increased risk of intracranial hemorrhage within 30 days of concomitant use compared with antidepressant use alone. There was no significant difference between the antidepressant drug classes and the increased risk; however, there was an increased risk associated with male patients compared with female patients [107].

3.5.1.CF] Feprazone

- 1) Interaction Effect: an increased risk of bleeding
- 2) Summary: Use caution when coadministering NSAIDs and serotonin norepinephrine reuptake inhibitors (SNRI) as this may cause an increased risk of bleeding[106]. During clinical trials, concomitant use of NSAIDs and antidepressants, including tricyclic antidepressants, SSRIs, selective serotonin-norepinephrine reuptake inhibitors, and MOAIs, resulted in an increased risk of intracranial hemorrhage within 30 days of concomitant use compared with antidepressant use alone [107]. When NSAIDs and SNRIs are given concurrently, monitor the patient for signs of increased bleeding.
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: established
- 6) Clinical Management: Serotonin norepinephrine reuptake inhibitors (SNRI) increase bleeding risk, especially with concomitant use of NSAIDs[106]. When NSAIDs and SNRIs are given concurrently, monitor the patient for signs of increased bleeding.
- 7) Probable Mechanism: unknown

8) Literature Reports

a) Concomitant use of NSAIDs and antidepressants, including tricyclic antidepressants, SSRIs, serotonin-norepinephrine reuptake inhibitors, and MAOIs, resulted in an increased risk of [intracranial hemorrhage](#) within 30 days of concomitant use compared with antidepressant use alone. There was no significant difference between the antidepressant drug classes and the increased risk; however, there was an increased risk associated with male patients compared with female patients [107].

3.5.1.CG| [Flecainide](#)

1) Interaction Effect: increased class IC antiarrhythmic serum concentrations and an increased risk of [cardiotoxicity](#) (QT prolongation, [torsades de pointes](#), [cardiac arrest](#))

2) Summary: [Duloxetine](#) is a moderately potent inhibitor of CYP2D6. Given the narrow therapeutic dosing index for the class IC antiarrhythmic agents as well as considering that they are CYP2D6 substrates, caution and close monitoring are recommended whenever [duloxetine](#) is coadministered with this class of antiarrhythmic agents[51].

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Use caution when prescribing [duloxetine](#) to patients who take a class IC antiarrhythmic agent as this may cause elevated plasma concentrations of the antiarrhythmic[51]. Monitor class IC antiarrhythmic serum concentrations and ECG for signs of potential [cardiotoxicity](#) (eg, bradycardia, [heart block](#), and hypotension); adjust dose accordingly. Alternatively, consider selecting another antidepressant that has less of a potential for altering the pharmacokinetics of class IC antiarrhythmic agents.

7) Probable Mechanism: inhibition of CYP2D6-mediated metabolism of class IC antiarrhythmic agents by [duloxetine](#)

3.5.1.CH| [Floctafenine](#)

1) Interaction Effect: an increased risk of bleeding

2) Summary: Use caution when coadministering NSAIDs and serotonin [norepinephrine](#) reuptake inhibitors (SNRI) as this may cause an increased risk of bleeding[106]. During clinical trials, concomitant use of NSAIDs and antidepressants, including tricyclic antidepressants, SSRIs, selective serotonin-norepinephrine reuptake inhibitors, and MOAIs, resulted in an increased risk of [intracranial hemorrhage](#) within 30 days of concomitant use compared with antidepressant use alone [107]. When NSAIDs and SNRIs are given concurrently, monitor the patient for signs of increased bleeding.

3) Severity: major

4) Onset: unspecified

5) Substantiation: established

6) Clinical Management: Serotonin [norepinephrine](#) reuptake inhibitors (SNRI) increase bleeding risk, especially with concomitant use of NSAIDs[106]. When NSAIDs and SNRIs are given concurrently, monitor the patient for signs of increased bleeding.

7) Probable Mechanism: unknown

8) Literature Reports

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

increased risk; however, there was an increased risk associated with male patients compared with female patients [107].

3.5.1.CI] Flufenamic Acid

- 1) Interaction Effect: an increased risk of bleeding
- 2) Summary: Use caution when coadministering NSAIDs and serotonin [norepinephrine](#) reuptake inhibitors (SNRI) as this may cause an increased risk of bleeding[106]. During clinical trials, concomitant use of NSAIDs and antidepressants, including tricyclic antidepressants, SSRIs, selective serotonin-norepinephrine reuptake inhibitors, and MAOIs, resulted in an increased risk of [intracranial hemorrhage](#) within 30 days of concomitant use compared with antidepressant use alone [107]. When NSAIDs and SNRIs are given concurrently, monitor the patient for signs of increased bleeding.
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: established
- 6) Clinical Management: Serotonin [norepinephrine](#) reuptake inhibitors (SNRI) increase bleeding risk, especially with concomitant use of NSAIDs[106]. When NSAIDs and SNRIs are given concurrently, monitor the patient for signs of increased bleeding.
- 7) Probable Mechanism: unknown
- 8) Literature Reports

a) Concomitant use of NSAIDs and antidepressants, including tricyclic antidepressants, SSRIs, serotonin-norepinephrine reuptake inhibitors, and MAOIs, resulted in an increased risk of [intracranial hemorrhage](#) within 30 days of concomitant use compared with antidepressant use alone. There was no significant difference between the antidepressant drug classes and the increased risk; however, there was an increased risk associated with male patients compared with female patients [107].

3.5.1.CJ] Fluoxetine

- 1) Interaction Effect: increased [duloxetine](#) and [fluoxetine](#) serum concentrations and an increased risk of [serotonin syndrome](#)
- 2) Summary: [Duloxetine](#) is a selective serotonin and [norepinephrine](#) reuptake inhibitor (SSNRI). The concomitant use of [duloxetine](#) with [fluoxetine](#), an SSRI, is not recommended due to the potential for [serotonin syndrome](#). In addition, the coadministration of [duloxetine](#) with [fluoxetine](#) is likely to increase the bioavailability of either drug, increasing the risk of serious adverse events. [Duloxetine](#) and [fluoxetine](#) are both substrates for, and moderately potent inhibitors of CYP2D6. Coadministration of [duloxetine](#) 40 mg once daily with another SSRI (the potent CYP2D6 inhibitor [paroxetine](#) 20 mg once daily) resulted in a 60% increase in the serum concentration of [duloxetine](#)[51].
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: probable
- 6) Clinical Management: The concomitant use of [duloxetine](#) and [fluoxetine](#) is not recommended due to the potential for development of [serotonin syndrome](#). Additionally, concomitant use has resulted in increased [duloxetine](#) and [fluoxetine](#) serum levels[51].
- 7) Probable Mechanism: [fluoxetine](#) inhibition of CYP2D6-mediated [duloxetine](#) metabolism; additive serotonergic effects

3.5.1.CK] Fluphenazine

- 1) Interaction Effect: increased phenothiazine serum concentrations and potential toxicity (sedation, confusion, [cardiac arrhythmias](#), orthostatic hypotension, [hyperthermia](#), extrapyramidal effects)
- 2) Summary: [Duloxetine](#) is a moderately potent inhibitor of CYP2D6; therefore, the coadministration of [duloxetine](#) with a phenothiazine is likely to increase bioavailability of the phenothiazine agent, increasing the risk of serious adverse events[51].
- 3) Severity: moderate
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Use caution when prescribing [duloxetine](#) to patients who take phenothiazines as concomitant use may cause elevated phenothiazine plasma concentrations. Monitor for increased phenothiazine side effects[51].
- 7) Probable Mechanism: [duloxetine](#) inhibition of CYP2D6-mediated phenothiazine metabolism

3.5.1.CL| [Flurbiprofen](#)

- 1) Interaction Effect: an increased risk of bleeding
- 2) Summary: Use caution when coadministering NSAIDs and serotonin [norepinephrine](#) reuptake inhibitors (SNRI) as this may cause an increased risk of bleeding[106]. During clinical trials, concomitant use of NSAIDs and antidepressants, including tricyclic antidepressants, SSRIs, selective serotonin-norepinephrine reuptake inhibitors, and MOAIs, resulted in an increased risk of [intracranial hemorrhage](#) within 30 days of concomitant use compared with antidepressant use alone [107]. When NSAIDs and SNRIs are given concurrently, monitor the patient for signs of increased bleeding.
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: established
- 6) Clinical Management: Serotonin [norepinephrine](#) reuptake inhibitors (SNRI) increase bleeding risk, especially with concomitant use of NSAIDs[106]. When NSAIDs and SNRIs are given concurrently, monitor the patient for signs of increased bleeding.
- 7) Probable Mechanism: unknown
- 8) Literature Reports

a) Concomitant use of NSAIDs and antidepressants, including tricyclic antidepressants, SSRIs, serotonin-norepinephrine reuptake inhibitors, and MAOIs, resulted in an increased risk of [intracranial hemorrhage](#) within 30 days of concomitant use compared with antidepressant use alone. There was no significant difference between the antidepressant drug classes and the increased risk; however, there was an increased risk associated with male patients compared with female patients [107].

3.5.1.CM| [Fluvoxamine](#)

- 1) Interaction Effect: increased [duloxetine](#) bioavailability and an increased risk of [serotonin syndrome](#)
- 2) Summary: [Duloxetine](#) is a selective serotonin and [norepinephrine](#) reuptake inhibitor (SSNRI) that is primarily metabolized by the CYP1A2 and CYP2D6 isozymes. The concomitant use of [duloxetine](#) with [fluvoxamine](#), a SSRI, is not recommended due to the potential for [serotonin syndrome](#). In addition, coadministration of [fluvoxamine](#) 100 mg (a CYP1A2 inhibitor) with [duloxetine](#) 40 mg twice a day in 14 CYP2D6 poor metabolizer subjects resulted in a 6-fold increase in [duloxetine](#) AUC and C_{max}. Also, when 14 male patients were given [duloxetine](#) 60 mg together with [fluvoxamine](#) 100 mg, [duloxetine](#) AUC, C_{max}, and half-life increased by 6-fold, about 2.5-fold, and 3-fold, respectively[51].
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: established

6) Clinical Management: The concomitant use of [duloxetine](#) and [fluvoxamine](#) is not recommended due to the potential for development of [serotonin syndrome](#). Additionally, concomitant use has resulted in significantly increased [duloxetine](#) exposure and serum levels[51].

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

3.5.1.CN] [Fondaparinux](#)

1) Interaction Effect: altered [anticoagulation](#) effects, increased risk of bleeding

2) Summary: Concomitant administration of [duloxetine](#) and an anticoagulant, such as [fondaparinux](#) may result in altered [anticoagulation](#) effects. Coadministration of the anticoagulant [warfarin](#) and SSRIs or serotonin [norepinephrine](#) reuptake inhibitors has resulted in altered [anticoagulation](#) effects, including increased bleeding. The release of serotonin by [platelets](#) is involved in hemostasis[53]. A population-based, case-controlled study of new coumarin users (acenocoumarol and phenprocoumon) receiving concomitant SSRIs suggested an increased risk of hospitalization due to nongastrointestinal bleeding; however, the risk of [gastrointestinal bleeding](#) was not significantly different [54] If concomitant use of an anticoagulant and [duloxetine](#) is required, closely monitor [anticoagulation](#) effects during initiation or discontinuation of [duloxetine](#) [53].

3) Severity: moderate

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Concomitant use of [duloxetine](#) and an anticoagulant, such as [fondaparinux](#), may increase the risk of bleeding. If concomitant use is required, carefully monitor [anticoagulation](#) effects during [duloxetine](#) initiation or discontinuation[53].

7) Probable Mechanism: unknown

8) Literature Reports

a) A population-based, case-controlled study of new coumarin users (acenocoumarol and phenprocoumon) receiving 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 [54].

3.5.1.CO] [Frovatriptan](#)

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

2) Summary: A life-threatening condition known as [serotonin syndrome](#) may occur when triptans, such as [frovatriptan](#), are used in combination with a serotonin and [norepinephrine](#) reuptake inhibitor (SNRI), such as [duloxetine](#). 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 SNRI 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](#), especially during treatment initiation and dose increases[51] [87].

3) Severity: major

4) Onset: unspecified

- 5J) Substantiation: theoretical
- 6J) Clinical Management: Coadministration of a triptan, such as [frovatriptan](#), and a serotonin and norepinephrine reuptake inhibitor (SNRI), such as [duloxetine](#), 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 SNRI 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), especially during treatment initiation and dose increases[51].
- 7J) Probable Mechanism: additive pharmacologic effects resulting in excessive serotonergic stimulation

3.5.1.CP| [Granisetron](#)

- 1J) Interaction Effect: increased risk of [serotonin syndrome](#)
- 2J) Summary: Concomitant use of [granisetron](#) with a serotonergic agent may increase the risk of [serotonin syndrome](#). Instruct patients of the increased risk of [serotonin syndrome](#) with concurrent use of these drugs. Monitor for the emergence of [serotonin syndrome](#) and discontinue treatment with [granisetron](#) and institute supportive therapy if symptoms of [serotonin syndrome](#) occur[69].
- 3J) Severity: major
- 4J) Onset: unspecified
- 5J) Substantiation: theoretical
- 6J) Clinical Management: Concomitant use of [granisetron](#) with a serotonergic agent may increase the risk of [serotonin syndrome](#). Instruct patients of the increased risk of [serotonin syndrome](#) with concurrent use of these drugs. Monitor for the emergence of [serotonin syndrome](#) and discontinue treatment with [granisetron](#) and institute supportive therapy if symptoms of [serotonin syndrome](#) occur[69].
- 7J) Probable Mechanism: unknown

3.5.1.CQ| [Heparin](#)

- 1J) Interaction Effect: altered [anticoagulation](#) effects, including increased risk of bleeding
- 2J) Summary: Concomitant administration of [duloxetine](#) and an anticoagulant, such as [heparin](#) may result in altered [anticoagulation](#) effects. Coadministration of the anticoagulant [warfarin](#) and SSRIs or serotonin norepinephrine reuptake inhibitors has resulted in altered [anticoagulation](#) effects, including increased bleeding. The release of serotonin by [platelets](#) is involved in hemostasis[53]. A population-based, case-controlled study of new coumarin users (acenocoumarol and phenprocoumon) receiving concomitant SSRIs suggested an increased risk of hospitalization due to nongastrointestinal bleeding; however, the risk of [gastrointestinal bleeding](#) was not significantly different [54] If concomitant use of an anticoagulant and [duloxetine](#) is required, closely monitor [anticoagulation](#) effects during initiation or discontinuation of [duloxetine](#) [53].
- 3J) Severity: moderate
- 4J) Onset: unspecified
- 5J) Substantiation: theoretical
- 6J) Clinical Management: Concomitant use of [duloxetine](#) and an anticoagulant, such as [heparin](#), may increase the risk of bleeding. If concomitant use is required, carefully monitor [anticoagulation](#) effects during [duloxetine](#) initiation or discontinuation[53].
- 7J) Probable Mechanism: unknown
- 8J) Literature Reports

- aJ) A population-based, case-controlled study of new coumarin users (acenocoumarol and phenprocoumon) receiving 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 [54].

3.5.1.CR] Hydroxytryptophan

- 1) Interaction Effect: increased risk of [serotonin syndrome](#) ([hypertension](#), [tachycardia](#), [hyperthermia](#), myoclonus, mental status changes)
- 2) Summary: [Duloxetine](#), a selective serotonin reuptake inhibitor, is known to cause [serotonin syndrome](#)[40]. Both [duloxetine](#) and hydroxytryptophan affect the serotonergic neurotransmitter systems. Concomitant use should be approached with caution due to the additive effects and the potential for increased risk of [serotonin syndrome](#). Monitoring for signs and symptoms of [serotonin syndrome](#) may be warranted if [duloxetine](#) and hydroxytryptophan are used concurrently [40].
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Use caution with concomitant administration of [duloxetine](#), a selective serotonin and [norepinephrine](#) reuptake inhibitor[40], and hydroxytryptophan, as this may result in additive serotonergic effects and may increase the risk of [serotonin syndrome](#). If coadministration is required, appropriate monitoring may be warranted [40].
- 7) Probable Mechanism: additive serotonergic effects

3.5.1.CS] Ibuprofen

- 1) Interaction Effect: an increased risk of bleeding
- 2) Summary: Use caution when coadministering NSAIDs and serotonin [norepinephrine](#) reuptake inhibitors (SNRI) as this may cause an increased risk of bleeding[106]. During clinical trials, concomitant use of NSAIDs and antidepressants, including tricyclic antidepressants, SSRIs, selective serotonin-norepinephrine reuptake inhibitors, and MAOIs, resulted in an increased risk of [intracranial hemorrhage](#) within 30 days of concomitant use compared with antidepressant use alone [107]. When NSAIDs and SNRIs are given concurrently, monitor the patient for signs of increased bleeding.
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: established
- 6) Clinical Management: Serotonin [norepinephrine](#) reuptake inhibitors (SNRI) increase bleeding risk, especially with concomitant use of NSAIDs[106]. When NSAIDs and SNRIs are given concurrently, monitor the patient for signs of increased bleeding.
- 7) Probable Mechanism: unknown
- 8) Literature Reports

a) Concomitant use of NSAIDs and antidepressants, including tricyclic antidepressants, SSRIs, serotonin-norepinephrine reuptake inhibitors, and MAOIs, resulted in an increased risk of [intracranial hemorrhage](#) within 30 days of concomitant use compared with antidepressant use alone. There was no significant difference between the antidepressant drug classes and the increased risk; however, there was an increased risk associated with male patients compared with female patients [107].

3.5.1.CT] Iloprost

- 1) Interaction Effect: an increased risk of bleeding
- 2) Summary: The release of serotonin by [platelets](#) is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of selective serotonin and [norepinephrine](#) reuptake inhibitors (such as [duloxetine](#)) 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[51].
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: probable
- 6) Clinical Management: When [duloxetine](#) and an antiplatelet agent are given concurrently, monitor patient for signs of increased bleeding[51].
- 7) Probable Mechanism: unknown

3.5.1.CU] [Imipramine](#)

- 1) Interaction Effect: increased tricyclic antidepressant serum concentrations and potential toxicity (eg, anticholinergic effects, sedation, confusion, [cardiac arrhythmias](#))
- 2) Summary: The coadministration of [duloxetine](#) with a tricyclic antidepressant is likely to increase bioavailability of the tricyclic agent, increasing the risk of adverse events. [Duloxetine](#) is a moderately potent inhibitor of CYP2D6. When a single dose of the CYP2D6 substrate [desipramine](#) 50 mg and [duloxetine](#) 60 mg twice daily were coadministered, the [desipramine](#) AUC increased 3-fold over baseline[51].
- 3) Severity: moderate
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Use caution with the combined use of [duloxetine](#) with tricyclic antidepressants (TCAs). If concomitant therapy with [duloxetine](#) and a TCA is unavoidable, plasma concentrations of the tricyclic should be closely monitored and dose adjustments made accordingly[51]. Also, monitor patients for signs and symptoms of TCA toxicity (eg, anticholinergic effects, sedation, confusion, and [cardiac arrhythmias](#)).
- 7) Probable Mechanism: [duloxetine](#) inhibition of CYP2D6-mediated tricyclic agent metabolism

3.5.1.CV] [Indecainide](#)

- 1) Interaction Effect: increased class IC antiarrhythmic serum concentrations and an increased risk of [cardiotoxicity](#) (QT prolongation, [torsades de pointes](#), [cardiac arrest](#))
- 2) Summary: [Duloxetine](#) is a moderately potent inhibitor of CYP2D6. Given the narrow therapeutic dosing index for the class IC antiarrhythmic agents as well as considering that they are CYP2D6 substrates, caution and close monitoring are recommended whenever [duloxetine](#) is coadministered with this class of antiarrhythmic agents[51].
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Use caution when prescribing [duloxetine](#) to patients who take a class IC antiarrhythmic agent as this may cause elevated plasma concentrations of the antiarrhythmic[51]. Monitor class IC antiarrhythmic serum concentrations and ECG for signs of potential [cardiotoxicity](#) (eg, bradycardia, [heart block](#), and hypotension); adjust dose accordingly. Alternatively, consider selecting another antidepressant that has less of a potential for altering the pharmacokinetics of class IC antiarrhythmic agents.
- 7) Probable Mechanism: inhibition of CYP2D6-mediated metabolism of class IC antiarrhythmic agents by [duloxetine](#)

3.5.1.CW] Indomethacin

- 1) Interaction Effect: an increased risk of bleeding
- 2) Summary: Use caution when coadministering NSAIDs and serotonin [norepinephrine](#) reuptake inhibitors (SNRI) as this may cause an increased risk of bleeding[106]. During clinical trials, concomitant use of NSAIDs and antidepressants, including tricyclic antidepressants, SSRIs, selective serotonin-norepinephrine reuptake inhibitors, and MAOIs, resulted in an increased risk of [intracranial hemorrhage](#) within 30 days of concomitant use compared with antidepressant use alone [107]. When NSAIDs and SNRIs are given concurrently, monitor the patient for signs of increased bleeding.
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: established
- 6) Clinical Management: Serotonin [norepinephrine](#) reuptake inhibitors (SNRI) increase bleeding risk, especially with concomitant use of NSAIDs[106]. When NSAIDs and SNRIs are given concurrently, monitor the patient for signs of increased bleeding.
- 7) Probable Mechanism: unknown
- 8) Literature Reports

a) Concomitant use of NSAIDs and antidepressants, including tricyclic antidepressants, SSRIs, serotonin-norepinephrine reuptake inhibitors, and MAOIs, resulted in an increased risk of [intracranial hemorrhage](#) within 30 days of concomitant use compared with antidepressant use alone. There was no significant difference between the antidepressant drug classes and the increased risk; however, there was an increased risk associated with male patients compared with female patients [107].

3.5.1.CX] 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[90].
- 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[90].
- 7) Probable Mechanism: inhibition of [norepinephrine](#) transporter function by antidepressants

3.5.1.CY] Isocarboxazid

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

2) Summary: Duloxetine exerts inhibitory effects on both norepinephrine and serotonin reuptake. Concurrent administration or overlapping therapy with duloxetine and an MAOI, such as isocarboxazid, may result in CNS toxicity or serotonin syndrome, a hyper-serotonergic state characterized by symptoms such as agitation and restlessness, myoclonus, changes in mental status, hyperreflexia, diaphoresis, shivering, and tremor. Serious, even fatal, reactions have been reported with concomitant use of serotonin-specific reuptake inhibitors and MAOIs. Concomitant administration of duloxetine and isocarboxazid is contraindicated, and a minimum of 14 days should elapse after discontinuing isocarboxazid before initiating therapy with duloxetine and a minimum of 5 days should elapse after discontinuing duloxetine before initiating therapy with isocarboxazid[78].

3) Severity: contraindicated

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Concurrent use of duloxetine and isocarboxazid is contraindicated. Wait at least 14 days after discontinuing isocarboxazid before initiating duloxetine. Wait at least 5 days after discontinuing duloxetine before initiating therapy with isocarboxazid[78].

7) Probable Mechanism: additive serotonergic effects

3.5.1.CZ| Ketoprofen

1) Interaction Effect: an increased risk of bleeding

2) Summary: Use caution when coadministering NSAIDs and serotonin norepinephrine reuptake inhibitors (SNRI) as this may cause an increased risk of bleeding[106]. During clinical trials, concomitant use of NSAIDs and antidepressants, including tricyclic antidepressants, SSRIs, selective serotonin-norepinephrine reuptake inhibitors, and MOAIs, resulted in an increased risk of intracranial hemorrhage within 30 days of concomitant use compared with antidepressant use alone [107]. When NSAIDs and SNRIs are given concurrently, monitor the patient for signs of increased bleeding.

3) Severity: major

4) Onset: unspecified

5) Substantiation: established

6) Clinical Management: Serotonin norepinephrine reuptake inhibitors (SNRI) increase bleeding risk, especially with concomitant use of NSAIDs[106]. When NSAIDs and SNRIs are given concurrently, monitor the patient for signs of increased bleeding.

7) Probable Mechanism: unknown

8) Literature Reports

a) Concomitant use of NSAIDs and antidepressants, including tricyclic antidepressants, SSRIs, serotonin-norepinephrine reuptake inhibitors, and MAOIs, resulted in an increased risk of intracranial hemorrhage within 30 days of concomitant use compared with antidepressant use alone. There was no significant difference between the antidepressant drug classes and the increased risk; however, there was an increased risk associated with male patients compared with female patients [107].

3.5.1.DA| Ketorolac

1) Interaction Effect: an increased risk of bleeding

2) Summary: Use caution when coadministering NSAIDs and serotonin norepinephrine reuptake inhibitors (SNRI) as this may cause an increased risk of bleeding[106]. During clinical trials, concomitant use of NSAIDs and antidepressants, including tricyclic antidepressants, SSRIs, selective serotonin-norepinephrine reuptake inhibitors, and MOAIs, resulted in an increased risk of intracranial hemorrhage within 30 days of concomitant use compared with antidepressant use alone [107]. When NSAIDs and SNRIs are given concurrently, monitor the patient for signs of increased bleeding.

- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: established
- 6) Clinical Management: Serotonin [norepinephrine](#) reuptake inhibitors (SNRI) increase bleeding risk, especially with concomitant use of NSAIDs[106]. When NSAIDs and SNRIs are given concurrently, monitor the patient for signs of increased bleeding.
- 7) Probable Mechanism: unknown
- 8) Literature Reports

a) Concomitant use of NSAIDs and antidepressants, including tricyclic antidepressants, SSRIs, serotonin-norepinephrine reuptake inhibitors, and MAOIs, resulted in an increased risk of [intracranial hemorrhage](#) within 30 days of concomitant use compared with antidepressant use alone. There was no significant difference between the antidepressant drug classes and the increased risk; however, there was an increased risk associated with male patients compared with female patients [107].

3.5.1.DB| Lamifiban

- 1) Interaction Effect: an increased risk of bleeding
- 2) Summary: The release of serotonin by [platelets](#) is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of selective serotonin and [norepinephrine](#) reuptake inhibitors (such as [duloxetine](#)) 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[51].
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: probable
- 6) Clinical Management: When [duloxetine](#) and an antiplatelet agent are given concurrently, monitor patient for signs of increased bleeding[51].
- 7) Probable Mechanism: unknown

3.5.1.DC| Lepirudin

- 1) Interaction Effect: altered [anticoagulation](#) effects, including increased risk of bleeding
- 2) Summary: Concomitant administration of [duloxetine](#) and an anticoagulant, such as [lepirudin](#) may result in altered [anticoagulation](#) effects. Coadministration of the anticoagulant [warfarin](#) and SSRIs or serotonin [norepinephrine](#) reuptake inhibitors has resulted in altered [anticoagulation](#) effects, including increased bleeding. The release of serotonin by [platelets](#) is involved in hemostasis[53]. A population-based, case-controlled study of new coumarin users (acenocoumarol and phenprocoumon) receiving concomitant SSRIs suggested an increased risk of hospitalization due to nongastrointestinal bleeding; however, the risk of [gastrointestinal bleeding](#) was not significantly different [54] If concomitant use of an anticoagulant and [duloxetine](#) is required, closely monitor [anticoagulation](#) effects during initiation or discontinuation of [duloxetine](#) [53].
- 3) Severity: moderate
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Concomitant use of [duloxetine](#) and an anticoagulant, such as [lepirudin](#), may increase the risk of bleeding. If concomitant use is required, carefully monitor [anticoagulation](#) effects during [duloxetine](#) initiation or discontinuation[53].
- 7) Probable Mechanism: unknown
- 8) Literature Reports

a) A population-based, case-controlled study of new coumarin users (acenocoumarol and phenprocoumon) receiving 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 [54].

3.5.1.DD] 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[135].

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[135].

7) Probable Mechanism: additive serotonergic effects

3.5.1.DE] Lexipafant

1) Interaction Effect: an increased risk of bleeding

2) Summary: The release of serotonin by [platelets](#) is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of selective serotonin and [norepinephrine](#) reuptake inhibitors (such as [duloxetine](#)) 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[51].

3) Severity: major

4) Onset: unspecified

5) Substantiation: probable

6) Clinical Management: When [duloxetine](#) and an antiplatelet agent are given concurrently, monitor patient for signs of increased bleeding[51].

7) Probable Mechanism: unknown

3.5.1.DF] Linezolid

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

2) Summary: [Linezolid](#) is a reversible, nonselective inhibitor of monoamine oxidase (MAO)[137]. Concurrent administration or overlapping therapy with [duloxetine](#) and a 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. There have been spontaneous reports of [serotonin syndrome](#) associated with concomitant use of [linezolid](#) and serotonergic agents, including one case report involving [duloxetine](#) [138]. Should concomitant therapy with [linezolid](#) and serotonergic agents be clinically necessary, closely observe the patient for signs and symptoms of [serotonin syndrome](#) (hyperreflexia, incoordination, [hyperpyrexia](#), or impaired cognition) [137]. [Serotonin syndrome](#) can be life-threatening. If [serotonin syndrome](#) develops, discontinue the offending agents and provide supportive care and other therapy as necessary [63].

3) Severity: contraindicated

4) Onset: rapid

5) Substantiation: probable

6) Clinical Management: Unless carefully monitored for [serotonin syndrome](#), [linezolid](#) should not be administered to patients taking [duloxetine](#)[137] . If [duloxetine](#) and [linezolid](#) are used concomitantly, monitor closely for symptoms of [serotonin syndrome](#) such as neuromuscular abnormalities (including hyper-reflexia, tremor, muscle rigidity, clonus, peripheral hypertonicity, and shivering), autonomic hyperactivity (including [tachycardia](#), mydriasis, diaphoresis, and diarrhea), and mental status changes (including agitation and [delirium](#)). [Serotonin syndrome](#) can be life-threatening. If [serotonin syndrome](#) develops, discontinue the offending agents and provide supportive care and other therapy as necessary [63].

7) Probable Mechanism: inhibition of monoamine oxidase-mediated serotonin metabolism

8) Literature Reports

a) [Serotonin syndrome](#) was induced in a 55-year-old woman maintained on [duloxetine](#) 60 mg/day for recurrent depression, following the addition of intravenous [linezolid](#) 600 mg every 12 hours to her treatment regimen. The patient was initially admitted to an inpatient oncology center for pain management and treatment of an infected dehiscing abdominal [wound](#). Due to persistence of vancomycin-resistant enterococcus in [wound](#) cultures, [linezolid](#) was added to the existing regimen. Approximately 3 hours after the first dose of [linezolid](#), the patient demonstrated mental status changes, including confusion, restlessness, agitation, and abnormal movements. Additional symptoms occurring over the following hours included new-onset dense insomnia, disorientation, nonsensical speech, involuntary movements of the extremities, continued agitation, and [roving eye movements](#). Laboratory data were noncontributory; a low-grade fever (38 degrees Celsius) was present. [Duloxetine](#) was discontinued and the patient improved throughout the day, returning to baseline mental and physical status by late afternoon. [Linezolid](#) was then discontinued, and 2 days later the patient chose to resume [duloxetine](#) at a 30-mg/day dose. [Duloxetine](#) was tolerated without incident for the remainder of her hospital stay. A week later, the patient died from malignancy-associated sepsis and [renal failure](#) [138].

3.5.1.DG| Lisdexamfetamine

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

2) Summary: Coadministration of an [amphetamine](#) and a serotonergic agent that inhibits CYP2D6 may result in increased [amphetamine](#) exposure and additional risk for [serotonin syndrome](#). If concomitant use of an [amphetamine](#) and such an agent is clinically required, initiate with lower doses and monitor patients carefully, especially during treatment initiation and dosage adjustment. Discontinue both drugs if [serotonin syndrome](#) is suspected[120].

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6J) Clinical Management: Coadministration of an [amphetamine](#) and another serotonergic agent may result in [serotonin syndrome](#), because both drugs affect the serotonergic neurotransmitter system. Additionally, coadministration of an [amphetamine](#) with a CYP2D6 inhibitor may increase [amphetamine](#) exposure, because [amphetamines](#) and their derivatives are metabolized to some degree by CYP2D6. An increase in [amphetamine](#) exposure may further increase risk of [serotonin syndrome](#). If concomitant use of an [amphetamine](#) and a serotonergic agent that inhibits CYP2D6 is clinically required, initiate with lower doses and monitor patients carefully, especially during treatment initiation and dosage adjustment. Discontinue both drugs if [serotonin syndrome](#) is suspected[120].

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

3.5.1.DHJ Lithium

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

2J) Summary: [Duloxetine](#) is a selective serotonin and [norepinephrine](#) reuptake inhibitor. Caution is advised when [duloxetine](#) is used concurrently with agents affecting the serotonergic neurotransmitter systems, such as [lithium](#), as this may increase the potential for [serotonin syndrome](#)[51]. If concomitant use is warranted, monitor for symptoms of [serotonin syndrome](#) such as neuromuscular abnormalities (including hyper-reflexia, tremor, muscle rigidity, clonus, peripheral hypertonicity, and shivering), autonomic hyperactivity (including [tachycardia](#), mydriasis, diaphoresis, and the presence of bowel sounds and diarrhea), and mental status changes (including agitation and [delirium](#)). Discuss the risks and symptoms of [serotonin syndrome](#) with patients who are prescribed this combination. If [serotonin syndrome](#) develops, discontinue the offending drugs, and provide supportive care, correction of vital signs, or other therapy, as necessary [63].

3J) Severity: major

4J) Onset: unspecified

5J) Substantiation: theoretical

6J) Clinical Management: Use caution if [duloxetine](#) is coadministered with [lithium](#) as this may result in an increased risk of [serotonin syndrome](#)[51]. In patients receiving these agents concurrently, monitor for symptoms of [serotonin syndrome](#) such as neuromuscular abnormalities (including hyper-reflexia, tremor, muscle rigidity, clonus, peripheral hypertonicity, and shivering), autonomic hyperactivity (including [tachycardia](#), mydriasis, diaphoresis, the presence of bowel sounds, and diarrhea), and mental status changes (including agitation and [delirium](#)). [Serotonin syndrome](#) can be life-threatening. If [serotonin syndrome](#) develops, discontinue the offending agents and provide supportive care, correction of vital signs, and other therapy as necessary [63].

7J) Probable Mechanism: additive serotonergic effects

3.5.1.DIJ Lofepramine

1J) Interaction Effect: increased tricyclic antidepressant serum concentrations and potential toxicity (eg, anticholinergic effects, sedation, confusion, [cardiac arrhythmias](#))

2J) Summary: The coadministration of [duloxetine](#) with a tricyclic antidepressant is likely to increase bioavailability of the tricyclic agent, increasing the risk of adverse events. [Duloxetine](#) is a moderately potent inhibitor of CYP2D6. When a single dose of the CYP2D6 substrate [desipramine](#) 50 mg and [duloxetine](#) 60 mg twice daily were coadministered, the [desipramine](#) AUC increased 3-fold over baseline[51].

3J) Severity: moderate

4J) Onset: unspecified

5J) Substantiation: theoretical

6J) Clinical Management: Use caution with the combined use of [duloxetine](#) with tricyclic antidepressants (TCAs). If concomitant therapy with [duloxetine](#) and a TCA is unavoidable, plasma concentrations of the

tricyclic should be closely monitored and dose adjustments made accordingly[51]. Also, monitor patients for signs and symptoms of TCA toxicity (eg, anticholinergic effects, sedation, confusion, and [cardiac arrhythmias](#)).

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

3.5.1.DJ] Lorcainide

1J) Interaction Effect: increased class IC antiarrhythmic serum concentrations and an increased risk of [cardiotoxicity](#) (QT prolongation, [torsades de pointes](#), [cardiac arrest](#))

2J) Summary: [Duloxetine](#) is a moderately potent inhibitor of CYP2D6. Given the narrow therapeutic dosing index for the class IC antiarrhythmic agents as well as considering that they are CYP2D6 substrates, caution and close monitoring are recommended whenever [duloxetine](#) is coadministered with this class of antiarrhythmic agents[51].

3J) Severity: major

4J) Onset: unspecified

5J) Substantiation: theoretical

6J) Clinical Management: Use caution when prescribing [duloxetine](#) to patients who take a class IC antiarrhythmic agent as this may cause elevated plasma concentrations of the antiarrhythmic[51]. Monitor class IC antiarrhythmic serum concentrations and ECG for signs of potential [cardiotoxicity](#) (eg, bradycardia, [heart block](#), and hypotension); adjust dose accordingly. Alternatively, consider selecting another antidepressant that has less of a potential for altering the pharmacokinetics of class IC antiarrhythmic agents.

7J) Probable Mechanism: inhibition of CYP2D6-mediated metabolism of class IC antiarrhythmic agents by [duloxetine](#)

3.5.1.DK] Lorcaserin

1J) Interaction Effect: increased [duloxetine](#) plasma concentrations; increased risk of [serotonin syndrome](#)

2J) Summary: In a clinical trial in 21 CYP2D6 extensive metabolizers, coadministration of lorcaserin, a CYP2D6 inhibitor, 10 mg twice a day for 4 days increased [dextromethorphan](#), a CYP2D6 substrate, peak concentrations (C_{max}) by approximately 76% and exposure (AUC) by approximately 2-fold[136]. Therefore the concomitant use of [duloxetine](#), a CYP2D6 substrate [40], and lorcaserin may cause increased [duloxetine](#) plasma concentrations resulting in increased [duloxetine](#) adverse effects. Lorcaserin is a serotonergic drug and concomitant use with another agent that affects the serotonergic neurotransmitter system, such as [duloxetine](#), may result in an increased risk of [serotonin syndrome](#) and should be approached with extreme caution [136].

3J) Severity: major

4J) Onset: unspecified

5J) Substantiation: theoretical

6J) Clinical Management: Use extreme caution with the concomitant use of [duloxetine](#) with lorcaserin as this may cause increased [duloxetine](#) plasma concentrations and may also result in additive serotonergic effects, increasing the risk of [serotonin syndrome](#)[136].

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

3.5.1.DL] Lornoxicam

1J) Interaction Effect: an increased risk of bleeding

2J) Summary: Use caution when coadministering NSAIDs and serotonin [norepinephrine](#) reuptake inhibitors (SNRI) as this may cause an increased risk of bleeding[106]. During clinical trials, concomitant use of NSAIDs and antidepressants, including tricyclic antidepressants, SSRIs, selective serotonin-

norepinephrine reuptake inhibitors, and MOAIs, resulted in an increased risk of [intracranial hemorrhage](#) within 30 days of concomitant use compared with antidepressant use alone [107]. When NSAIDs and SNRIs are given concurrently, monitor the patient for signs of increased bleeding.

3) Severity: major

4) Onset: unspecified

5) Substantiation: established

6) Clinical Management: Serotonin [norepinephrine](#) reuptake inhibitors (SNRI) increase bleeding risk, especially with concomitant use of NSAIDs[106]. When NSAIDs and SNRIs are given concurrently, monitor the patient for signs of increased bleeding.

7) Probable Mechanism: unknown

8) Literature Reports

a) Concomitant use of NSAIDs and antidepressants, including tricyclic antidepressants, SSRIs, serotonin-norepinephrine reuptake inhibitors, and MAOIs, resulted in an increased risk of [intracranial hemorrhage](#) within 30 days of concomitant use compared with antidepressant use alone. There was no significant difference between the antidepressant drug classes and the increased risk; however, there was an increased risk associated with male patients compared with female patients [107].

3.5.1.DM] Loxoprofen

1) Interaction Effect: an increased risk of bleeding

2) Summary: Use caution when coadministering NSAIDs and serotonin [norepinephrine](#) reuptake inhibitors (SNRI) as this may cause an increased risk of bleeding[106]. During clinical trials, concomitant use of NSAIDs and antidepressants, including tricyclic antidepressants, SSRIs, selective serotonin-norepinephrine reuptake inhibitors, and MOAIs, resulted in an increased risk of [intracranial hemorrhage](#) within 30 days of concomitant use compared with antidepressant use alone [107]. When NSAIDs and SNRIs are given concurrently, monitor the patient for signs of increased bleeding.

3) Severity: major

4) Onset: unspecified

5) Substantiation: established

6) Clinical Management: Serotonin [norepinephrine](#) reuptake inhibitors (SNRI) increase bleeding risk, especially with concomitant use of NSAIDs[106]. When NSAIDs and SNRIs are given concurrently, monitor the patient for signs of increased bleeding.

7) Probable Mechanism: unknown

8) Literature Reports

a) Concomitant use of NSAIDs and antidepressants, including tricyclic antidepressants, SSRIs, serotonin-norepinephrine reuptake inhibitors, and MAOIs, resulted in an increased risk of [intracranial hemorrhage](#) within 30 days of concomitant use compared with antidepressant use alone. There was no significant difference between the antidepressant drug classes and the increased risk; however, there was an increased risk associated with male patients compared with female patients [107].

3.5.1.DN] Lumiracoxib

1) Interaction Effect: an increased risk of bleeding

2) Summary: Use caution when coadministering NSAIDs and serotonin [norepinephrine](#) reuptake inhibitors (SNRI) as this may cause an increased risk of bleeding[106]. During clinical trials, concomitant use of NSAIDs and antidepressants, including tricyclic antidepressants, SSRIs, selective serotonin-norepinephrine reuptake inhibitors, and MOAIs, resulted in an increased risk of [intracranial hemorrhage](#)

within 30 days of concomitant use compared with antidepressant use alone [107]. When NSAIDs and SNRIs are given concurrently, monitor the patient for signs of increased bleeding.

3) Severity: major

4) Onset: unspecified

5) Substantiation: established

6) Clinical Management: Serotonin [norepinephrine](#) reuptake inhibitors (SNRI) increase bleeding risk, especially with concomitant use of NSAIDs[106]. When NSAIDs and SNRIs are given concurrently, monitor the patient for signs of increased bleeding.

7) Probable Mechanism: unknown

8) Literature Reports

a) Concomitant use of NSAIDs and antidepressants, including tricyclic antidepressants, SSRIs, serotonin-norepinephrine reuptake inhibitors, and MAOIs, resulted in an increased risk of [intracranial hemorrhage](#) within 30 days of concomitant use compared with antidepressant use alone. There was no significant difference between the antidepressant drug classes and the increased risk; however, there was an increased risk associated with male patients compared with female patients [107].

3.5.1.DO| [Meclofenamate](#)

1) Interaction Effect: an increased risk of bleeding

2) Summary: Use caution when coadministering NSAIDs and serotonin [norepinephrine](#) reuptake inhibitors (SNRI) as this may cause an increased risk of bleeding[106]. During clinical trials, concomitant use of NSAIDs and antidepressants, including tricyclic antidepressants, SSRIs, selective serotonin-norepinephrine reuptake inhibitors, and MOAIs, resulted in an increased risk of [intracranial hemorrhage](#) within 30 days of concomitant use compared with antidepressant use alone [107]. When NSAIDs and SNRIs are given concurrently, monitor the patient for signs of increased bleeding.

3) Severity: major

4) Onset: unspecified

5) Substantiation: established

6) Clinical Management: Serotonin [norepinephrine](#) reuptake inhibitors (SNRI) increase bleeding risk, especially with concomitant use of NSAIDs[106]. When NSAIDs and SNRIs are given concurrently, monitor the patient for signs of increased bleeding.

7) Probable Mechanism: unknown

8) Literature Reports

a) Concomitant use of NSAIDs and antidepressants, including tricyclic antidepressants, SSRIs, serotonin-norepinephrine reuptake inhibitors, and MAOIs, resulted in an increased risk of [intracranial hemorrhage](#) within 30 days of concomitant use compared with antidepressant use alone. There was no significant difference between the antidepressant drug classes and the increased risk; however, there was an increased risk associated with male patients compared with female patients [107].

3.5.1.DP| [Mefenamic Acid](#)

1) Interaction Effect: an increased risk of bleeding

2) Summary: Use caution when coadministering NSAIDs and serotonin [norepinephrine](#) reuptake inhibitors (SNRI) as this may cause an increased risk of bleeding[106]. During clinical trials, concomitant use of NSAIDs and antidepressants, including tricyclic antidepressants, SSRIs, selective serotonin-norepinephrine reuptake inhibitors, and MOAIs, resulted in an increased risk of [intracranial hemorrhage](#)

within 30 days of concomitant use compared with antidepressant use alone [107]. When NSAIDs and SNRIs are given concurrently, monitor the patient for signs of increased bleeding.

3) Severity: major

4) Onset: unspecified

5) Substantiation: established

6) Clinical Management: Serotonin [norepinephrine](#) reuptake inhibitors (SNRI) increase bleeding risk, especially with concomitant use of NSAIDs[106]. When NSAIDs and SNRIs are given concurrently, monitor the patient for signs of increased bleeding.

7) Probable Mechanism: unknown

8) Literature Reports

a) Concomitant use of NSAIDs and antidepressants, including tricyclic antidepressants, SSRIs, serotonin-norepinephrine reuptake inhibitors, and MAOIs, resulted in an increased risk of [intracranial hemorrhage](#) within 30 days of concomitant use compared with antidepressant use alone. There was no significant difference between the antidepressant drug classes and the increased risk; however, there was an increased risk associated with male patients compared with female patients [107].

3.5.1.DQ] Melitracen

1) Interaction Effect: increased tricyclic antidepressant serum concentrations and potential toxicity (eg, anticholinergic effects, sedation, confusion, [cardiac arrhythmias](#))

2) Summary: The coadministration of [duloxetine](#) with a tricyclic antidepressant is likely to increase bioavailability of the tricyclic agent, increasing the risk of adverse events. [Duloxetine](#) is a moderately potent inhibitor of CYP2D6. When a single dose of the CYP2D6 substrate [desipramine](#) 50 mg and [duloxetine](#) 60 mg twice daily were coadministered, the [desipramine](#) AUC increased 3-fold over baseline[51].

3) Severity: moderate

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Use caution with the combined use of [duloxetine](#) with tricyclic antidepressants (TCAs). If concomitant therapy with [duloxetine](#) and a TCA is unavoidable, plasma concentrations of the tricyclic should be closely monitored and dose adjustments made accordingly[51]. Also, monitor patients for signs and symptoms of TCA toxicity (eg, anticholinergic effects, sedation, confusion, and [cardiac arrhythmias](#)).

7) Probable Mechanism: [duloxetine](#) inhibition of CYP2D6-mediated tricyclic agent metabolism

3.5.1.DR] Meloxicam

1) Interaction Effect: an increased risk of bleeding

2) Summary: Use caution when coadministering NSAIDs and serotonin [norepinephrine](#) reuptake inhibitors (SNRI) as this may cause an increased risk of bleeding[106]. During clinical trials, concomitant use of NSAIDs and antidepressants, including tricyclic antidepressants, SSRIs, selective serotonin-norepinephrine reuptake inhibitors, and MOAIs, resulted in an increased risk of [intracranial hemorrhage](#) within 30 days of concomitant use compared with antidepressant use alone [107]. When NSAIDs and SNRIs are given concurrently, monitor the patient for signs of increased bleeding.

3) Severity: major

4) Onset: unspecified

5) Substantiation: established

6) Clinical Management: Serotonin [norepinephrine](#) reuptake inhibitors (SNRI) increase bleeding risk, especially with concomitant use of NSAIDs[106]. When NSAIDs and SNRIs are given concurrently, monitor the patient for signs of increased bleeding.

7J) Probable Mechanism: unknown

8J) Literature Reports

aJ) Concomitant use of NSAIDs and antidepressants, including tricyclic antidepressants, SSRIs, serotonin-norepinephrine reuptake inhibitors, and MAOIs, resulted in an increased risk of [intracranial hemorrhage](#) within 30 days of concomitant use compared with antidepressant use alone. There was no significant difference between the antidepressant drug classes and the increased risk; however, there was an increased risk associated with male patients compared with female patients [107].

3.5.1.DS] [Meperidine](#)

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

2J) Summary: [Meperidine](#) is considered a proserotonergic opioid and has been associated with [serotonin syndrome](#) when used concomitantly with other serotonergic agents[73]. Increased serotonin levels which may produce additive serotonergic effects can occur if serotonergic agents are taken concurrently with [meperidine](#). Symptoms of [serotonin syndrome](#) include neuromuscular abnormalities (including hyperreflexia, tremor, muscle rigidity, clonus, peripheral hypertonicity, and shivering), autonomic hyperactivity (including [tachycardia](#), mydriasis, diaphoresis, the presence of bowel sounds, and diarrhea), and mental status changes (including agitation and [delirium](#)). [Serotonin syndrome](#) can be life-threatening. If [serotonin syndrome](#) develops, discontinue the offending agents and provide supportive care and other therapy as necessary [63]. Use caution if [meperidine](#) and a serotonergic agent are coadministered and monitor patients for signs and symptoms of [serotonin syndrome](#).

3J) Severity: major

4J) Onset: unspecified

5J) Substantiation: theoretical

6J) Clinical Management: Use caution with concomitant administration of [meperidine](#) and this drug as this interaction may result in additive serotonergic effects and increase the risk of [serotonin syndrome](#). If coadministration is required, appropriate monitoring may be warranted.

7J) Probable Mechanism: additive serotonergic effects

3.5.1.DT] [Mesoridazine](#)

1J) Interaction Effect: increased phenothiazine serum concentrations and potential toxicity (sedation, confusion, [cardiac arrhythmias](#), orthostatic hypotension, [hyperthermia](#), extrapyramidal effects)

2J) Summary: [Duloxetine](#) is a moderately potent inhibitor of CYP2D6; therefore, the coadministration of [duloxetine](#) with a phenothiazine is likely to increase bioavailability of the phenothiazine agent, increasing the risk of serious adverse events[51].

3J) Severity: moderate

4J) Onset: unspecified

5J) Substantiation: theoretical

6J) Clinical Management: Use caution when prescribing [duloxetine](#) to patients who take phenothiazines as concomitant use may cause elevated phenothiazine plasma concentrations. Monitor for increased phenothiazine side effects[51].

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

3.5.1.DU] [Methadone](#)

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

2) Summary: Concurrent use of [duloxetine](#) and [methadone](#) may increase the risk of [serotonin syndrome](#). In a 45-year-old man treated with concurrent [duloxetine](#) and [methadone](#), [serotonin syndrome](#) occurred 2 weeks after the patient self-increased the [methadone](#) dose. All symptoms resolved upon discontinuation of [duloxetine](#) and [methadone](#) dose reduction[73]. If concomitant use is indicated, monitor for signs and symptoms of [serotonin syndrome](#); furthermore, dose reduction or change in therapy may be necessary.

3) Severity: major

4) Onset: unspecified

5) Substantiation: probable

6) Clinical Management: Concurrent use of [duloxetine](#) and [methadone](#) may increase the risk of [serotonin syndrome](#). If concomitant use is indicated, monitor for [serotonin syndrome](#) effects including confusion, [delirium](#), restlessness, tremors, blushing, diaphoresis, and [hyperpyrexia](#). Dose adjustment or change in therapy may be necessary.

7) Probable Mechanism: unknown

8) Literature Reports

a) [Serotonin syndrome](#) was reported in a 45-year-old man treated with concurrent [duloxetine](#) and [methadone](#). Although previously stable on a medication regimen including [duloxetine](#), low-dose [desipramine](#), and [methadone](#) 30 mg three times daily, the patient self-increased his [methadone](#) dose due to inadequate pain control. Two weeks later, he presented with complaints of tremulousness, fatigue, bilateral weakness in all extremities, and worsening insomnia and anxiety. Upon physical exam, he was hypertensive, diaphoretic, and tremulous; stiff extremities with passive range of motion without clonus and 3 patella reflexes were noted. A diagnosis of [serotonin syndrome](#) was established. [Duloxetine](#) was discontinued, and his [methadone](#) dose was reduced to the previously prescribed regimen. He continued [desipramine](#) at the same dosage, which he had been taking long term for insomnia. All symptoms resolved within 2 days [73].

3.5.1.DV] [Methamphetamine](#)

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

2) Summary: Coadministration of an [amphetamine](#) and a serotonergic agent that inhibits CYP2D6 may result in increased [amphetamine](#) exposure and additional risk for [serotonin syndrome](#). If concomitant use of an [amphetamine](#) and such an agent is clinically required, initiate with lower doses and monitor patients carefully, especially during treatment initiation and dosage adjustment. Discontinue both drugs if [serotonin syndrome](#) is suspected[120].

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Coadministration of an [amphetamine](#) and another serotonergic agent may result in [serotonin syndrome](#), because both drugs affect the serotonergic neurotransmitter system. Additionally, coadministration of an [amphetamine](#) with a CYP2D6 inhibitor may increase [amphetamine](#) exposure, because [amphetamines](#) and their derivatives are metabolized to some degree by CYP2D6. An increase in [amphetamine](#) exposure may further increase risk of [serotonin syndrome](#). If concomitant use of an [amphetamine](#) and a serotonergic agent that inhibits CYP2D6 is clinically required, initiate with lower doses and monitor patients carefully, especially during treatment initiation and dosage adjustment. Discontinue both drugs if [serotonin syndrome](#) is suspected[120].

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

3.5.1.DW] [Methdilazine](#)

- 1) Interaction Effect: increased phenothiazine serum concentrations and potential toxicity (sedation, confusion, [cardiac arrhythmias](#), orthostatic hypotension, [hyperthermia](#), extrapyramidal effects)
- 2) Summary: [Duloxetine](#) is a moderately potent inhibitor of CYP2D6; therefore, the coadministration of [duloxetine](#) with a phenothiazine is likely to increase bioavailability of the phenothiazine agent, increasing the risk of serious adverse events[51].
- 3) Severity: moderate
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Use caution when prescribing [duloxetine](#) to patients who take phenothiazines as concomitant use may cause elevated phenothiazine plasma concentrations. Monitor for increased phenothiazine side effects[51].
- 7) Probable Mechanism: [duloxetine](#) inhibition of CYP2D6-mediated phenothiazine metabolism

3.5.1.DX] [Methotrimeprazine](#)

- 1) Interaction Effect: increased phenothiazine serum concentrations and potential toxicity (sedation, confusion, [cardiac arrhythmias](#), orthostatic hypotension, [hyperthermia](#), extrapyramidal effects)
- 2) Summary: [Duloxetine](#) is a moderately potent inhibitor of CYP2D6; therefore, the coadministration of [duloxetine](#) with a phenothiazine is likely to increase bioavailability of the phenothiazine agent, increasing the risk of serious adverse events[51].
- 3) Severity: moderate
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Use caution when prescribing [duloxetine](#) to patients who take phenothiazines as concomitant use may cause elevated phenothiazine plasma concentrations. Monitor for increased phenothiazine side effects[51].
- 7) Probable Mechanism: [duloxetine](#) inhibition of CYP2D6-mediated phenothiazine metabolism

3.5.1.DY] [Methylene Blue](#)

- 1) Interaction Effect: an increased risk of [serotonin syndrome](#) (labile blood pressure, [hyperthermia](#), neuromuscular abnormalities, mental status changes, gastrointestinal symptoms) or neuroleptic malignant syndrome-like reactions
- 2) Summary: Concurrent use of [duloxetine](#) and methylene blue (an MAOI) is contraindicated. Concurrent administration may result in [serotonin syndrome](#) or neuroleptic malignant syndrome-like reactions with symptoms including neuromuscular abnormalities, autonomic instability, and mental status changes[53]. In settings where urgent treatment with methylene blue is not required, discontinue [duloxetine](#) at least 14 days prior to initiating treatment with methylene blue. If no alternative treatment is available and urgent methylene blue therapy is required, and the potential benefits outweigh the risk of [serotonin syndrome](#), [duloxetine](#) must be discontinued immediately [56]. Use the lowest possible dose of methylene blue [57]. Monitor for [serotonin syndrome](#) or [neuroleptic malignant syndrome](#) reactions for 2 weeks or until 24 hours after the last dose of methylene blue has been administered, whichever comes first. [Duloxetine](#) may be resumed 24 hours after the last dose of methylene blue has been given [56].
- 3) Severity: contraindicated
- 4) Onset: unspecified
- 5) Substantiation: probable
- 6) Clinical Management: Concurrent use of [duloxetine](#) and methylene blue (an MAOI) is contraindicated[53]. In settings where urgent treatment with methylene blue is not required, discontinue [duloxetine](#) at least 14 days prior to initiating treatment with methylene blue. If no alternative treatment is available and urgent methylene blue therapy is required for a patient on [duloxetine](#) therapy, and the

potential benefits outweigh the risk of [serotonin syndrome](#), [duloxetine](#) must be discontinued immediately [56]. Use the lowest possible dose of methylene blue [57]. Monitor for [serotonin syndrome](#) for 2 weeks or until 24 hours after the last dose of methylene blue has been administered, whichever comes first. [Duloxetine](#) may be resumed 24 hours after the last dose of methylene blue has been given [56].

7J) Probable Mechanism: inhibition of MAO-mediated serotonin metabolism by methylene blue

8J) Literature Reports

aJ) There have been reports of serious reactions, including fatalities, in patients receiving concomitant [duloxetine](#) and MAOIs. Reactions have included myoclonus, [hyperthermia](#), rapid fluctuations of vital signs, and extreme agitation progressing to [delirium](#) and coma [53].

3.5.1.DZJ [Metoclopramide](#)

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

2J) Summary: Concomitant use of [duloxetine](#) with [metoclopramide](#) may increase the risk of extrapyramidal symptoms, such as [tardive dyskinesia](#) or [neuroleptic malignant syndrome](#), and is contraindicated[125]. 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 [126].

3J) Severity: contraindicated

4J) Onset: unspecified

5J) Substantiation: theoretical

6J) Clinical Management: Concomitant use of [duloxetine](#) with [metoclopramide](#) is contraindicated[125]. 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 [126].

7J) Probable Mechanism: unknown

3.5.1.EAJ [Metopimazine](#)

1J) Interaction Effect: increased phenothiazine serum concentrations and potential toxicity (sedation, confusion, [cardiac arrhythmias](#), orthostatic hypotension, [hyperthermia](#), extrapyramidal effects)

2J) Summary: [Duloxetine](#) is a moderately potent inhibitor of CYP2D6; therefore, the coadministration of [duloxetine](#) with a phenothiazine is likely to increase bioavailability of the phenothiazine agent, increasing the risk of serious adverse events[51].

3J) Severity: moderate

4J) Onset: unspecified

5J) Substantiation: theoretical

6J) Clinical Management: Use caution when prescribing [duloxetine](#) to patients who take phenothiazines as concomitant use may cause elevated phenothiazine plasma concentrations. Monitor for increased phenothiazine side effects[51].

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

3.5.1.EBJ [Milnacipran](#)

1J) 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[99].

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[99].

7) Probable Mechanism: additive serotonergic effect

3.5.1.EC] Mirabegron

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

2) Summary: Patients concurrently treated with mirabegron, a moderate CYP2D6 inhibitor[127], and [duloxetine](#), a CYP2D6 substrate [40], may have an increase in [duloxetine](#) exposure and risk of adverse events. Appropriate monitoring is advised when mirabegron is used concomitantly with a CYP2D6 substrate [127] and [duloxetine](#) dose adjustments may be necessary.

3) Severity: moderate

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Concomitant use of mirabegron, a moderate CYP2D6 inhibitor[127], and [duloxetine](#), a CYP2D6 substrate [40], may result in increased [duloxetine](#) exposure. If concurrent use is warranted, monitoring is recommended, and dose adjustments may be necessary.[127].

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

3.5.1.ED] 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[96]. 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 [63].

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](#)[96].

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 [97].

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 [98].

3.5.1.EE] Morniflumate

1)) Interaction Effect: an increased risk of bleeding

2)) Summary: Use caution when coadministering NSAIDs and serotonin [norepinephrine](#) reuptake inhibitors (SNRI) as this may cause an increased risk of bleeding[106]. During clinical trials, concomitant use of NSAIDs and antidepressants, including tricyclic antidepressants, SSRIs, selective serotonin-norepinephrine reuptake inhibitors, and MOAIs, resulted in an increased risk of [intracranial hemorrhage](#) within 30 days of concomitant use compared with antidepressant use alone [107]. When NSAIDs and SNRIs are given concurrently, monitor the patient for signs of increased bleeding.

3)) Severity: major

4)) Onset: unspecified

5)) Substantiation: established

6)) Clinical Management: Serotonin [norepinephrine](#) reuptake inhibitors (SNRI) increase bleeding risk, especially with concomitant use of NSAIDs[106]. When NSAIDs and SNRIs are given concurrently, monitor the patient for signs of increased bleeding.

7)) Probable Mechanism: unknown

8)) Literature Reports

a)) Concomitant use of NSAIDs and antidepressants, including tricyclic antidepressants, SSRIs, serotonin-norepinephrine reuptake inhibitors, and MAOIs, resulted in an increased risk of [intracranial hemorrhage](#) within 30 days of concomitant use compared with antidepressant use alone. There was no significant difference between the antidepressant drug classes and the increased risk; however, there was an increased risk associated with male patients compared with female patients [107].

3.5.1.EF] Nabumetone

1)) Interaction Effect: an increased risk of bleeding

2)) Summary: Use caution when coadministering NSAIDs and serotonin [norepinephrine](#) reuptake inhibitors (SNRI) as this may cause an increased risk of bleeding[106]. During clinical trials, concomitant

use of NSAIDs and antidepressants, including tricyclic antidepressants, SSRIs, selective serotonin-norepinephrine reuptake inhibitors, and MAOIs, resulted in an increased risk of [intracranial hemorrhage](#) within 30 days of concomitant use compared with antidepressant use alone [107]. When NSAIDs and SNRIs are given concurrently, monitor the patient for signs of increased bleeding.

3) Severity: major

4) Onset: unspecified

5) Substantiation: established

6) Clinical Management: Serotonin [norepinephrine](#) reuptake inhibitors (SNRI) increase bleeding risk, especially with concomitant use of NSAIDs[106]. When NSAIDs and SNRIs are given concurrently, monitor the patient for signs of increased bleeding.

7) Probable Mechanism: unknown

8) Literature Reports

a) Concomitant use of NSAIDs and antidepressants, including tricyclic antidepressants, SSRIs, serotonin-norepinephrine reuptake inhibitors, and MAOIs, resulted in an increased risk of [intracranial hemorrhage](#) within 30 days of concomitant use compared with antidepressant use alone. There was no significant difference between the antidepressant drug classes and the increased risk; however, there was an increased risk associated with male patients compared with female patients [107].

3.5.1.EG] Nadroparin

1) Interaction Effect: altered [anticoagulation](#) effects, including increased risk of bleeding

2) Summary: Concomitant administration of [duloxetine](#) and an anticoagulant, such as nadroparin, may result in altered [anticoagulation](#) effects. Coadministration of the anticoagulant [warfarin](#) and SSRIs or serotonin [norepinephrine](#) reuptake inhibitors has resulted in altered [anticoagulation](#) effects, including increased bleeding. The release of serotonin by [platelets](#) is involved in hemostasis[53]. A population-based, case-controlled study of new coumarin users (acenocoumarol and phenprocoumon) receiving concomitant SSRIs suggested an increased risk of hospitalization due to nongastrointestinal bleeding; however, the risk of [gastrointestinal bleeding](#) was not significantly different [54]. If concomitant use of an anticoagulant and [duloxetine](#) is required, closely monitor [anticoagulation](#) effects during initiation or discontinuation of [duloxetine](#) [53].

3) Severity: moderate

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Concomitant use of [duloxetine](#) and an anticoagulant, such as nadroparin, may increase the risk of bleeding. If concomitant use is required, carefully monitor [anticoagulation](#) effects during [duloxetine](#) initiation or discontinuation[53].

7) Probable Mechanism: unknown

8) Literature Reports

a) A population-based, case-controlled study of new coumarin users (acenocoumarol and phenprocoumon) receiving 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 [54].

3.5.1.EH] Naproxen

- 1) Interaction Effect: an increased risk of bleeding
- 2) Summary: Use caution when coadministering NSAIDs and serotonin [norepinephrine](#) reuptake inhibitors (SNRI) as this may cause an increased risk of bleeding[106]. During clinical trials, concomitant use of NSAIDs and antidepressants, including tricyclic antidepressants, SSRIs, selective serotonin-norepinephrine reuptake inhibitors, and MAOIs, resulted in an increased risk of [intracranial hemorrhage](#) within 30 days of concomitant use compared with antidepressant use alone [107]. When NSAIDs and SNRIs are given concurrently, monitor the patient for signs of increased bleeding.
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: established
- 6) Clinical Management: Serotonin [norepinephrine](#) reuptake inhibitors (SNRI) increase bleeding risk, especially with concomitant use of NSAIDs[106]. When NSAIDs and SNRIs are given concurrently, monitor the patient for signs of increased bleeding.
- 7) Probable Mechanism: unknown
- 8) Literature Reports

a) Concomitant use of NSAIDs and antidepressants, including tricyclic antidepressants, SSRIs, serotonin-norepinephrine reuptake inhibitors, and MAOIs, resulted in an increased risk of [intracranial hemorrhage](#) within 30 days of concomitant use compared with antidepressant use alone. There was no significant difference between the antidepressant drug classes and the increased risk; however, there was an increased risk associated with male patients compared with female patients [107].

3.5.1.EI] Naratriptan

- 1) Interaction Effect: increased risk of [serotonin syndrome](#)
- 2) Summary: A life-threatening condition known as [serotonin syndrome](#) may occur when triptans, such as [naratriptan](#), are used in combination with a serotonin and [norepinephrine](#) reuptake inhibitor (SNRI), such as [duloxetine](#). 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 SNRI 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](#), especially during treatment initiation and dose increases[51] [87].
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Coadministration of a triptan, such as [naratriptan](#), and a serotonin and [norepinephrine](#) reuptake inhibitor (SNRI), such as [duloxetine](#), 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 SNRI 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), especially during treatment initiation and dose increases[51].
- 7) Probable Mechanism: additive pharmacologic effects resulting in excessive serotonergic stimulation

3.5.1.EJ] Nebivolol

- 1) Interaction Effect: increased exposure to nebivolol
- 2) Summary: Nebivolol is partially metabolized by the CYP2D6 isozyme. Concomitant use of nebivolol and a CYP2D6 inhibitor should be avoided[82] as it may increase plasma concentrations of nebivolol [82] [83]. If coadministration is required, patients should be closely monitored, and dose adjustment may be required [83].
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Concomitant use of nebivolol and a CYP2D6 inhibitor should be avoided[82] as it may increase plasma concentrations of nebivolol[82][83]. If coadministration is required, patients should be closely monitored, and dose adjustment may be required [83].
- 7) Probable Mechanism: inhibition of CYP2D6-mediated metabolism of nebivolol
- 8) Literature Reports

a) Coadministration of single dose of nebivolol 5 mg to healthy volunteers (n=23) who received [paroxetine](#) 20 to 40 mg/day for 6 days resulted in a 6.1-fold increase in nebivolol exposure and a 5.7-fold increase in the exposure of the nebivolol active metabolite. Significant increases were seen in nebivolol C_{max} (1.78 to 4.24 ng/mL), T_{max} (1.37 to 3.11 hours), and AUC (17.26 to 106.2 ng x hr/mL) [84].

b) Coadministration of a single 10-mg dose of nebivolol in healthy adults (n=10) who received [fluoxetine](#) at a dose of 20 mg/day for 21 days led to an 8-fold increase in AUC and 3-fold increase in C_{max} of d-nebivolol (pharmacologically active isomer) [82].

3.5.1.EK] Nepafenac

- 1) Interaction Effect: an increased risk of bleeding
- 2) Summary: Use caution when coadministering NSAIDs and serotonin [norepinephrine](#) reuptake inhibitors (SNRI) as this may cause an increased risk of bleeding[106]. During clinical trials, concomitant use of NSAIDs and antidepressants, including tricyclic antidepressants, SSRIs, selective serotonin-norepinephrine reuptake inhibitors, and MOAIs, resulted in an increased risk of [intracranial hemorrhage](#) within 30 days of concomitant use compared with antidepressant use alone [107]. When NSAIDs and SNRIs are given concurrently, monitor the patient for signs of increased bleeding.
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: established
- 6) Clinical Management: Serotonin [norepinephrine](#) reuptake inhibitors (SNRI) increase bleeding risk, especially with concomitant use of NSAIDs[106]. When NSAIDs and SNRIs are given concurrently, monitor the patient for signs of increased bleeding.
- 7) Probable Mechanism: unknown
- 8) Literature Reports

a) Concomitant use of NSAIDs and antidepressants, including tricyclic antidepressants, SSRIs, serotonin-norepinephrine reuptake inhibitors, and MAOIs, resulted in an increased risk of [intracranial hemorrhage](#) within 30 days of concomitant use compared with antidepressant use alone. There was no significant difference between the antidepressant drug classes and the increased risk; however, there was an increased risk associated with male patients compared with female patients [107].

3.5.1.EL] Niflumic Acid

- 1) Interaction Effect: an increased risk of bleeding
- 2) Summary: Use caution when coadministering NSAIDs and serotonin [norepinephrine](#) reuptake inhibitors (SNRI) as this may cause an increased risk of bleeding[106]. During clinical trials, concomitant use of NSAIDs and antidepressants, including tricyclic antidepressants, SSRIs, selective serotonin-norepinephrine reuptake inhibitors, and MOAIs, resulted in an increased risk of [intracranial hemorrhage](#) within 30 days of concomitant use compared with antidepressant use alone [107]. When NSAIDs and SNRIs are given concurrently, monitor the patient for signs of increased bleeding.
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: established
- 6) Clinical Management: Serotonin [norepinephrine](#) reuptake inhibitors (SNRI) increase bleeding risk, especially with concomitant use of NSAIDs[106]. When NSAIDs and SNRIs are given concurrently, monitor the patient for signs of increased bleeding.
- 7) Probable Mechanism: unknown
- 8) Literature Reports

a) Concomitant use of NSAIDs and antidepressants, including tricyclic antidepressants, SSRIs, serotonin-norepinephrine reuptake inhibitors, and MAOIs, resulted in an increased risk of [intracranial hemorrhage](#) within 30 days of concomitant use compared with antidepressant use alone. There was no significant difference between the antidepressant drug classes and the increased risk; however, there was an increased risk associated with male patients compared with female patients [107].

3.5.1.EM] Nimesulide

- 1) Interaction Effect: an increased risk of bleeding
- 2) Summary: Use caution when coadministering NSAIDs and serotonin [norepinephrine](#) reuptake inhibitors (SNRI) as this may cause an increased risk of bleeding[106]. During clinical trials, concomitant use of NSAIDs and antidepressants, including tricyclic antidepressants, SSRIs, selective serotonin-norepinephrine reuptake inhibitors, and MOAIs, resulted in an increased risk of [intracranial hemorrhage](#) within 30 days of concomitant use compared with antidepressant use alone [107]. When NSAIDs and SNRIs are given concurrently, monitor the patient for signs of increased bleeding.
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: established
- 6) Clinical Management: Serotonin [norepinephrine](#) reuptake inhibitors (SNRI) increase bleeding risk, especially with concomitant use of NSAIDs[106]. When NSAIDs and SNRIs are given concurrently, monitor the patient for signs of increased bleeding.
- 7) Probable Mechanism: unknown
- 8) Literature Reports

a) Concomitant use of NSAIDs and antidepressants, including tricyclic antidepressants, SSRIs, serotonin-norepinephrine reuptake inhibitors, and MAOIs, resulted in an increased risk of [intracranial hemorrhage](#) within 30 days of concomitant use compared with antidepressant use alone. There was no significant difference between the antidepressant drug classes and the increased risk; however, there was an increased risk associated with male patients compared with female patients [107].

3.5.1.EN] Nimesulide Beta Cyclodextrin

- 1) Interaction Effect: an increased risk of bleeding
- 2) Summary: Use caution when coadministering NSAIDs and serotonin [norepinephrine](#) reuptake inhibitors (SNRI) as this may cause an increased risk of bleeding[106]. During clinical trials, concomitant use of NSAIDs and antidepressants, including tricyclic antidepressants, SSRIs, selective serotonin-norepinephrine reuptake inhibitors, and MAOIs, resulted in an increased risk of [intracranial hemorrhage](#) within 30 days of concomitant use compared with antidepressant use alone [107]. When NSAIDs and SNRIs are given concurrently, monitor the patient for signs of increased bleeding.
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: established
- 6) Clinical Management: Serotonin [norepinephrine](#) reuptake inhibitors (SNRI) increase bleeding risk, especially with concomitant use of NSAIDs[106]. When NSAIDs and SNRIs are given concurrently, monitor the patient for signs of increased bleeding.
- 7) Probable Mechanism: unknown
- 8) Literature Reports

a) Concomitant use of NSAIDs and antidepressants, including tricyclic antidepressants, SSRIs, serotonin-norepinephrine reuptake inhibitors, and MAOIs, resulted in an increased risk of [intracranial hemorrhage](#) within 30 days of concomitant use compared with antidepressant use alone. There was no significant difference between the antidepressant drug classes and the increased risk; however, there was an increased risk associated with male patients compared with female patients [107].

3.5.1.EO] Nortriptyline

- 1) Interaction Effect: increased tricyclic antidepressant serum concentrations and potential toxicity (eg, anticholinergic effects, sedation, confusion, [cardiac arrhythmias](#))
- 2) Summary: The coadministration of [duloxetine](#) with a tricyclic antidepressant is likely to increase bioavailability of the tricyclic agent, increasing the risk of adverse events. [Duloxetine](#) is a moderately potent inhibitor of CYP2D6. When a single dose of the CYP2D6 substrate [desipramine](#) 50 mg and [duloxetine](#) 60 mg twice daily were coadministered, the [desipramine](#) AUC increased 3-fold over baseline[51].
- 3) Severity: moderate
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Use caution with the combined use of [duloxetine](#) with tricyclic antidepressants (TCAs). If concomitant therapy with [duloxetine](#) and a TCA is unavoidable, plasma concentrations of the tricyclic should be closely monitored and dose adjustments made accordingly[51]. Also, monitor patients for signs and symptoms of TCA toxicity (eg, anticholinergic effects, sedation, confusion, and [cardiac arrhythmias](#)).
- 7) Probable Mechanism: [duloxetine](#) inhibition of CYP2D6-mediated tricyclic agent metabolism

3.5.1.EP] Opipramol

- 1) Interaction Effect: increased tricyclic antidepressant serum concentrations and potential toxicity (eg, anticholinergic effects, sedation, confusion, [cardiac arrhythmias](#))
- 2) Summary: The coadministration of [duloxetine](#) with a tricyclic antidepressant is likely to increase bioavailability of the tricyclic agent, increasing the risk of adverse events. [Duloxetine](#) is a moderately

potent inhibitor of CYP2D6. When a single dose of the CYP2D6 substrate [desipramine](#) 50 mg and [duloxetine](#) 60 mg twice daily were coadministered, the [desipramine](#) AUC increased 3-fold over baseline[51].

3) Severity: moderate

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Use caution with the combined use of [duloxetine](#) with tricyclic antidepressants (TCAs). If concomitant therapy with [duloxetine](#) and a TCA is unavoidable, plasma concentrations of the tricyclic should be closely monitored and dose adjustments made accordingly[51]. Also, monitor patients for signs and symptoms of TCA toxicity (eg, anticholinergic effects, sedation, confusion, and [cardiac arrhythmias](#)).

7) Probable Mechanism: [duloxetine](#) inhibition of CYP2D6-mediated tricyclic agent metabolism

3.5.1.EQ| [Oxaprozin](#)

1) Interaction Effect: an increased risk of bleeding

2) Summary: Use caution when coadministering NSAIDs and serotonin [norepinephrine](#) reuptake inhibitors (SNRI) as this may cause an increased risk of bleeding[106]. During clinical trials, concomitant use of NSAIDs and antidepressants, including tricyclic antidepressants, SSRIs, selective serotonin-norepinephrine reuptake inhibitors, and MAOIs, resulted in an increased risk of [intracranial hemorrhage](#) within 30 days of concomitant use compared with antidepressant use alone [107]. When NSAIDs and SNRIs are given concurrently, monitor the patient for signs of increased bleeding.

3) Severity: major

4) Onset: unspecified

5) Substantiation: established

6) Clinical Management: Serotonin [norepinephrine](#) reuptake inhibitors (SNRI) increase bleeding risk, especially with concomitant use of NSAIDs[106]. When NSAIDs and SNRIs are given concurrently, monitor the patient for signs of increased bleeding.

7) Probable Mechanism: unknown

8) Literature Reports

a) Concomitant use of NSAIDs and antidepressants, including tricyclic antidepressants, SSRIs, serotonin-norepinephrine reuptake inhibitors, and MAOIs, resulted in an increased risk of [intracranial hemorrhage](#) within 30 days of concomitant use compared with antidepressant use alone. There was no significant difference between the antidepressant drug classes and the increased risk; however, there was an increased risk associated with male patients compared with female patients [107].

3.5.1.ER| [Oxycodone](#)

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

2) Summary: Coadministration of [oxycodone](#) and another serotonergic agent may result in [serotonin syndrome](#), because both drugs affect the serotonergic neurotransmitter system. If concomitant use of [oxycodone](#) and such an agent is clinically required, monitor patients carefully, especially during treatment initiation and dosage adjustment. Discontinue [oxycodone](#) if [serotonin syndrome](#) is suspected[95].

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Coadministration of [oxycodone](#) and another serotonergic agent may result in [serotonin syndrome](#), because both drugs affect the serotonergic neurotransmitter system. If concomitant use of [oxycodone](#) and such an agent is clinically required, monitor patients carefully, especially

during treatment initiation and dosage adjustment. Discontinue [oxycodone](#) if [serotonin syndrome](#) is suspected[95].

7J) Probable Mechanism: additive serotonergic effect

3.5.1.ES] Oxyphenbutazone

1J) Interaction Effect: an increased risk of bleeding

2J) Summary: Use caution when coadministering NSAIDs and serotonin [norepinephrine](#) reuptake inhibitors (SNRI) as this may cause an increased risk of bleeding[106]. During clinical trials, concomitant use of NSAIDs and antidepressants, including tricyclic antidepressants, SSRIs, selective serotonin-norepinephrine reuptake inhibitors, and MAOIs, resulted in an increased risk of [intracranial hemorrhage](#) within 30 days of concomitant use compared with antidepressant use alone [107]. When NSAIDs and SNRIs are given concurrently, monitor the patient for signs of increased bleeding.

3J) Severity: major

4J) Onset: unspecified

5J) Substantiation: established

6J) Clinical Management: Serotonin [norepinephrine](#) reuptake inhibitors (SNRI) increase bleeding risk, especially with concomitant use of NSAIDs[106]. When NSAIDs and SNRIs are given concurrently, monitor the patient for signs of increased bleeding.

7J) Probable Mechanism: unknown

8J) Literature Reports

aJ) Concomitant use of NSAIDs and antidepressants, including tricyclic antidepressants, SSRIs, serotonin-norepinephrine reuptake inhibitors, and MAOIs, resulted in an increased risk of [intracranial hemorrhage](#) within 30 days of concomitant use compared with antidepressant use alone. There was no significant difference between the antidepressant drug classes and the increased risk; however, there was an increased risk associated with male patients compared with female patients [107].

3.5.1.ET] Palonosetron

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

2J) 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](#)[119].

3J) Severity: major

4J) Onset: unspecified

5J) Substantiation: theoretical

6J) 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](#)[119].

7J) Probable Mechanism: unknown

3.5.1.EU] Parecoxib

1J) Interaction Effect: an increased risk of bleeding

2) Summary: Use caution when coadministering NSAIDs and serotonin [norepinephrine](#) reuptake inhibitors (SNRI) as this may cause an increased risk of bleeding[106]. During clinical trials, concomitant use of NSAIDs and antidepressants, including tricyclic antidepressants, SSRIs, selective serotonin-norepinephrine reuptake inhibitors, and MAOIs, resulted in an increased risk of [intracranial hemorrhage](#) within 30 days of concomitant use compared with antidepressant use alone [107]. When NSAIDs and SNRIs are given concurrently, monitor the patient for signs of increased bleeding.

3) Severity: major

4) Onset: unspecified

5) Substantiation: established

6) Clinical Management: Serotonin [norepinephrine](#) reuptake inhibitors (SNRI) increase bleeding risk, especially with concomitant use of NSAIDs[106]. When NSAIDs and SNRIs are given concurrently, monitor the patient for signs of increased bleeding.

7) Probable Mechanism: unknown

8) Literature Reports

a) Concomitant use of NSAIDs and antidepressants, including tricyclic antidepressants, SSRIs, serotonin-norepinephrine reuptake inhibitors, and MAOIs, resulted in an increased risk of [intracranial hemorrhage](#) within 30 days of concomitant use compared with antidepressant use alone. There was no significant difference between the antidepressant drug classes and the increased risk; however, there was an increased risk associated with male patients compared with female patients [107].

3.5.1.EV] [Paroxetine](#)

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

2) Summary: [Duloxetine](#) is a selective serotonin and [norepinephrine](#) reuptake inhibitor (SNRI). The concomitant use of [duloxetine](#) with [paroxetine](#), an SSRI, is not recommended due to the potential for [serotonin syndrome](#). In addition, coadministration of [paroxetine](#), a potent CYP2D6 inhibitor, at a dose of 20 mg once daily with [duloxetine](#) 40 mg once daily resulted in a 60% increase in [duloxetine](#) serum concentration[51].

3) Severity: major

4) Onset: unspecified

5) Substantiation: probable

6) Clinical Management: The concomitant use of [duloxetine](#) and [paroxetine](#) is not recommended due to the potential for development of [serotonin syndrome](#). Additionally, concomitant use has resulted in significantly increased [duloxetine](#) serum levels[51].

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

3.5.1.EW] [Perazine](#)

1) Interaction Effect: increased phenothiazine serum concentrations and potential toxicity (sedation, confusion, [cardiac arrhythmias](#), orthostatic hypotension, [hyperthermia](#), extrapyramidal effects)

2) Summary: [Duloxetine](#) is a moderately potent inhibitor of CYP2D6; therefore, the coadministration of [duloxetine](#) with a phenothiazine is likely to increase bioavailability of the phenothiazine agent, increasing the risk of serious adverse events[51].

3) Severity: moderate

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Use caution when prescribing [duloxetine](#) to patients who take phenothiazines as concomitant use may cause elevated phenothiazine plasma concentrations. Monitor for increased phenothiazine side effects[51].

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

3.5.1.EX] Periciazine

1) Interaction Effect: increased phenothiazine serum concentrations and potential toxicity (sedation, confusion, [cardiac arrhythmias](#), orthostatic hypotension, [hyperthermia](#), extrapyramidal effects)

2) Summary: [Duloxetine](#) is a moderately potent inhibitor of CYP2D6; therefore, the coadministration of [duloxetine](#) with a phenothiazine is likely to increase bioavailability of the phenothiazine agent, increasing the risk of serious adverse events[51].

3) Severity: moderate

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Use caution when prescribing [duloxetine](#) to patients who take phenothiazines as concomitant use may cause elevated phenothiazine plasma concentrations. Monitor for increased phenothiazine side effects[51].

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

3.5.1.EY] Perphenazine

1) Interaction Effect: increased phenothiazine serum concentrations and potential toxicity (sedation, confusion, [cardiac arrhythmias](#), orthostatic hypotension, [hyperthermia](#), extrapyramidal effects)

2) Summary: [Duloxetine](#) is a moderately potent inhibitor of CYP2D6; therefore, the coadministration of [duloxetine](#) with a phenothiazine is likely to increase bioavailability of the phenothiazine agent, increasing the risk of serious adverse events[51].

3) Severity: moderate

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Use caution when prescribing [duloxetine](#) to patients who take phenothiazines as concomitant use may cause elevated phenothiazine plasma concentrations. Monitor for increased phenothiazine side effects[51].

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

3.5.1.EZ] Phenelzine

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

2) Summary: [Duloxetine](#) exerts inhibitory effects on both [norepinephrine](#) and serotonin reuptake. Concurrent administration or overlapping therapy with [duloxetine](#) and an MAOI, such as [phenelzine](#), may result in [serotonin syndrome](#), a hyperserotonergic state characterized by symptoms such as agitation and restlessness, myoclonus, changes in mental status, hyperreflexia, diaphoresis, shivering, and tremor. Serious, even fatal, reactions have been reported with concomitant use of serotonin-specific reuptake inhibitors and MAOIs. Concomitant administration of [duloxetine](#) and [phenelzine](#) is contraindicated. A minimum of 14 days should elapse after discontinuing [phenelzine](#) before initiating therapy with [duloxetine](#), and a minimum of 5 days should elapse after discontinuing [duloxetine](#) before initiating therapy with [phenelzine](#)[35].

3) Severity: contraindicated

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Concurrent use of [duloxetine](#) and [phenelzine](#) is contraindicated. Wait at least 14 days after discontinuing [phenelzine](#) before initiating [duloxetine](#). Wait at least 5 days after discontinuing [duloxetine](#) before initiating therapy with [phenelzine](#)[35].

7) Probable Mechanism: additive serotonergic effect

3.5.1.FA] Phenindione

1) Interaction Effect: altered [anticoagulation](#) effects, including increased risk of bleeding

2) Summary: Concomitant administration of [duloxetine](#) and an anticoagulant, such as phenindione may result in altered [anticoagulation](#) effects. Coadministration of the anticoagulant [warfarin](#) and SSRIs or serotonin [norepinephrine](#) reuptake inhibitors has resulted in altered [anticoagulation](#) effects, including increased bleeding. The release of serotonin by [platelets](#) is involved in hemostasis[53]. A population-based, case-controlled study of new coumarin users (acenocoumarol and phenprocoumon) receiving concomitant SSRIs suggested an increased risk of hospitalization due to nongastrointestinal bleeding; however, the risk of [gastrointestinal bleeding](#) was not significantly different [54] If concomitant use of [duloxetine](#) and an anticoagulant is required, closely monitor [anticoagulation](#) effects during initiation or discontinuation of [duloxetine](#) [53].

3) Severity: moderate

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Concomitant use of [duloxetine](#) and an anticoagulant, such as phenindione, may increase the risk of bleeding. If concomitant use is required, carefully monitor [anticoagulation](#) effects during [duloxetine](#) initiation or discontinuation[53].

7) Probable Mechanism: unknown

8) Literature Reports

a) A population-based, case-controlled study of new coumarin users (acenocoumarol and phenprocoumon) receiving 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 [54].

3.5.1.FB] Phenprocoumon

1) Interaction Effect: altered [anticoagulation](#) including increased risk of bleeding

2) Summary: Concomitant use of [duloxetine](#) and phenprocoumon may result in altered [anticoagulation](#), including increased risk of bleeding. The release of serotonin by [platelets](#) is involved in hemostasis[53]. A population-based, case-controlled study of new coumarin users (acenocoumarol and phenprocoumon) receiving concomitant SSRIs suggested an increased risk of hospitalization due to nongastrointestinal bleeding; however, the risk of [gastrointestinal bleeding](#) was not significantly different [54]. If concomitant use is required, close monitoring of [anticoagulation](#) during initiation or discontinuation of [duloxetine](#) is recommended [53].

3) Severity: moderate

4) Onset: unspecified

5) Substantiation: established

6) Clinical Management: Concomitant use of [duloxetine](#) and phenprocoumon may alter [anticoagulation](#). Carefully monitor [anticoagulation](#) effects during [duloxetine](#) initiation or discontinuation[53].

7) Probable Mechanism: unknown

8) Literature Reports

a) 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 [54].

3.5.1.FC] [Phenylbutazone](#)

1) Interaction Effect: an increased risk of bleeding

2) Summary: Use caution when coadministering NSAIDs and serotonin [norepinephrine](#) reuptake inhibitors (SNRI) as this may cause an increased risk of bleeding[106]. During clinical trials, concomitant use of NSAIDs and antidepressants, including tricyclic antidepressants, SSRIs, selective serotonin-norepinephrine reuptake inhibitors, and MOAIs, resulted in an increased risk of [intracranial hemorrhage](#) within 30 days of concomitant use compared with antidepressant use alone [107]. When NSAIDs and SNRIs are given concurrently, monitor the patient for signs of increased bleeding.

3) Severity: major

4) Onset: unspecified

5) Substantiation: established

6) Clinical Management: Serotonin [norepinephrine](#) reuptake inhibitors (SNRI) increase bleeding risk, especially with concomitant use of NSAIDs[106]. When NSAIDs and SNRIs are given concurrently, monitor the patient for signs of increased bleeding.

7) Probable Mechanism: unknown

8) Literature Reports

a) Concomitant use of NSAIDs and antidepressants, including tricyclic antidepressants, SSRIs, serotonin-norepinephrine reuptake inhibitors, and MAOIs, resulted in an increased risk of [intracranial hemorrhage](#) within 30 days of concomitant use compared with antidepressant use alone. There was no significant difference between the antidepressant drug classes and the increased risk; however, there was an increased risk associated with male patients compared with female patients [107].

3.5.1.FD] [Piketoprofen](#)

1) Interaction Effect: an increased risk of bleeding

2) Summary: Use caution when coadministering NSAIDs and serotonin [norepinephrine](#) reuptake inhibitors (SNRI) as this may cause an increased risk of bleeding[106]. During clinical trials, concomitant use of NSAIDs and antidepressants, including tricyclic antidepressants, SSRIs, selective serotonin-norepinephrine reuptake inhibitors, and MOAIs, resulted in an increased risk of [intracranial hemorrhage](#) within 30 days of concomitant use compared with antidepressant use alone [107]. When NSAIDs and SNRIs are given concurrently, monitor the patient for signs of increased bleeding.

3) Severity: major

4) Onset: unspecified

5) Substantiation: established

6) Clinical Management: Serotonin [norepinephrine](#) reuptake inhibitors (SNRI) increase bleeding risk, especially with concomitant use of NSAIDs[106]. When NSAIDs and SNRIs are given concurrently, monitor the patient for signs of increased bleeding.

7) Probable Mechanism: unknown

8) Literature Reports

a) Concomitant use of NSAIDs and antidepressants, including tricyclic antidepressants, SSRIs, serotonin-norepinephrine reuptake inhibitors, and MAOIs, resulted in an increased risk of [intracranial hemorrhage](#) within 30 days of concomitant use compared with antidepressant use alone. There was no significant difference between the antidepressant drug classes and the increased risk; however, there was an increased risk associated with male patients compared with female patients [107].

3.5.1.FE] Pipotiazine

1) Interaction Effect: increased phenothiazine serum concentrations and potential toxicity (sedation, confusion, [cardiac arrhythmias](#), orthostatic hypotension, [hyperthermia](#), extrapyramidal effects)

2) Summary: [Duloxetine](#) is a moderately potent inhibitor of CYP2D6; therefore, the coadministration of [duloxetine](#) with a phenothiazine is likely to increase bioavailability of the phenothiazine agent, increasing the risk of serious adverse events[51].

3) Severity: moderate

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Use caution when prescribing [duloxetine](#) to patients who take phenothiazines as concomitant use may cause elevated phenothiazine plasma concentrations. Monitor for increased phenothiazine side effects[51].

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

3.5.1.FF] Piroxicam

1) Interaction Effect: an increased risk of bleeding

2) Summary: Use caution when coadministering NSAIDs and serotonin [norepinephrine](#) reuptake inhibitors (SNRI) as this may cause an increased risk of bleeding[106]. During clinical trials, concomitant use of NSAIDs and antidepressants, including tricyclic antidepressants, SSRIs, selective serotonin-norepinephrine reuptake inhibitors, and MOAIs, resulted in an increased risk of [intracranial hemorrhage](#) within 30 days of concomitant use compared with antidepressant use alone [107]. When NSAIDs and SNRIs are given concurrently, monitor the patient for signs of increased bleeding.

3) Severity: major

4) Onset: unspecified

5) Substantiation: established

6) Clinical Management: Serotonin [norepinephrine](#) reuptake inhibitors (SNRI) increase bleeding risk, especially with concomitant use of NSAIDs[106]. When NSAIDs and SNRIs are given concurrently, monitor the patient for signs of increased bleeding.

7) Probable Mechanism: unknown

8) Literature Reports

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

increased risk; however, there was an increased risk associated with male patients compared with female patients [107].

3.5.1.FG] Pixantrone

- 1) Interaction Effect: increased exposure of CYP1A2 substrates
- 2) Summary: Concurrent administration of pixantrone (a CYP1A2 inhibitor) and a CYP1A2 substrate may increase the exposure of the CYP1A2 substrate. If concomitant administration is required, use caution and monitor the patient closely[94].
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Concurrent administration of pixantrone (a CYP1A2 inhibitor) and a CYP1A2 substrate may increase the exposure of the CYP1A2 substrate. If concomitant administration is required, use caution and monitor the patient closely[94].
- 7) Probable Mechanism: inhibition of CYP1A2-mediated metabolism by pixantrone

3.5.1.FH] Pranoprofen

- 1) Interaction Effect: an increased risk of bleeding
- 2) Summary: Use caution when coadministering NSAIDs and serotonin [norepinephrine](#) reuptake inhibitors (SNRI) as this may cause an increased risk of bleeding[106]. During clinical trials, concomitant use of NSAIDs and antidepressants, including tricyclic antidepressants, SSRIs, selective serotonin-norepinephrine reuptake inhibitors, and MAOIs, resulted in an increased risk of [intracranial hemorrhage](#) within 30 days of concomitant use compared with antidepressant use alone [107]. When NSAIDs and SNRIs are given concurrently, monitor the patient for signs of increased bleeding.
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: established
- 6) Clinical Management: Serotonin [norepinephrine](#) reuptake inhibitors (SNRI) increase bleeding risk, especially with concomitant use of NSAIDs[106]. When NSAIDs and SNRIs are given concurrently, monitor the patient for signs of increased bleeding.
- 7) Probable Mechanism: unknown
- 8) Literature Reports

a) Concomitant use of NSAIDs and antidepressants, including tricyclic antidepressants, SSRIs, serotonin-norepinephrine reuptake inhibitors, and MAOIs, resulted in an increased risk of [intracranial hemorrhage](#) within 30 days of concomitant use compared with antidepressant use alone. There was no significant difference between the antidepressant drug classes and the increased risk; however, there was an increased risk associated with male patients compared with female patients [107].

3.5.1.FI] Procarbazine

- 1) Interaction Effect: CNS toxicity or [serotonin syndrome](#) (hypertension, hyperthermia, myoclonus, mental status changes)
- 2) Summary: [Duloxetine](#) exerts inhibitory effects on both [norepinephrine](#) and serotonin reuptake. Concurrent administration or overlapping therapy with [duloxetine](#) and an MAOI, such as [procarbazine](#), may result in CNS toxicity or [serotonin syndrome](#), a hyper-serotonergic state characterized by symptoms such as agitation and restlessness, myoclonus, changes in mental status, hyperreflexia, diaphoresis, shivering, and tremor. Serious, even fatal, reactions have been reported with concomitant use of serotonin-

specific reuptake inhibitors and MAOIs. Concomitant administration of [duloxetine](#) and [procarbazine](#) is contraindicated, and a minimum of 14 days should elapse after discontinuing [procarbazine](#) before initiating therapy with [duloxetine](#) and a minimum of 5 days should elapse after discontinuing [duloxetine](#) before initiating therapy with [procarbazine](#)[78].

3) Severity: contraindicated

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Concurrent use of [duloxetine](#) and [procarbazine](#) is contraindicated. Wait at least 14 days after discontinuing [procarbazine](#) before initiating [duloxetine](#). Wait at least 5 days after discontinuing [duloxetine](#) before initiating therapy with [procarbazine](#)[78].

7) Probable Mechanism: additive serotonergic effects

3.5.1.FJ] [Prochlorperazine](#)

1) Interaction Effect: increased phenothiazine serum concentrations and potential toxicity (sedation, confusion, [cardiac arrhythmias](#), orthostatic hypotension, [hyperthermia](#), extrapyramidal effects)

2) Summary: [Duloxetine](#) is a moderately potent inhibitor of CYP2D6; therefore, the coadministration of [duloxetine](#) with a phenothiazine is likely to increase bioavailability of the phenothiazine agent, increasing the risk of serious adverse events[51].

3) Severity: moderate

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Use caution when prescribing [duloxetine](#) to patients who take phenothiazines as concomitant use may cause elevated phenothiazine plasma concentrations. Monitor for increased phenothiazine side effects[51].

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

3.5.1.FK] [Proglumetacin](#)

1) Interaction Effect: an increased risk of bleeding

2) Summary: Use caution when coadministering NSAIDs and serotonin [norepinephrine](#) reuptake inhibitors (SNRI) as this may cause an increased risk of bleeding[106]. During clinical trials, concomitant use of NSAIDs and antidepressants, including tricyclic antidepressants, SSRIs, selective serotonin-norepinephrine reuptake inhibitors, and MOAIs, resulted in an increased risk of [intracranial hemorrhage](#) within 30 days of concomitant use compared with antidepressant use alone [107]. When NSAIDs and SNRIs are given concurrently, monitor the patient for signs of increased bleeding.

3) Severity: major

4) Onset: unspecified

5) Substantiation: established

6) Clinical Management: Serotonin [norepinephrine](#) reuptake inhibitors (SNRI) increase bleeding risk, especially with concomitant use of NSAIDs[106]. When NSAIDs and SNRIs are given concurrently, monitor the patient for signs of increased bleeding.

7) Probable Mechanism: unknown

8) Literature Reports

a) Concomitant use of NSAIDs and antidepressants, including tricyclic antidepressants, SSRIs, serotonin-norepinephrine reuptake inhibitors, and MAOIs, resulted in an increased risk of [intracranial hemorrhage](#) within 30 days of concomitant use compared with antidepressant use alone. There was no significant difference between the antidepressant drug classes and the increased risk; however, there was an increased risk associated with male patients compared with female patients [107].

3.5.1.FL] Promazine

- 1) Interaction Effect: increased phenothiazine serum concentrations and potential toxicity (sedation, confusion, [cardiac arrhythmias](#), orthostatic hypotension, [hyperthermia](#), extrapyramidal effects)
- 2) Summary: [Duloxetine](#) is a moderately potent inhibitor of CYP2D6; therefore, the coadministration of [duloxetine](#) with a phenothiazine is likely to increase bioavailability of the phenothiazine agent, increasing the risk of serious adverse events[51].
- 3) Severity: moderate
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Use caution when prescribing [duloxetine](#) to patients who take phenothiazines as concomitant use may cause elevated phenothiazine plasma concentrations. Monitor for increased phenothiazine side effects[51].
- 7) Probable Mechanism: [duloxetine](#) inhibition of CYP2D6-mediated phenothiazine metabolism

3.5.1.FM] Promethazine

- 1) Interaction Effect: increased phenothiazine serum concentrations and potential toxicity (sedation, confusion, [cardiac arrhythmias](#), orthostatic hypotension, [hyperthermia](#), extrapyramidal effects)
- 2) Summary: [Duloxetine](#) is a moderately potent inhibitor of CYP2D6; therefore, the coadministration of [duloxetine](#) with a phenothiazine is likely to increase bioavailability of the phenothiazine agent, increasing the risk of serious adverse events[51].
- 3) Severity: moderate
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Use caution when prescribing [duloxetine](#) to patients who take phenothiazines as concomitant use may cause elevated phenothiazine plasma concentrations. Monitor for increased phenothiazine side effects[51].
- 7) Probable Mechanism: [duloxetine](#) inhibition of CYP2D6-mediated phenothiazine metabolism

3.5.1.FN] Propafenone

- 1) Interaction Effect: increased class IC antiarrhythmic serum concentrations and an increased risk of [cardiotoxicity](#) (QT prolongation, [torsades de pointes](#), [cardiac arrest](#))
- 2) Summary: [Duloxetine](#) is a moderately potent inhibitor of CYP2D6. Given the narrow therapeutic dosing index for the class IC antiarrhythmic agents as well as considering that they are CYP2D6 substrates, caution and close monitoring are recommended whenever [duloxetine](#) is coadministered with this class of antiarrhythmic agents[51].
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Use caution when prescribing [duloxetine](#) to patients who take a class IC antiarrhythmic agent as this may cause elevated plasma concentrations of the antiarrhythmic[51]. Monitor class IC antiarrhythmic serum concentrations and ECG for signs of potential [cardiotoxicity](#) (eg, bradycardia, [heart block](#), and hypotension); adjust dose accordingly. Alternatively, consider selecting another antidepressant that has less of a potential for altering the pharmacokinetics of class IC antiarrhythmic agents.
- 7) Probable Mechanism: inhibition of CYP2D6-mediated metabolism of class IC antiarrhythmic agents by [duloxetine](#)

3.5.1.FO] Propiomazine

- 1) Interaction Effect: increased phenothiazine serum concentrations and potential toxicity (sedation, confusion, [cardiac arrhythmias](#), orthostatic hypotension, [hyperthermia](#), extrapyramidal effects)
- 2) Summary: [Duloxetine](#) is a moderately potent inhibitor of CYP2D6; therefore, the coadministration of [duloxetine](#) with a phenothiazine is likely to increase bioavailability of the phenothiazine agent, increasing the risk of serious adverse events[51].
- 3) Severity: moderate
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Use caution when prescribing [duloxetine](#) to patients who take phenothiazines as concomitant use may cause elevated phenothiazine plasma concentrations. Monitor for increased phenothiazine side effects[51].
- 7) Probable Mechanism: [duloxetine](#) inhibition of CYP2D6-mediated phenothiazine metabolism

3.5.1.FP] Propranolol

- 1) Interaction Effect: increased [propranolol](#) exposure
- 2) Summary: Use caution when coadministering [propranolol](#) (CYP2D6 substrate) and a CYP2D6 inhibitor as this interaction may result in increased [propranolol](#) exposure. If concomitant use is required, monitor patients for bradycardia or hypotension[124].
- 3) Severity: moderate
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Concomitant use of [propranolol](#), CYP2D6 substrate, and a CYP2D6 inhibitor may result in increased [propranolol](#) exposure. If coadministration is required, monitor patients for bradycardia or hypotension[124].
- 7) Probable Mechanism: inhibition of CYP2D6-mediated [propranolol](#) metabolism

3.5.1.FQ] Propyphenazone

- 1) Interaction Effect: an increased risk of bleeding
- 2) Summary: Use caution when coadministering NSAIDs and serotonin [norepinephrine](#) reuptake inhibitors (SNRI) as this may cause an increased risk of bleeding[106]. During clinical trials, concomitant use of NSAIDs and antidepressants, including tricyclic antidepressants, SSRIs, selective serotonin-norepinephrine reuptake inhibitors, and MAOIs, resulted in an increased risk of [intracranial hemorrhage](#) within 30 days of concomitant use compared with antidepressant use alone [107]. When NSAIDs and SNRIs are given concurrently, monitor the patient for signs of increased bleeding.
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: established
- 6) Clinical Management: Serotonin [norepinephrine](#) reuptake inhibitors (SNRI) increase bleeding risk, especially with concomitant use of NSAIDs[106]. When NSAIDs and SNRIs are given concurrently, monitor the patient for signs of increased bleeding.
- 7) Probable Mechanism: unknown
- 8) Literature Reports

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

alone. There was no significant difference between the antidepressant drug classes and the increased risk; however, there was an increased risk associated with male patients compared with female patients [107].

3.5.1.FR] Proquazone

- 1) Interaction Effect: an increased risk of bleeding
- 2) Summary: Use caution when coadministering NSAIDs and serotonin [norepinephrine](#) reuptake inhibitors (SNRI) as this may cause an increased risk of bleeding[106]. During clinical trials, concomitant use of NSAIDs and antidepressants, including tricyclic antidepressants, SSRIs, selective serotonin-norepinephrine reuptake inhibitors, and MOAIs, resulted in an increased risk of [intracranial hemorrhage](#) within 30 days of concomitant use compared with antidepressant use alone [107]. When NSAIDs and SNRIs are given concurrently, monitor the patient for signs of increased bleeding.
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: established
- 6) Clinical Management: Serotonin [norepinephrine](#) reuptake inhibitors (SNRI) increase bleeding risk, especially with concomitant use of NSAIDs[106]. When NSAIDs and SNRIs are given concurrently, monitor the patient for signs of increased bleeding.
- 7) Probable Mechanism: unknown
- 8) Literature Reports

a) Concomitant use of NSAIDs and antidepressants, including tricyclic antidepressants, SSRIs, serotonin-norepinephrine reuptake inhibitors, and MAOIs, resulted in an increased risk of [intracranial hemorrhage](#) within 30 days of concomitant use compared with antidepressant use alone. There was no significant difference between the antidepressant drug classes and the increased risk; however, there was an increased risk associated with male patients compared with female patients [107].

3.5.1.FS] Protein C

- 1) Interaction Effect: altered [anticoagulation](#) effects, including increased risk of bleeding
- 2) Summary: Concomitant administration of [duloxetine](#) and an anticoagulant, such as protein C may result in altered [anticoagulation](#) effects. Coadministration of the anticoagulant [warfarin](#) and SSRIs or serotonin [norepinephrine](#) reuptake inhibitors has resulted in altered [anticoagulation](#) effects, including increased bleeding. The release of serotonin by [platelets](#) is involved in hemostasis[53]. A population-based, case-controlled study of new coumarin users (acenocoumarol and phenprocoumon) receiving concomitant SSRIs suggested an increased risk of hospitalization due to nongastrointestinal bleeding; however, the risk of [gastrointestinal bleeding](#) was not significantly different [54] If concomitant use of [duloxetine](#) and an anticoagulant is required, closely monitor [anticoagulation](#) effects during initiation or discontinuation of [duloxetine](#) [53].
- 3) Severity: moderate
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Concomitant use of [duloxetine](#) and an anticoagulant, such as protein C, may increase the risk of bleeding. If concomitant use is required, carefully monitor [anticoagulation](#) effects during [duloxetine](#) initiation or discontinuation[53].
- 7) Probable Mechanism: unknown
- 8) Literature Reports

a)) A population-based, case-controlled study of new coumarin users (acenocoumarol and phenprocoumon) receiving 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 [54].

3.5.1.FT] [Protriptyline](#)

- 1)) Interaction Effect: increased tricyclic antidepressant serum concentrations and potential toxicity (eg, anticholinergic effects, sedation, confusion, [cardiac arrhythmias](#))
- 2)) Summary: The coadministration of [duloxetine](#) with a tricyclic antidepressant is likely to increase bioavailability of the tricyclic agent, increasing the risk of adverse events. [Duloxetine](#) is a moderately potent inhibitor of CYP2D6. When a single dose of the CYP2D6 substrate [desipramine](#) 50 mg and [duloxetine](#) 60 mg twice daily were coadministered, the [desipramine](#) AUC increased 3-fold over baseline[51].
- 3)) Severity: moderate
- 4)) Onset: unspecified
- 5)) Substantiation: theoretical
- 6)) Clinical Management: Use caution with the combined use of [duloxetine](#) with tricyclic antidepressants (TCAs). If concomitant therapy with [duloxetine](#) and a TCA is unavoidable, plasma concentrations of the tricyclic should be closely monitored and dose adjustments made accordingly[51]. Also, monitor patients for signs and symptoms of TCA toxicity (eg, anticholinergic effects, sedation, confusion, and [cardiac arrhythmias](#)).
- 7)) Probable Mechanism: [duloxetine](#) inhibition of CYP2D6-mediated tricyclic agent metabolism

3.5.1.FU] [Quinidine](#)

- 1)) Interaction Effect: increased [duloxetine](#) serum concentrations and risk of adverse effects
- 2)) Summary: The coadministration of [duloxetine](#) (a substrate of CYP2D6) with [quinidine](#) (a potent inhibitor of CYP2D6) is likely to increase the bioavailability of [duloxetine](#), increasing the risk of serious adverse events. Coadministration of [duloxetine](#) 40 mg once daily with another potent CYP2D6 inhibitor ([paroxetine](#) 20 mg once daily) resulted in a 60% increase in the serum concentration of [duloxetine](#)[51].
- 3)) Severity: moderate
- 4)) Onset: unspecified
- 5)) Substantiation: theoretical
- 6)) Clinical Management: Use caution when prescribing [duloxetine](#) to patients who take [quinidine](#) as concomitant use of [duloxetine](#) and [quinidine](#) may cause elevated [duloxetine](#) plasma concentrations[51].
- 7)) Probable Mechanism: [quinidine](#) inhibition of CYP2D6-mediated [duloxetine](#) metabolism

3.5.1.FV] [Rasagiline](#)

- 1)) Interaction Effect: CNS toxicity or [serotonin syndrome](#) (hypertension, hyperthermia, myoclonus, mental status changes)
- 2)) Summary: [Duloxetine](#) exerts inhibitory effects on both [norepinephrine](#) and serotonin reuptake. Concurrent administration or overlapping therapy with [duloxetine](#) and an MAOI, such as [rasagiline](#), may result in CNS toxicity or [serotonin syndrome](#), a hyper-serotonergic state characterized by symptoms such as agitation and restlessness, myoclonus, changes in mental status, hyperreflexia, diaphoresis,

shivering, and tremor. Serious, even fatal, reactions have been reported with concomitant use of serotonin-specific reuptake inhibitors and MAOIs. Concomitant administration of [duloxetine](#) and [rasagiline](#) is contraindicated, and a minimum of 14 days should elapse after discontinuing [rasagiline](#) before initiating therapy with [duloxetine](#) and a minimum of 5 days should elapse after discontinuing [duloxetine](#) before initiating therapy with [rasagiline](#)[78].

3J) Severity: contraindicated

4J) Onset: unspecified

5J) Substantiation: theoretical

6J) Clinical Management: Concurrent use of [duloxetine](#) and [rasagiline](#) is contraindicated. Wait at least 14 days after discontinuing [rasagiline](#) before initiating [duloxetine](#). Wait at least 5 days after discontinuing [duloxetine](#) before initiating therapy with [rasagiline](#)[78].

7J) Probable Mechanism: additive serotonergic effects

3.5.1.FW] Recainam

1J) Interaction Effect: increased class IC antiarrhythmic serum concentrations and an increased risk of [cardiotoxicity](#) (QT prolongation, [torsades de pointes](#), [cardiac arrest](#))

2J) Summary: [Duloxetine](#) is a moderately potent inhibitor of CYP2D6. Given the narrow therapeutic dosing index for the class IC antiarrhythmic agents as well as considering that they are CYP2D6 substrates, caution and close monitoring are recommended whenever [duloxetine](#) is coadministered with this class of antiarrhythmic agents[51].

3J) Severity: major

4J) Onset: unspecified

5J) Substantiation: theoretical

6J) Clinical Management: Use caution when prescribing [duloxetine](#) to patients who take a class IC antiarrhythmic agent as this may cause elevated plasma concentrations of the antiarrhythmic[51]. Monitor class IC antiarrhythmic serum concentrations and ECG for signs of potential [cardiotoxicity](#) (eg, bradycardia, [heart block](#), and hypotension); adjust dose accordingly. Alternatively, consider selecting another antidepressant that has less of a potential for altering the pharmacokinetics of class IC antiarrhythmic agents.

7J) Probable Mechanism: inhibition of CYP2D6-mediated metabolism of class IC antiarrhythmic agents by [duloxetine](#)

3.5.1.FX] Rivaroxaban

1J) Interaction Effect: increased risk of bleeding

2J) Summary: Use caution with concomitant use of rivaroxaban and a serotonin [norepinephrine](#) reuptake inhibitor or SSRI, as additive effects on bleeding may occur. If signs or symptoms of blood loss occur following coadministration, promptly evaluate the patient and consider whether blood replacement is needed, as bleeding may be serious or fatal[81].

3J) Severity: major

4J) Onset: unspecified

5J) Substantiation: theoretical

6J) Clinical Management: Use caution with concomitant use of rivaroxaban and a serotonin [norepinephrine](#) reuptake inhibitor or SSRI, as additive effects on bleeding may occur. If signs or symptoms of blood loss occur following coadministration, promptly evaluate the patient and consider whether blood replacement is needed, as bleeding may be serious or fatal[81].

7J) Probable Mechanism: additive effects on bleeding

3.5.1.FY] Rizatriptan

- 1) Interaction Effect: increased risk of [serotonin syndrome](#)
- 2) Summary: A life-threatening condition known as [serotonin syndrome](#) may occur when triptans, such as [rizatriptan](#), are used in combination with a serotonin and [norepinephrine](#) reuptake inhibitor (SNRI), such as [duloxetine](#). 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 SNRI 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](#), especially during treatment initiation and dose increases[51] [87].
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Coadministration of a triptan, such as [rizatriptan](#), and a serotonin and [norepinephrine](#) reuptake inhibitor (SNRI), such as [duloxetine](#), 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 SNRI 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), especially during treatment initiation and dose increases[51].
- 7) Probable Mechanism: additive pharmacologic effects resulting in excessive serotonergic stimulation

3.5.1.FZ] [Rofecoxib](#)

- 1) Interaction Effect: an increased risk of bleeding
- 2) Summary: Use caution when coadministering NSAIDs and serotonin [norepinephrine](#) reuptake inhibitors (SNRI) as this may cause an increased risk of bleeding[106]. During clinical trials, concomitant use of NSAIDs and antidepressants, including tricyclic antidepressants, SSRIs, selective serotonin-norepinephrine reuptake inhibitors, and MAOIs, resulted in an increased risk of [intracranial hemorrhage](#) within 30 days of concomitant use compared with antidepressant use alone [107]. When NSAIDs and SNRIs are given concurrently, monitor the patient for signs of increased bleeding.
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: established
- 6) Clinical Management: Serotonin [norepinephrine](#) reuptake inhibitors (SNRI) increase bleeding risk, especially with concomitant use of NSAIDs[106]. When NSAIDs and SNRIs are given concurrently, monitor the patient for signs of increased bleeding.
- 7) Probable Mechanism: unknown
- 8) Literature Reports

a) Concomitant use of NSAIDs and antidepressants, including tricyclic antidepressants, SSRIs, serotonin-norepinephrine reuptake inhibitors, and MAOIs, resulted in an increased risk of [intracranial hemorrhage](#) within 30 days of concomitant use compared with antidepressant use alone. There was no significant difference between the antidepressant drug classes and the increased risk; however, there was an increased risk associated with male patients compared with female patients [107].

3.5.1.GA] [Safinamide](#)

- 1) Interaction Effect: Risk of [serotonin syndrome](#)

- 2) Summary: Concomitant use of serotonergic agents with safinamide (a MAOI-type B) is contraindicated due to the potential for [serotonin syndrome](#). Use of serotonergic agents within 14 days of discontinuing a MAOI is also contraindicated[88].
- 3) Severity: contraindicated
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Concomitant use of serotonergic agents with safinamide (a MAOI-type B) is contraindicated due to the potential for [serotonin syndrome](#). Use of serotonergic agents within 14 days of discontinuing a MAOI is also contraindicated[88].
- 7) Probable Mechanism: Additive serotonergic effects

3.5.1.GB] [Salicylic Acid](#)

- 1) Interaction Effect: an increased risk of bleeding
- 2) Summary: Use caution when coadministering NSAIDs and serotonin [norepinephrine](#) reuptake inhibitors (SNRI) as this may cause an increased risk of bleeding[106]. During clinical trials, concomitant use of NSAIDs and antidepressants, including tricyclic antidepressants, SSRIs, selective serotonin-norepinephrine reuptake inhibitors, and MOAIs, resulted in an increased risk of [intracranial hemorrhage](#) within 30 days of concomitant use compared with antidepressant use alone [107]. When NSAIDs and SNRIs are given concurrently, monitor the patient for signs of increased bleeding.
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: established
- 6) Clinical Management: Serotonin [norepinephrine](#) reuptake inhibitors (SNRI) increase bleeding risk, especially with concomitant use of NSAIDs[106]. When NSAIDs and SNRIs are given concurrently, monitor the patient for signs of increased bleeding.
- 7) Probable Mechanism: unknown
- 8) Literature Reports

a) Concomitant use of NSAIDs and antidepressants, including tricyclic antidepressants, SSRIs, serotonin-norepinephrine reuptake inhibitors, and MAOIs, resulted in an increased risk of [intracranial hemorrhage](#) within 30 days of concomitant use compared with antidepressant use alone. There was no significant difference between the antidepressant drug classes and the increased risk; however, there was an increased risk associated with male patients compared with female patients [107].

3.5.1.GC] [Salsalate](#)

- 1) Interaction Effect: an increased risk of bleeding
- 2) Summary: Use caution when coadministering NSAIDs and serotonin [norepinephrine](#) reuptake inhibitors (SNRI) as this may cause an increased risk of bleeding[106]. During clinical trials, concomitant use of NSAIDs and antidepressants, including tricyclic antidepressants, SSRIs, selective serotonin-norepinephrine reuptake inhibitors, and MOAIs, resulted in an increased risk of [intracranial hemorrhage](#) within 30 days of concomitant use compared with antidepressant use alone [107]. When NSAIDs and SNRIs are given concurrently, monitor the patient for signs of increased bleeding.
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: established
- 6) Clinical Management: Serotonin [norepinephrine](#) reuptake inhibitors (SNRI) increase bleeding risk, especially with concomitant use of NSAIDs[106]. When NSAIDs and SNRIs are given concurrently, monitor the patient for signs of increased bleeding.

7J) Probable Mechanism: unknown

8J) Literature Reports

aJ) Concomitant use of NSAIDs and antidepressants, including tricyclic antidepressants, SSRIs, serotonin-norepinephrine reuptake inhibitors, and MAOIs, resulted in an increased risk of [intracranial hemorrhage](#) within 30 days of concomitant use compared with antidepressant use alone. There was no significant difference between the antidepressant drug classes and the increased risk; however, there was an increased risk associated with male patients compared with female patients [107].

3.5.1.GD] [Selegiline](#)

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

2J) Summary: [Duloxetine](#) exerts inhibitory effects on both [norepinephrine](#) and serotonin reuptake. Concurrent administration or overlapping therapy with [duloxetine](#) and an MAOI, such as [selegiline](#), may result in CNS toxicity or [serotonin syndrome](#), a hyper-serotonergic state characterized by symptoms such as agitation and restlessness, myoclonus, changes in mental status, hyperreflexia, diaphoresis, shivering, and tremor. Serious, even fatal, reactions have been reported with concomitant use of serotonin-specific reuptake inhibitors and MAOIs. Concomitant administration of [duloxetine](#) and [selegiline](#) is contraindicated, and a minimum of 14 days should elapse after discontinuing [selegiline](#) before initiating therapy with [duloxetine](#) and a minimum of 5 days should elapse after discontinuing [duloxetine](#) before initiating therapy with [selegiline](#)[78].

3J) Severity: contraindicated

4J) Onset: unspecified

5J) Substantiation: theoretical

6J) Clinical Management: Concurrent use of [duloxetine](#) and [selegiline](#) is contraindicated. Wait at least 14 days after discontinuing [selegiline](#) before initiating [duloxetine](#). Wait at least 5 days after discontinuing [duloxetine](#) before initiating therapy with [selegiline](#)[78].

7J) Probable Mechanism: additive serotonergic effects

3.5.1.GE] [Sertraline](#)

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

2J) Summary: [Duloxetine](#) is a selective serotonin and [norepinephrine](#) reuptake inhibitor. The concomitant use of [duloxetine](#) with [sertraline](#), a selective serotonin reuptake inhibitor, is not recommended due to the potential for [serotonin syndrome](#)[51].

3J) Severity: major

4J) Onset: unspecified

5J) Substantiation: theoretical

6J) Clinical Management: The concomitant use of [duloxetine](#) and [sertraline](#) is not recommended due to the potential for development of [serotonin syndrome](#)[51].

7J) Probable Mechanism: additive serotonergic effects

3.5.1.GF] [Sibrafiban](#)

1J) Interaction Effect: an increased risk of bleeding

2J) Summary: The release of serotonin by [platelets](#) is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of selective serotonin and [norepinephrine](#) reuptake inhibitors (such as [duloxetine](#)) 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[51].

3J) Severity: major

4J) Onset: unspecified

5J) Substantiation: probable

6J) Clinical Management: When [duloxetine](#) and an antiplatelet agent are given concurrently, monitor patient for signs of increased bleeding[51].

7J) Probable Mechanism: unknown

3.5.1.GG| [Sodium Salicylate](#)

1J) Interaction Effect: an increased risk of bleeding

2J) Summary: Use caution when coadministering NSAIDs and serotonin [norepinephrine](#) reuptake inhibitors (SNRI) as this may cause an increased risk of bleeding[106]. During clinical trials, concomitant use of NSAIDs and antidepressants, including tricyclic antidepressants, SSRIs, selective serotonin-norepinephrine reuptake inhibitors, and MOAIs, resulted in an increased risk of [intracranial hemorrhage](#) within 30 days of concomitant use compared with antidepressant use alone [107]. When NSAIDs and SNRIs are given concurrently, monitor the patient for signs of increased bleeding.

3J) Severity: major

4J) Onset: unspecified

5J) Substantiation: established

6J) Clinical Management: Serotonin [norepinephrine](#) reuptake inhibitors (SNRI) increase bleeding risk, especially with concomitant use of NSAIDs[106]. When NSAIDs and SNRIs are given concurrently, monitor the patient for signs of increased bleeding.

7J) Probable Mechanism: unknown

8J) Literature Reports

aJ) Concomitant use of NSAIDs and antidepressants, including tricyclic antidepressants, SSRIs, serotonin-norepinephrine reuptake inhibitors, and MAOIs, resulted in an increased risk of [intracranial hemorrhage](#) within 30 days of concomitant use compared with antidepressant use alone. There was no significant difference between the antidepressant drug classes and the increased risk; however, there was an increased risk associated with male patients compared with female patients [107].

3.5.1.GH| [St John's Wort](#)

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

2J) Summary: [Duloxetine](#) is a selective serotonin and [norepinephrine](#) reuptake inhibitor. Concomitant use with St. John's Wort, which can affect the serotonergic neurotransmitter systems, may result in an increased risk of [serotonin syndrome](#)[51].

3J) Severity: major

4J) Onset: unspecified

5J) Substantiation: theoretical

6J) Clinical Management: Use caution if [duloxetine](#) is coadministered with St. John's Wort as this may result in an increased risk of [serotonin syndrome](#)[51]. Advise patients to avoid using this combination.

7J) Probable Mechanism: additive serotonergic effects

3.5.1.GI| [Sulfinpyrazone](#)

1J) Interaction Effect: an increased risk of bleeding

2J) Summary: The release of serotonin by [platelets](#) is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of selective serotonin and [norepinephrine](#) reuptake inhibitors (such as [duloxetine](#)) 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[51].

3J) Severity: major

4J) Onset: unspecified

5J) Substantiation: probable

6J) Clinical Management: When [duloxetine](#) and an antiplatelet agent are given concurrently, monitor patient for signs of increased bleeding[51].

7J) Probable Mechanism: unknown

3.5.1.GJ] [Sulindac](#)

1J) Interaction Effect: an increased risk of bleeding

2J) Summary: Use caution when coadministering NSAIDs and serotonin [norepinephrine](#) reuptake inhibitors (SNRI) as this may cause an increased risk of bleeding[106]. During clinical trials, concomitant use of NSAIDs and antidepressants, including tricyclic antidepressants, SSRIs, selective serotonin-norepinephrine reuptake inhibitors, and MAOIs, resulted in an increased risk of [intracranial hemorrhage](#) within 30 days of concomitant use compared with antidepressant use alone [107]. When NSAIDs and SNRIs are given concurrently, monitor the patient for signs of increased bleeding.

3J) Severity: major

4J) Onset: unspecified

5J) Substantiation: established

6J) Clinical Management: Serotonin [norepinephrine](#) reuptake inhibitors (SNRI) increase bleeding risk, especially with concomitant use of NSAIDs[106]. When NSAIDs and SNRIs are given concurrently, monitor the patient for signs of increased bleeding.

7J) Probable Mechanism: unknown

8J) Literature Reports

aJ) Concomitant use of NSAIDs and antidepressants, including tricyclic antidepressants, SSRIs, serotonin-norepinephrine reuptake inhibitors, and MAOIs, resulted in an increased risk of [intracranial hemorrhage](#) within 30 days of concomitant use compared with antidepressant use alone. There was no significant difference between the antidepressant drug classes and the increased risk; however, there was an increased risk associated with male patients compared with female patients [107].

3.5.1.GK] [Sulodexide](#)

1J) Interaction Effect: an increased risk of bleeding

2J) Summary: The release of serotonin by [platelets](#) is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of selective serotonin and [norepinephrine](#) reuptake inhibitors (such as [duloxetine](#)) 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[51].

3J) Severity: major

4J) Onset: unspecified

5J) Substantiation: probable

6J) Clinical Management: When [duloxetine](#) and an antiplatelet agent are given concurrently, monitor patient for signs of increased bleeding[51].

7J) Probable Mechanism: unknown

3.5.1.GL] Sumatriptan

- 1) Interaction Effect: increased risk of [serotonin syndrome](#)
- 2) Summary: A life-threatening condition known as [serotonin syndrome](#) may occur when triptans, such as [sumatriptan](#), are used in combination with a serotonin and [norepinephrine](#) reuptake inhibitor (SNRI), such as [duloxetine](#). 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 SNRI 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](#), especially during treatment initiation and dose increases[51] [87].
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Coadministration of a triptan, such as [sumatriptan](#), and a serotonin and [norepinephrine](#) reuptake inhibitor (SNRI), such as [duloxetine](#), 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 SNRI 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), especially during treatment initiation and dose increases[51].
- 7) Probable Mechanism: additive pharmacologic effects resulting in excessive serotonergic stimulation

3.5.1.GM] Tamoxifen

- 1) Interaction Effect: decreased plasma concentrations of the active metabolites of [tamoxifen](#)
- 2) Summary: [Duloxetine](#) is a moderate CYP2D6 inhibitor[51] and [tamoxifen](#) is a prodrug metabolized to active metabolites by CYP450 enzymes. Concomitant use of [tamoxifen](#) and CYP2D6 inhibitors may affect [tamoxifen](#) efficacy by inhibiting the formation of endoxifen, an active metabolite of [tamoxifen](#) [114]. CYP2D6 drug interactions may result in variations in endoxifen concentrations, which may affect [tamoxifen](#) side effects and may reduce its antitumoral efficacy [116]. [Tamoxifen](#) use in the presence of CYP2D6 inhibition, either genetic or through concomitant medication use, may substantially reduce the plasma concentrations of endoxifen and may increase the risk of [breast cancer relapse](#) [117]. However, one small case control study found that pharmacokinetic alterations in [tamoxifen](#) metabolism did not significantly increase [tumor recurrence](#) in [breast cancer](#) patients [115].
- 3) Severity: moderate
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Coadministration of [tamoxifen](#) and [paroxetine](#), an inhibitor of CYP2D6, has resulted in decreased plasma concentrations of 4-hydroxy-N-desmethyl [tamoxifen](#), an active metabolite of [tamoxifen](#)[111]. As [duloxetine](#) is classified as a moderate CYP2D6 inhibitor [51], monitoring for decreased [tamoxifen](#) efficacy with coadministration may be necessary.
- 7) Probable Mechanism: inhibition of CYP2D6-mediated [tamoxifen](#) metabolism
- 8) Literature Reports

a) The use of CYP2D6 inhibitors should be avoided in [breast cancer](#) patients receiving [tamoxifen](#) due to the risk of substantially reduced plasma concentrations of the antiestrogenic [tamoxifen](#) metabolite, endoxifen. In a prospective randomized trial, 256 postmenopausal [breast cancer](#) patients receiving [tamoxifen](#) were genotyped and grouped according to CYP2D6 metabolism

and medication history. Adjusted analysis showed that decreased metabolizers (n=65) had significantly worse relapse-free survival (hazard ratio 1.74; 95% confidence interval (CI), 1.1 to 2.74; p=0.017), disease-free survival (hazard ratio 1.6; 95% CI, 1.06 to 2.43; p=0.027), and shorter time to recurrence (hazard ratio 1.91; 95% CI, 1.05 to 3.45; p=0.034) compared with extensive metabolizers (n=115). The greatest risk of [breast cancer relapse](#) was found in the poor metabolizer group (hazard ratio 3.12; 95% CI, 1.37 to 7.55; p=0.007) [112]. Decreased metabolizers had either one or two CYP2D6*4 alleles or was receiving a CYP2D6 inhibitor together with [tamoxifen](#) (regardless of genotype), and extensive metabolizers did not have a *4 allele and were not receiving a CYP2D6 inhibitor [113].

b)) Plasma concentrations of 4-hydroxy-N-desmethyl [tamoxifen](#) (endoxifen), a metabolite of [tamoxifen](#), is highly dependent on the CYP2D6 metabolic pathway. Studies have shown that concomitant use of [tamoxifen](#) and [paroxetine](#), a potent CYP2D6 inhibitor, has resulted in reduced plasma concentrations of endoxifen [114]. While not studied with [duloxetine](#), a moderate CYP2D6 inhibitor [51], similar results could be expected.

c)) Concomitant use of [paroxetine](#), a potent inhibitor of CYP2D6, and [tamoxifen](#), which requires activation by CYP2D6 enzymes to the antiestrogenic metabolite (endoxifen), results in substantially reduced plasma concentrations of endoxifen. Eighty newly diagnosed [breast cancer](#) patients taking [tamoxifen](#) 20 mg/day were genotyped for the common alleles of the CYP2D6, CYP2C9, CYP3A5, and sulfotransferase (SULT) 1A1 genes. After 1 and 4 months of [tamoxifen](#) treatment, plasma concentrations of [tamoxifen](#) and endoxifen were measured. After 4 months of [tamoxifen](#), plasma endoxifen concentrations were statistically significantly lower in those with a CYP2D6 homozygous variant genotype (20 nM; 95% CI, 11.1 to 28.9) or a heterozygous genotype (43.1 nM; 95% CI, 33.3 to 52.9) than those with a homozygous wild-type genotype (78 nM; 95% CI, 65.9 to 90.1; both p=0.003). The mean plasma endoxifen concentration for subjects with a homozygous wild-type genotype who were taking CYP2D6 inhibitors was 58% lower than those not taking such inhibitors (38.6 nM versus 91.4 nM, 95% CI of difference, -86.1 to -19.5; p=0.0025). Concomitant use of [venlafaxine](#), a weak inhibitor of CYP2D6, resulted in slightly reduced plasma concentrations of endoxifen, while the use of [paroxetine](#), a potent inhibitor of CYP2D6, resulted in substantial reductions in endoxifen concentrations. Plasma concentrations of [tamoxifen](#) and metabolites were not altered significantly by genetic variations of CYP2C9, CYP3A5 or SULT1A1 [111].

d)) A case control study (n=28) designed to evaluate the effect of CYP isoform inhibitors on therapeutic outcome in women taking [tamoxifen](#) for estrogen receptor-positive [breast cancer](#) found no significant impact on [breast cancer](#) recurrence from chronic exposure (3 months or greater) to CYP2D6, 2C9, or 3A4 inhibitors or substrates. Cases (recurrences of [breast cancer](#)) and controls (patients without [recurrent breast cancer](#)) were matched by [cancer](#) stage, year of diagnosis, and CYP inhibitor or substrate exposure. Selective serotonin reuptake inhibitors, including [paroxetine](#), are inhibitors of CYP2D6, 2C9, and 3A isoforms responsible for the metabolism of [tamoxifen](#) to the potent antiestrogen 4-hydroxy metabolite [115]. As selective serotonin and [norepinephrine](#) reuptake inhibitors are also inhibitors of CYP2D6, similar results could be expected.

3.5.1.GN] [Tamsulosin](#)

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

2)) Summary: Concomitant use of [tamsulosin](#) (a CYP2D6 substrate) with a strong or moderate CYP2D6 inhibitor may result in increased exposure of [tamsulosin](#). In a [pharmacokinetic study](#), concomitant treatment with [tamsulosin](#) and [paroxetine](#), a strong CYP2D6 inhibitor, resulted in a 1.3-fold increase in

C_{max} and a 1.6-fold increase in the AUC of [tamsulosin](#). If concomitant use of [tamsulosin](#) and a moderate or strong CYP2D6 inhibitor is necessary, use caution[91] and consider monitoring patients for increased [tamsulosin](#) adverse effects.

3) Severity: moderate

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Concomitant use of [tamsulosin](#) (a CYP2D6 substrate) with a moderate or strong CYP2D6 inhibitor can increase [tamsulosin](#) exposure. Use caution if coadministration is necessary[91], and consider monitoring patients for increased [tamsulosin](#) adverse effects.

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

8) Literature Reports

a) In a [pharmacokinetic study](#) involving 24 healthy volunteers aged 23 to 47 years, administration of a strong CYP2D6 inhibitor, [paroxetine](#) 20 mg daily for 9 days, followed by a single dose of [tamsulosin](#) 0.4 mg resulted in a 1.3-fold increase in C_{max} and a 1.6-fold increase in the AUC of [tamsulosin](#) [91].

3.5.1.GO| Tapentadol

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

2) Summary: Concurrent use of [duloxetine](#) and tapentadol 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[109].

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Coadministration of [duloxetine](#) and tapentadol 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[109].

7) Probable Mechanism: additive serotonergic effect

3.5.1.GP| Tenoxicam

1) Interaction Effect: an increased risk of bleeding

2) Summary: Use caution when coadministering NSAIDs and serotonin [norepinephrine](#) reuptake inhibitors (SNRI) as this may cause an increased risk of bleeding[106]. During clinical trials, concomitant use of NSAIDs and antidepressants, including tricyclic antidepressants, SSRIs, selective serotonin-norepinephrine reuptake inhibitors, and MOAIs, resulted in an increased risk of [intracranial hemorrhage](#) within 30 days of concomitant use compared with antidepressant use alone [107]. When NSAIDs and SNRIs are given concurrently, monitor the patient for signs of increased bleeding.

3) Severity: major

4) Onset: unspecified

5) Substantiation: established

6) Clinical Management: Serotonin [norepinephrine](#) reuptake inhibitors (SNRI) increase bleeding risk, especially with concomitant use of NSAIDs[106]. When NSAIDs and SNRIs are given concurrently, monitor the patient for signs of increased bleeding.

7) Probable Mechanism: unknown

8) Literature Reports

a) Concomitant use of NSAIDs and antidepressants, including tricyclic antidepressants, SSRIs, serotonin-norepinephrine reuptake inhibitors, and MAOIs, resulted in an increased risk of [intracranial hemorrhage](#) within 30 days of concomitant use compared with antidepressant use alone. There was no significant difference between the antidepressant drug classes and the increased risk; however, there was an increased risk associated with male patients compared with female patients [107].

3.5.1.GQ] [Thiethylperazine](#)

- 1) Interaction Effect: increased phenothiazine serum concentrations and potential toxicity (sedation, confusion, [cardiac arrhythmias](#), orthostatic hypotension, [hyperthermia](#), extrapyramidal effects)
- 2) Summary: [Duloxetine](#) is a moderately potent inhibitor of CYP2D6; therefore, the coadministration of [duloxetine](#) with a phenothiazine is likely to increase bioavailability of the phenothiazine agent, increasing the risk of serious adverse events[51].
- 3) Severity: moderate
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Use caution when prescribing [duloxetine](#) to patients who take phenothiazines as concomitant use may cause elevated phenothiazine plasma concentrations. Monitor for increased phenothiazine side effects[51].
- 7) Probable Mechanism: [duloxetine](#) inhibition of CYP2D6-mediated phenothiazine metabolism

3.5.1.GR] [Thiopropazate](#)

- 1) Interaction Effect: increased phenothiazine serum concentrations and potential toxicity (sedation, confusion, [cardiac arrhythmias](#), orthostatic hypotension, [hyperthermia](#), extrapyramidal effects)
- 2) Summary: [Duloxetine](#) is a moderately potent inhibitor of CYP2D6; therefore, the coadministration of [duloxetine](#) with a phenothiazine is likely to increase bioavailability of the phenothiazine agent, increasing the risk of serious adverse events[51].
- 3) Severity: moderate
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Use caution when prescribing [duloxetine](#) to patients who take phenothiazines as concomitant use may cause elevated phenothiazine plasma concentrations. Monitor for increased phenothiazine side effects[51].
- 7) Probable Mechanism: [duloxetine](#) inhibition of CYP2D6-mediated phenothiazine metabolism

3.5.1.GS] [Thiopropazine](#)

- 1) Interaction Effect: increased phenothiazine serum concentrations and potential toxicity (sedation, confusion, [cardiac arrhythmias](#), orthostatic hypotension, [hyperthermia](#), extrapyramidal effects)
- 2) Summary: [Duloxetine](#) is a moderately potent inhibitor of CYP2D6; therefore, the coadministration of [duloxetine](#) with a phenothiazine is likely to increase bioavailability of the phenothiazine agent, increasing the risk of serious adverse events[51].
- 3) Severity: moderate
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Use caution when prescribing [duloxetine](#) to patients who take phenothiazines as concomitant use may cause elevated phenothiazine plasma concentrations. Monitor for increased phenothiazine side effects[51].

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

3.5.1.GT] [Thioridazine](#)

1J) Interaction Effect: increased [thioridazine](#) serum concentrations and risk of [cardiac arrhythmia](#)

2J) Summary: Given [thioridazine's](#) tendency to prolong the QTc-interval in a dose-dependent manner, the attendant risk for developing serious or fatal [ventricular arrhythmias](#) precludes the safe concomitant use of [duloxetine](#) and [thioridazine](#). [Duloxetine](#) is a moderately potent inhibitor of CYP2D6 (for which [thioridazine](#) is a substrate) and therefore, the coadministration of [duloxetine](#) with [thioridazine](#) is likely to produce elevated [thioridazine](#) plasma concentrations with attendant [cardiotoxicity](#)[68][51].

3J) Severity: contraindicated

4J) Onset: unspecified

5J) Substantiation: theoretical

6J) Clinical Management: Concomitant use of [duloxetine](#) and [thioridazine](#) is contraindicated[68].

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

3.5.1.GU] [Tiaprofenic Acid](#)

1J) Interaction Effect: an increased risk of bleeding

2J) Summary: Use caution when coadministering NSAIDs and serotonin [norepinephrine](#) reuptake inhibitors (SNRI) as this may cause an increased risk of bleeding[106]. During clinical trials, concomitant use of NSAIDs and antidepressants, including tricyclic antidepressants, SSRIs, selective serotonin-norepinephrine reuptake inhibitors, and MOAIs, resulted in an increased risk of [intracranial hemorrhage](#) within 30 days of concomitant use compared with antidepressant use alone [107]. When NSAIDs and SNRIs are given concurrently, monitor the patient for signs of increased bleeding.

3J) Severity: major

4J) Onset: unspecified

5J) Substantiation: established

6J) Clinical Management: Serotonin [norepinephrine](#) reuptake inhibitors (SNRI) increase bleeding risk, especially with concomitant use of NSAIDs[106]. When NSAIDs and SNRIs are given concurrently, monitor the patient for signs of increased bleeding.

7J) Probable Mechanism: unknown

8J) Literature Reports

aJ) Concomitant use of NSAIDs and antidepressants, including tricyclic antidepressants, SSRIs, serotonin-norepinephrine reuptake inhibitors, and MAOIs, resulted in an increased risk of [intracranial hemorrhage](#) within 30 days of concomitant use compared with antidepressant use alone. There was no significant difference between the antidepressant drug classes and the increased risk; however, there was an increased risk associated with male patients compared with female patients [107].

3.5.1.GV] [Ticlopidine](#)

1J) Interaction Effect: an increased risk of bleeding

2J) Summary: The release of serotonin by [platelets](#) is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of selective serotonin and [norepinephrine](#) reuptake inhibitors (such as [duloxetine](#)) 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[51].

3J) Severity: major

4J) Onset: unspecified

- 5) Substantiation: probable
- 6) Clinical Management: When [duloxetine](#) and an antiplatelet agent are given concurrently, monitor patient for signs of increased bleeding[51].
- 7) Probable Mechanism: unknown

3.5.1.GW] [Tinzaparin](#)

- 1) Interaction Effect: altered [anticoagulation](#) effects, including increased risk of bleeding
- 2) Summary: Concomitant administration of [duloxetine](#) and an anticoagulant, such as [tinzaparin](#) may result in altered [anticoagulation](#) effects. Coadministration of the anticoagulant [warfarin](#) and SSRIs or serotonin [norepinephrine](#) reuptake inhibitors has resulted in altered [anticoagulation](#) effects, including increased bleeding. The release of serotonin by [platelets](#) is involved in hemostasis[53]. A population-based, case-controlled study of new coumarin users (acenocoumarol and phenprocoumon) receiving concomitant SSRIs suggested an increased risk of hospitalization due to nongastrointestinal bleeding; however, the risk of [gastrointestinal bleeding](#) was not significantly different [54] If concomitant use of [duloxetine](#) and an anticoagulant is required, closely monitor [anticoagulation](#) effects during initiation or discontinuation of [duloxetine](#) [53].
- 3) Severity: moderate
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Concomitant use of [duloxetine](#) and an anticoagulant, such as [tinzaparin](#), may increase the risk of bleeding. If concomitant use is required, carefully monitor [anticoagulation](#) effects during [duloxetine](#) initiation or discontinuation[53].
- 7) Probable Mechanism: unknown
- 8) Literature Reports

a) A population-based, case-controlled study of new coumarin users (acenocoumarol and phenprocoumon) receiving 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 [54].

3.5.1.GX] [Tirofiban](#)

- 1) Interaction Effect: an increased risk of bleeding
- 2) Summary: The release of serotonin by [platelets](#) is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of selective serotonin and [norepinephrine](#) reuptake inhibitors (such as [duloxetine](#)) 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[51].
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: probable
- 6) Clinical Management: When [duloxetine](#) and an antiplatelet agent are given concurrently, monitor patient for signs of increased bleeding[51].
- 7) Probable Mechanism: unknown

3.5.1.GY] Tolfenamic Acid

- 1) Interaction Effect: an increased risk of bleeding
- 2) Summary: Use caution when coadministering NSAIDs and serotonin [norepinephrine](#) reuptake inhibitors (SNRI) as this may cause an increased risk of bleeding[106]. During clinical trials, concomitant use of NSAIDs and antidepressants, including tricyclic antidepressants, SSRIs, selective serotonin-norepinephrine reuptake inhibitors, and MOAIs, resulted in an increased risk of [intracranial hemorrhage](#) within 30 days of concomitant use compared with antidepressant use alone [107]. When NSAIDs and SNRIs are given concurrently, monitor the patient for signs of increased bleeding.
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: established
- 6) Clinical Management: Serotonin [norepinephrine](#) reuptake inhibitors (SNRI) increase bleeding risk, especially with concomitant use of NSAIDs[106]. When NSAIDs and SNRIs are given concurrently, monitor the patient for signs of increased bleeding.
- 7) Probable Mechanism: unknown
- 8) Literature Reports

a) Concomitant use of NSAIDs and antidepressants, including tricyclic antidepressants, SSRIs, serotonin-norepinephrine reuptake inhibitors, and MAOIs, resulted in an increased risk of [intracranial hemorrhage](#) within 30 days of concomitant use compared with antidepressant use alone. There was no significant difference between the antidepressant drug classes and the increased risk; however, there was an increased risk associated with male patients compared with female patients [107].

3.5.1.GZ] Tolmetin

- 1) Interaction Effect: an increased risk of bleeding
- 2) Summary: Use caution when coadministering NSAIDs and serotonin [norepinephrine](#) reuptake inhibitors (SNRI) as this may cause an increased risk of bleeding[106]. During clinical trials, concomitant use of NSAIDs and antidepressants, including tricyclic antidepressants, SSRIs, selective serotonin-norepinephrine reuptake inhibitors, and MOAIs, resulted in an increased risk of [intracranial hemorrhage](#) within 30 days of concomitant use compared with antidepressant use alone [107]. When NSAIDs and SNRIs are given concurrently, monitor the patient for signs of increased bleeding.
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: established
- 6) Clinical Management: Serotonin [norepinephrine](#) reuptake inhibitors (SNRI) increase bleeding risk, especially with concomitant use of NSAIDs[106]. When NSAIDs and SNRIs are given concurrently, monitor the patient for signs of increased bleeding.
- 7) Probable Mechanism: unknown
- 8) Literature Reports

a) Concomitant use of NSAIDs and antidepressants, including tricyclic antidepressants, SSRIs, serotonin-norepinephrine reuptake inhibitors, and MAOIs, resulted in an increased risk of [intracranial hemorrhage](#) within 30 days of concomitant use compared with antidepressant use alone. There was no significant difference between the antidepressant drug classes and the increased risk; however, there was an increased risk associated with male patients compared with female patients [107].

3.5.1.HA| Tramadol

1) Interaction Effect: an increased risk of seizures, [serotonin syndrome](#) (hypertension, hyperthermia, myoclonus, mental status changes), opioid toxicity, and increased concentrations of [tramadol](#) and decreased concentrations of [tramadol](#) active metabolite, M1

2) Summary: Caution is advised with concomitant use of [duloxetine](#) and [tramadol](#). [Duloxetine](#) is a serotonin/[norepinephrine](#) reuptake inhibitor and a CYP2D6 inhibitor. Concomitant use of [tramadol](#) with serotonergic agents may increase the risk for seizures and [serotonin syndrome](#) even if [tramadol](#) is used within the recommended dosage range. Additionally, concomitant use of [tramadol](#) and CYP2D6 inhibitors, such as [duloxetine](#), can decrease metabolism of [tramadol](#) to the active metabolite, M1, potentially causing reduced analgesia. Furthermore, elevated [tramadol](#) concentrations, because of inhibition of CYP2D6-mediated metabolism, may cause opioid toxicity. If concomitant use of [tramadol](#) with a serotonergic agent is clinically warranted, careful observation of the patient is recommended, particularly during treatment initiation and dose increases[64]. If [serotonin syndrome](#) develops, discontinue the offending agents and provide supportive care, correction of vital signs, and other therapy as necessary [63]. Also consider monitoring patients for signs and symptoms of opioid toxicity or decreased analgesic effect of [tramadol](#).

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Caution is advised with concomitant use of [duloxetine](#) and [tramadol](#). Concomitant use of [tramadol](#) with serotonergic agents, such as [duloxetine](#), may increase the risk for seizures and [serotonin syndrome](#), even if [tramadol](#) is used within the recommended dosage range. Additionally, opioid toxicity and reduced analgesia may occur. If concomitant use of [tramadol](#) with a serotonergic agent is clinically warranted, careful observation is recommended, particularly during treatment initiation and dose increases[64]. If [serotonin syndrome](#) develops, discontinue the offending agents and provide supportive care, correction of vital signs, and other therapy as necessary [63]. Also consider monitoring patients for signs and symptoms of opioid toxicity and decreased analgesic effect of [tramadol](#).

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

3.5.1.HB| Tranlycypromine

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

2) Summary: [Duloxetine](#) exerts inhibitory effects on both [norepinephrine](#) and serotonin reuptake. Concurrent administration or overlapping therapy with [duloxetine](#) and an MAOI, such as [tranlycypromine](#), may result in CNS toxicity or [serotonin syndrome](#), a hyper-serotonergic state characterized by symptoms such as agitation and restlessness, myoclonus, changes in mental status, hyperreflexia, diaphoresis, shivering, and tremor. Serious, even fatal, reactions have been reported with concomitant use of serotonin-specific reuptake inhibitors and MAOIs. Concomitant administration of [duloxetine](#) and [tranlycypromine](#) is contraindicated, and a minimum of 14 days should elapse after discontinuing [tranlycypromine](#) before initiating therapy with [duloxetine](#) and a minimum of 5 days should elapse after discontinuing [duloxetine](#) before initiating therapy with [tranlycypromine](#)[78].

3) Severity: contraindicated

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Concurrent use of [duloxetine](#) and [tranylcypromine](#) is contraindicated. Wait at least 14 days after discontinuing [tranylcypromine](#) before initiating [duloxetine](#). Wait at least 5 days after discontinuing [duloxetine](#) before initiating therapy with [tranylcypromine](#)[78].

7) Probable Mechanism: additive serotonergic effects

3.5.1.HC] [Trazodone](#)

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

2) Summary: Use caution when prescribing [duloxetine](#) to patients who take [trazodone](#). Concurrent administration may result in potentially fatal [serotonin syndrome](#) or neuroleptic malignant syndrome-like reactions with symptoms including neuromuscular aberrations (eg, hyperreflexia, incoordination), autonomic instability (eg, [tachycardia](#), labile blood pressure, [hyperthermia](#)), and mental status changes (eg, agitation, hallucinations, coma). Serious reactions have been reported in patients receiving concomitant serotonergic drugs[118]. If concomitant use is necessary, monitor patients closely for signs/symptoms of [serotonin syndrome](#) or neuroleptic malignant syndrome-like reactions, especially during initiation of treatment and dose increases [40]. [Serotonin syndrome](#) can be life-threatening. If [serotonin syndrome](#) develops, discontinue the offending agents and provide supportive care and other therapy as necessary [63].

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Use caution when prescribing [duloxetine](#) to patients who take [trazodone](#). Concurrent use of [duloxetine](#), a selective serotonin and [norepinephrine](#) reuptake inhibitor, and [trazodone](#) may result in potentially fatal [serotonin syndrome](#)[118]. If concomitant use is necessary, monitor patients closely for signs/symptoms of [serotonin syndrome](#) or neuroleptic malignant syndrome-like reactions, especially during initiation of treatment and dose increases [40].

7) Probable Mechanism: additive serotonergic effect

3.5.1.HD] [Trifluoperazine](#)

1) Interaction Effect: increased phenothiazine serum concentrations and potential toxicity (sedation, confusion, [cardiac arrhythmias](#), orthostatic hypotension, [hyperthermia](#), extrapyramidal effects)

2) Summary: [Duloxetine](#) is a moderately potent inhibitor of CYP2D6; therefore, the coadministration of [duloxetine](#) with a phenothiazine is likely to increase bioavailability of the phenothiazine agent, increasing the risk of serious adverse events[51].

3) Severity: moderate

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Use caution when prescribing [duloxetine](#) to patients who take phenothiazines as concomitant use may cause elevated phenothiazine plasma concentrations. Monitor for increased phenothiazine side effects[51].

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

3.5.1.HE] [Triflupromazine](#)

1) Interaction Effect: increased phenothiazine serum concentrations and potential toxicity (sedation, confusion, [cardiac arrhythmias](#), orthostatic hypotension, [hyperthermia](#), extrapyramidal effects)

2) Summary: [Duloxetine](#) is a moderately potent inhibitor of CYP2D6; therefore, the coadministration of [duloxetine](#) with a phenothiazine is likely to increase bioavailability of the phenothiazine agent, increasing the risk of serious adverse events[51].

- 3) Severity: moderate
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Use caution when prescribing [duloxetine](#) to patients who take phenothiazines as concomitant use may cause elevated phenothiazine plasma concentrations. Monitor for increased phenothiazine side effects[51].
- 7) Probable Mechanism: [duloxetine](#) inhibition of CYP2D6-mediated phenothiazine metabolism

3.5.1.HF] [Trimeprazine](#)

- 1) Interaction Effect: increased phenothiazine serum concentrations and potential toxicity (sedation, confusion, [cardiac arrhythmias](#), orthostatic hypotension, [hyperthermia](#), extrapyramidal effects)
- 2) Summary: [Duloxetine](#) is a moderately potent inhibitor of CYP2D6; therefore, the coadministration of [duloxetine](#) with a phenothiazine is likely to increase bioavailability of the phenothiazine agent, increasing the risk of serious adverse events[51].
- 3) Severity: moderate
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Use caution when prescribing [duloxetine](#) to patients who take phenothiazines as concomitant use may cause elevated phenothiazine plasma concentrations. Monitor for increased phenothiazine side effects[51].
- 7) Probable Mechanism: [duloxetine](#) inhibition of CYP2D6-mediated phenothiazine metabolism

3.5.1.HG] [Trimipramine](#)

- 1) Interaction Effect: increased tricyclic antidepressant serum concentrations and potential toxicity (eg, anticholinergic effects, sedation, confusion, [cardiac arrhythmias](#))
- 2) Summary: The coadministration of [duloxetine](#) with a tricyclic antidepressant is likely to increase bioavailability of the tricyclic agent, increasing the risk of adverse events. [Duloxetine](#) is a moderately potent inhibitor of CYP2D6. When a single dose of the CYP2D6 substrate [desipramine](#) 50 mg and [duloxetine](#) 60 mg twice daily were coadministered, the [desipramine](#) AUC increased 3-fold over baseline[51].
- 3) Severity: moderate
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Use caution with the combined use of [duloxetine](#) with tricyclic antidepressants (TCAs). If concomitant therapy with [duloxetine](#) and a TCA is unavoidable, plasma concentrations of the tricyclic should be closely monitored and dose adjustments made accordingly[51]. Also, monitor patients for signs and symptoms of TCA toxicity (eg, anticholinergic effects, sedation, confusion, and [cardiac arrhythmias](#)).
- 7) Probable Mechanism: [duloxetine](#) inhibition of CYP2D6-mediated tricyclic agent metabolism

3.5.1.HH] [Tryptophan](#)

- 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 other serotonergic agents such as tryptophan (serotonin precursor) is not recommended due to the potential for [serotonin syndrome](#)[51].
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical

- 6J) Clinical Management: The concomitant use of [duloxetine](#) and tryptophan is not recommended due to the potential for development of [serotonin syndrome](#)[51].
- 7J) Probable Mechanism: potentiation of serotonergic activity in the CNS by [duloxetine](#) and tryptophan (serotonin precursor)

3.5.1.HI] [Valdecixib](#)

- 1J) Interaction Effect: an increased risk of bleeding
- 2J) Summary: Use caution when coadministering NSAIDs and serotonin [norepinephrine](#) reuptake inhibitors (SNRI) as this may cause an increased risk of bleeding[106]. During clinical trials, concomitant use of NSAIDs and antidepressants, including tricyclic antidepressants, SSRIs, selective serotonin-norepinephrine reuptake inhibitors, and MOAIs, resulted in an increased risk of [intracranial hemorrhage](#) within 30 days of concomitant use compared with antidepressant use alone [107]. When NSAIDs and SNRIs are given concurrently, monitor the patient for signs of increased bleeding.
- 3J) Severity: major
- 4J) Onset: unspecified
- 5J) Substantiation: established
- 6J) Clinical Management: Serotonin [norepinephrine](#) reuptake inhibitors (SNRI) increase bleeding risk, especially with concomitant use of NSAIDs[106]. When NSAIDs and SNRIs are given concurrently, monitor the patient for signs of increased bleeding.
- 7J) Probable Mechanism: unknown
- 8J) Literature Reports
 - aJ) Concomitant use of NSAIDs and antidepressants, including tricyclic antidepressants, SSRIs, serotonin-norepinephrine reuptake inhibitors, and MAOIs, resulted in an increased risk of [intracranial hemorrhage](#) within 30 days of concomitant use compared with antidepressant use alone. There was no significant difference between the antidepressant drug classes and the increased risk; however, there was an increased risk associated with male patients compared with female patients [107].

3.5.1.HJ] [Venlafaxine](#)

- 1J) Interaction Effect: an increased risk of [serotonin syndrome](#)
- 2J) Summary: [Duloxetine](#) is a selective serotonin and [norepinephrine](#) reuptake inhibitor. The concomitant use of [duloxetine](#) with [venlafaxine](#), also a selective serotonin and [norepinephrine](#) reuptake inhibitor, is not recommended due to the potential for [serotonin syndrome](#)[51].
- 3J) Severity: major
- 4J) Onset: unspecified
- 5J) Substantiation: theoretical
- 6J) Clinical Management: The concomitant use of [duloxetine](#) and [venlafaxine](#) is not recommended due to the potential for development of [serotonin syndrome](#)[51].
- 7J) Probable Mechanism: additive serotonergic effects

3.5.1.HK] [Vilazodone](#)

- 1J) Interaction Effect: increased risk for [serotonin syndrome](#) ([hypertension](#), [hyperthermia](#), myoclonus, mental status changes)
- 2J) 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](#)[62]. 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 [63]. 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 [62].

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[62].

7) Probable Mechanism: additive serotonergic effects

3.5.1.HL] Vortioxetine

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

2) Summary: Vortioxetine is a serotonergic drug; concomitant use with another agent that affects the serotonergic neurotransmitter system may result in an increased risk of [serotonin syndrome](#) and should be approached with caution. [Serotonin syndrome](#) may be life-threatening. Symptoms may include mental status changes (eg, agitation, hallucinations, coma), autonomic instability (eg, [tachycardia](#), labile blood pressure, [hyperthermia](#)), neuromuscular aberrations (eg, hyperreflexia, incoordination), and/or gastrointestinal symptoms (eg, nausea, vomiting, diarrhea). If coadministration is required, monitor closely for signs and symptoms of [serotonin syndrome](#), especially during initiation of the coadministered drug and during dosage increases of either drug. If [serotonin syndrome](#) develops, discontinue both agents and initiate supportive symptomatic therapy[129].

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[129].

7) Probable Mechanism: additive serotonergic effects

3.5.1.HM] Warfarin

1) Interaction Effect: altered [anticoagulation](#) effects including increased risk of bleeding

2) Summary: Coadministration of [duloxetine](#) and [warfarin](#) may result in altered [anticoagulation](#) effects including an increased risk of bleeding. The release of serotonin by [platelets](#) is involved in hemostasis[53]. Bleeding events and increases in INR with concomitant therapy have been reported [133]; however, a study in healthy subjects (n=30) found no clinically significant changes in INR with concomitant administration of [duloxetine](#) and [warfarin](#) at steady state conditions, or with dosage increase or duration of [duloxetine](#) therapy [132]. If coadministration is required, closely monitor [anticoagulation](#) effects during [duloxetine](#) initiation and discontinuation [53].

3) Severity: moderate

- 4) Onset: unspecified
- 5) Substantiation: probable
- 6) Clinical Management: Concomitant use of [duloxetine](#) and [warfarin](#) may increase the risk of bleeding. If concomitant use is required, carefully monitor [anticoagulation](#) effects during [duloxetine](#) initiation or discontinuation[53].
- 7) Probable Mechanism: unknown
- 8) Literature Reports

a) No clinically significant changes in INR or bleeding time were observed with coadministration of [duloxetine](#) and [warfarin](#) (at steady state conditions) compared with [warfarin](#) alone in healthy subjects (n=30; age range, 19 to 62 years). All subjects received [warfarin](#) 10 on day 1 then individualized dosing (range, 2 to 9 mg) daily on days 2 to 9 for a goal INR range of 1.5 to 2.0 for 3 consecutive days. After [warfarin](#) steady state was achieved, all subjects received [duloxetine](#) 60 mg once daily for 4 days, then either continued 60 mg daily (n=15; group 1) or increased to 120 mg daily (n=15; group 2) for 10 days. [Warfarin](#) was discontinued on day 14. During concomitant administration among group 1 and 2, the mean INR changes from baseline ranged from -0.05 to +0.07 (90% confidence interval, -0.12 to +0.14). Additionally, mean INR changes from baseline were not significantly affected by dosage increase or by duration of [duloxetine](#) therapy. Notably, a statistically significant prolongation in bleeding time was observed at day 14 in group 1 compared with [warfarin](#) alone; however, the difference was considered small (less than 2 minutes); whereas, no prolongation in bleeding time was observed in group 2. Additionally, the AUC (steady state) of [warfarin](#) R- and S-enantiomers was not affected with either dosage of [duloxetine](#). One subject discontinued due to mild [epistaxis](#) [132].

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 [54].

c) A case report describes a 44-year-old female patient maintained on [warfarin](#) (INR 2.2) who developed [petechiae/purpura](#) (INR 5) after 55 days of concomitant [duloxetine](#) treatment. [Warfarin](#) was initiated one year prior following [ischemic stroke](#). Her daily, stable medication regimen included [atorvastatin](#) 10 mg, [warfarin](#) 7.5 mg to 10 mg, [lamotrigine](#) 50 mg, [topiramate](#) 200 mg, [clonazepam](#) 2 mg, and [albuterol](#) extended-release 4 mg twice a day. [Duloxetine](#) 30 mg/day was added to treat depression-related insomnia. On day 58, only the [warfarin](#) was discontinued, and by day 85 the patient's INR exceeded 19. At this time, plasma [warfarin](#) level was 5.3 mcg/mL (17 mcg/mL; therapeutic range 2 to 8 mcg/mL (6 to 30 mcg/mL). Intravenous vitamin K 10 mg was administered, briefly decreasing the INR. By day 94, the INR was again elevated at 6.4, vitamin K-dependent clotting factors II, VII, and X were critically low, and [fibrinogen](#) level was normal. [Duloxetine](#) was then discontinued and 4 days later the INR measured 1.2, factor II increased to 48% and factor X increased to 54%. INR was 0.9 by day 105, and [warfarin](#) was restarted on day 110. By day 140, INR was stable at 2.2, with the patient again maintained on 7.5 to 10 mg/day. According to the Naranjo algorithm, the probability score for this adverse event was 12, or highly probable. The authors suggest that [duloxetine](#) may have an effect on the CYP1A2

metabolism of [warfarin](#), may have displaced [warfarin](#) from its protein-binding sites, or may have unique metabolic properties not yet determined [133].

3.5.1.HN] [Xemilofiban](#)

- 1) Interaction Effect: an increased risk of bleeding
- 2) Summary: The release of serotonin by [platelets](#) is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of selective serotonin and [norepinephrine](#) reuptake inhibitors (such as [duloxetine](#)) 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[51].
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: probable
- 6) Clinical Management: When [duloxetine](#) and an antiplatelet agent are given concurrently, monitor patient for signs of increased bleeding[51].
- 7) Probable Mechanism: unknown

3.5.1.HO] [Ziprasidone](#)

- 1) Interaction Effect: increased risk for [serotonin syndrome](#) ([hypertension](#), [hyperthermia](#), myoclonus, mental status changes)
- 2) Summary: [Serotonin syndrome](#) has been reported with [ziprasidone](#) monotherapy and in combination with other serotonergic drugs[100][101]; coadministration with another serotonergic drug may increase risk for [serotonin syndrome](#). Therefore, exercise caution with concomitant use.
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: [Serotonin syndrome](#) has been reported with [ziprasidone](#) monotherapy and in combination with other serotonergic drugs[100][101]; coadministration with another serotonergic drug may increase risk for [serotonin syndrome](#). Therefore, exercise caution with concomitant use.
- 7) Probable Mechanism: Additive serotonergic effect

3.5.1.HP] [Zolmitriptan](#)

- 1) Interaction Effect: an increased risk of [serotonin syndrome](#)
- 2) Summary: Concurrent use of a triptan and a serotonin [norepinephrine](#) reuptake inhibitor (SNRI) 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[86]. 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 serotonergic agent 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](#) [87]. Discontinue use of [zolmitriptan](#) if [serotonin syndrome](#) is suspected [86].
- 3) Severity: major
- 4) Onset: rapid
- 5) Substantiation: probable
- 6) Clinical Management: Life-threatening [serotonin syndrome](#) has been reported with coadministration of triptans and serotonin [norepinephrine](#) reuptake inhibitors (SNRIs)[86]. Consider potential intermittent

use of triptans in patients who receive SNRIs and closely monitor patients receiving both medications for symptoms of [serotonin syndrome](#) [87]. Discontinue [zolmitriptan](#) if [serotonin syndrome](#) is suspected [86].

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

3.5.4] Drug-Tobacco Combinations

3.5.4.A] Tobacco

- 1J) Interaction Effect: decreased exposure of CYP1A2 substrates
- 2J) Summary: Cigarette smoking releases polycyclic aromatic hydrocarbons that induce CYP1A2 substrate metabolism[140][150], which may reduce CYP1A2 substrate bioavailability. Advise patients to stop smoking during treatment with a CYP1A2 substrate due to the potential reduction in efficacy [139]. If CYP1A2 substrate therapy is required in patients who smoke, consider monitoring for reduced efficacy [140] and adjusting the CYP1A2 substrate dosage if needed [141].
- 3J) Severity: major
- 4J) Onset: unspecified
- 5J) Substantiation: theoretical
- 6J) Clinical Management: CYP1A2 substrate bioavailability may be reduced with tobacco smoking. Advise patients to stop smoking during treatment due to the potential reduction in CYP1A2 substrate efficacy[139]. If therapy with a CYP1A2 substrate is required in patients who smoke, consider monitoring for reduced efficacy [140] and adjusting the CYP1A2 substrate dosage if needed [141].
- 7J) Probable Mechanism: induction of CYP1A2-mediated metabolism by tobacco smoke
- 8J) Literature Reports

aJ) Smoking 7 to 12 cigarettes/day produced maximum enzyme induction and a significantly lower mean [clozapine](#) concentration/dose (C/D) ratio in smokers than in nonsmokers (2.8 vs 6 nanograms/mL/mg/day), and similarly with [olanzapine](#) C/D ratio in another study (6.1 vs 12.8 nanograms/mL/mg/day). Smoking more than 12 cigarettes/day did not produce any further induction nor lower C/D ratio of [clozapine](#) or [olanzapine](#) [142].

bJ) Among patients treated with [mirtazapine](#) 30 mg/day for 4 weeks, smokers had significantly lower concentrations of S(+)-[mirtazapine](#) (23 vs 39 nmol/L) and [mirtazapine](#) S(+)/R(-) ratio (0.28 vs 0.37) than nonsmokers. These effects from smoking remained significant after multivariate analysis [141].

cJ) In patients receiving stable [clozapine](#) 100 mg/day, heavy smokers (30 or more cigarettes/day) had a significantly higher mean plasma [clozapine](#) concentration coefficient of variation (CV) than smokers (30% vs 16%); however, no difference was seen in patients receiving stable [clozapine](#) 300 or 600 mg/day in a study of patients with [schizophrenia](#) or [schizoaffective disorder](#) (N=47) [143].

dJ) In a study of patients receiving an average [clozapine](#) dose of 304 mg/day (N=18), [clozapine](#) and nortclozapine (active metabolite) plasma concentrations were significantly lower in smokers (median of 25 cigarettes or 4 pipes/day) compared with nonsmokers. The [clozapine](#) plasma concentration in smokers was a significant 3.2-fold lower and nortclozapine was 2.3-fold lower compared with plasma concentration in nonsmokers [144].

eJ) Induction of CYP1A2 activity by cigarette smoking significantly reduced [olanzapine](#) plasma concentrations and clinical effectiveness in smokers (10 to 40 cigarettes/day), compared with nonsmokers in a study of adults with thought disorder (N=17). After 15 days of [olanzapine](#) 10 mg/day, the dose-corrected steady-state [olanzapine](#) plasma concentration (C:D) ratio was about 5-fold lower in smokers compared with nonsmokers (1.56 vs 7.9 nanograms/mL/mg). At the same

time, Brief Psychiatric Rating Scale total scores were significantly higher for nonsmokers than for smokers (30.4% vs 12.5%) and were positively correlated with the steady-state plasma [olanzapine](#) C:D ratio. Smoking induced a significant 6-fold higher level of CYP1A2 activity in smokers compared with nonsmokers and the index was closely correlated with the steady-state plasma [olanzapine](#) C:D ratio[145].

f) Cigarette smoking appears to release polycyclic aromatic hydrocarbons that induce CYP1A2 substrate metabolism. In vivo blood clearance and urine metabolite data from [caffeine](#) demethylation has clearly demonstrated the link between CYP1A2 activity and cigarette smoking, which may have clinical consequences when cigarette smoking occurs with [theophylline](#), [caffeine](#), [tacrine](#), [imipramine](#), [haloperidol](#), [pentazocine](#), [propranolol](#), or [flecainide](#) therapy [140].

g) In a study of healthy volunteers (N=14), chronically-exposed passive smokers had a significantly higher mean [theophylline](#) clearance of 60.1 mL/kg/hr compared with 40.9 mL/kg/hr for the nonsmokers. [146]. However, in another study of volunteers (N=5), intense, short-term (5 days) passive smoking did not effect [theophylline](#) disposition [147]. It was concluded that the short duration of exposure to tobacco smoke explained the lack of effect.

h) A retrospective study of patients with [schizophrenia](#) (N=50) revealed that cigarette smokers (more than 1 pack/day) had significantly lower plasma concentrations of [haloperidol](#) (16.83 vs 28.8 nanograms/mL) and reduced [haloperidol](#) (active metabolite; 16.76 vs 34.23 nanograms/mL) and significantly increased [haloperidol](#) oral clearance (1.58 vs 1.1 L/min) compared with nonsmokers [148].

i) The administration of oral [imipramine](#) 3.5 mg/kg to smokers (15 cigarettes/day) resulted in significantly lower mean plasma levels of combined [imipramine](#) and desmethylinipramine when compared with nonsmokers (160 vs 290 nanograms/mL) [149].

4.0] Clinical Applications

[Monitoring Parameters](#)

[Patient Instructions](#)

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[Mechanism of Action / Pharmacology](#)

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[Comparative Efficacy / Evaluation With Other Therapies](#)

4.1] Monitoring Parameters

A) [Duloxetine](#) Hydrochloride

1) Therapeutic

a) Physical Findings

1) Chronic Musculoskeletal Pain

a) Reduction in pain scale score is indicative of efficacy

2) Diabetic Peripheral Neuropathy

a) Reduction in pain scale score indicates efficacy.

3) Fibromyalgia

a) Reduction of pain scale score and improvement of associated symptoms are indicative of efficacy.

4) Generalized Anxiety Disorder

a) Improvement in anxiety and associated symptoms indicate efficacy.

b) Periodically reassess efficacy to determine the continued need for and the appropriate dose of maintenance treatment [1].

5) Major Depressive Disorder

a) Reduction or improvement of depression and associated symptoms are indicative of efficacy.

b) Periodically reassess efficacy to determine the need for and the appropriate dose of maintenance treatment [1].

2) Toxic

a) Physical Findings

1) Prior to initiation of treatment, screen patients with depressive symptoms for risk of bipolar disorder (unapproved use) [1].

2) Monitor for worsening of depression, suicidality, or unusual changes in behavior, especially at the initiation of therapy or with dose increases or decreases [1].

3) Evaluate for signs and symptoms of serotonin syndrome [1].

4) Assess blood pressure before treatment initiation and periodically during therapy [1].

5) Regularly monitor height and weight in pediatric and adolescent patients, as decreased appetite and weight loss have been observed with the use of SSRIs and SNRIs [1].

4.2] Patient Instructions

A) Duloxetine (By mouth)

Duloxetine

Treats depression, anxiety, [diabetic peripheral neuropathy](#), [fibromyalgia](#), and chronic muscle or bone pain. This medicine is an SSNRI.

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 [duloxetine](#).

How to Use This Medicine:

Capsule, Delayed Release Capsule

Take your medicine as directed. Your dose may need to be changed several times to find what works best for you.

Delayed-release capsule: Swallow the capsule whole. Do not crush, chew, break, or open it.

This medicine should come with a Medication Guide. Ask your pharmacist for a copy if you do not have one.

Missed dose: Take a dose as soon as you remember. If it is almost time for your next dose, wait until then and take a regular dose. Do not take extra medicine to make up for a missed dose.

Store the medicine in a closed container at room temperature, away from heat, moisture, and direct light.

Drugs and Foods to Avoid:

Ask your doctor or pharmacist before using any other medicine, including over-the-counter medicines, vitamins, and herbal products.

Do not take [duloxetine](#) if you have used an MAO inhibitor (MAOI) within the past 14 days. Do not start taking an MAO inhibitor within 5 days of stopping [duloxetine](#).

Some medicines can affect how [duloxetine](#) works. Tell your doctor if you are using any of the following:

[Buspirone](#), [fentanyl](#), [lithium](#), St John's wort, [tramadol](#), tryptophan, or [warfarin](#)

Diuretic (water pill)

Medicine for heart rhythm problems (including [flecainide](#), [propafenone](#), [quinidine](#))

Triptan medicine to treat migraine headaches

NSAID pain or [arthritis](#) medicine (including [aspirin](#), [celecoxib](#), [diclofenac](#), [ibuprofen](#), [naproxen](#))

Other medicine to treat depression or mood disorders (including [desipramine](#), [fluoxetine](#), [paroxetine](#))

Phenothiazine medicine (including [chlorpromazine](#), [perphenazine](#), [prochlorperazine](#), [promethazine](#), [thioridazine](#))

Tell your doctor if you use anything else that makes you sleepy. Some examples are allergy medicine, narcotic pain medicine, and alcohol.

Warnings While Using This Medicine:

Tell your doctor if you are pregnant or breastfeeding, or if you have [kidney disease](#), liver disease, [diabetes](#), digestion problems, [glaucoma](#), [heart disease](#), high or low blood pressure, or problems with urination. Tell your doctor if you have a history of seizures, or drug or [alcohol addiction](#).

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:

Serious liver problems

A serious drug reaction called [serotonin syndrome](#) (more likely when used with certain other medicines)

Increased risk of bleeding problems

Serious skin reactions

Low sodium levels in the blood

This medicine can cause changes in your blood pressure. This may make you dizzy or drowsy. Do not drive or do anything that could be dangerous until you know how this medicine affects you. Stand up slowly to avoid falls.

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

Blistering, **peeling**, red skin rash

Confusion, weakness, muscle twitching

Dark urine or pale stools, nausea, vomiting, loss of appetite, stomach pain, yellow skin or eyes

Decrease in how much or how often you urinate

Eye pain, vision changes, seeing halos around lights

Feeling more energetic than usual

Lightheadedness, dizziness, or fainting

Restlessness, fever, fast heartbeat, sweating, muscle spasms, diarrhea, seeing or hearing things that are not there

Unusual moods or behaviors, worsening depression, thoughts about hurting yourself, trouble sleeping

Unusual bleeding or bruising

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

Decrease in appetite or weight

Dry mouth, constipation, mild nausea

Unusual drowsiness or tiredness

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

4.3] Place In Therapy

A) **Duloxetine** Hydrochloride

1) Depression

a) **Duloxetine** hydrochloride is indicated for the acute and maintenance treatment of **major depressive disorder**. Similar to milnacipran and **venlafaxine**, **duloxetine** is a serotonin/norepinephrine reuptake inhibitor (SNRI) [51]. These agents are claimed to be at least as effective as tricyclics but with lower toxicity, and more efficacious than selective serotonin reuptake inhibitors (SSRIs). The primary role of SNRIs is as an alternative in patients with **major depressive disorder** who have responded poorly to other agents (eg, tricyclics or SSRIs).

b) At present, **duloxetine** is not recommended over other available SNRIs in poorly-responsive patients.

2) Diabetic Peripheral Neuropathic Pain

a) **Duloxetine** is indicated for the treatment of neuropathic pain associated with **diabetic neuropathy** [51]. At doses of either 60 milligrams (mg) once daily or twice daily, **duloxetine** improved diabetic peripheral neuropathic pain compared to placebo in randomized, double-blind, phase 3 clinical trials. While there were no differences in pain relief between the once-daily and twice-daily dose, the once-daily dose was better tolerated in these trials [173][174][175].

3) Fibromyalgia

a) **Duloxetine** is indicated for the management of **fibromyalgia** [51]. Efficacy was established in several randomized, placebo-controlled, double-blind trials; however, trials were conducted in women predominantly or women alone. In a 12-week, randomized, double-blind, placebo-controlled trial (n=354), **duloxetine** (60 mg once daily or twice daily) was effective and safe in the treatment of **fibromyalgia** in female patients with or without **major depressive disorder** (MDD) [176]. In another randomized, double-blind trial (n=207) trial, a 12-week course of **duloxetine** was safe and improved some symptoms of **fibromyalgia** compared with placebo, and women were affected to significantly greater extent than men [177]. Notably, reduction in pain severity seen at 3 months following treatment with oral **duloxetine** 60 or 120 mg/day was maintained at 6 months in another multicenter, randomized, double-blind, placebo-controlled trial (n=520) [34].

4) Generalized Anxiety Disorder

a) **Duloxetine** is approved for the treatment of **generalized anxiety disorder** in adults and pediatric patients 7 years or older. **Duloxetine** significantly improved generalized anxiety symptoms in 3 placebo-controlled trials of adults with moderately severe **generalized anxiety disorder** [1][7][8]. Efficacy was also demonstrated in placebo-controlled trials of pediatric patients (N=271) and in patients 65 years or older (N=291) [1].

b) Significantly fewer patients relapsed (13.7% vs 41.8%) and significantly more maintained remission (68.1% vs 39.3%) while taking **duloxetine** for up to 1 year, compared with placebo, in a double-blind trial (N=405) [9].

5) Chronic Musculoskeletal Pain

a) **Duloxetine** hydrochloride is indicated for the management of chronic musculoskeletal pain in adults. In 3 double-blind, randomized, placebo-controlled studies among patients with chronic low back pain or chronic pain secondary to **osteoarthritis**, **duloxetine** was associated with greater pain reduction relative to placebo [4].

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

See Drug Consult reference: Chemotherapy-Induced **Peripheral Neuropathy**- Guidelines

4.4] Mechanism of Action / Pharmacology

A) **Duloxetine** Hydrochloride

1) Mechanism of Action

a) **Duloxetine** is a dual-selective serotonin (5HT) and **norepinephrine** reuptake inhibitor [166]. Although structurally unrelated, the mechanism and pharmacodynamic characteristics of **duloxetine** are generally like those of **venlafaxine** and milnacipran [161][167][162]. **Duloxetine** is the (+)-isomer of the racemic compound [166]. It bears structural similarity to **fluoxetine** and **tomoxetine**.

b) **Duloxetine** is a secondary amine, whereas **venlafaxine** and milnacipran are tertiary amines. All three agents have been demonstrated to inhibit **norepinephrine** and 5HT uptake in preclinical

studies; both [duloxetine](#) and [venlafaxine](#) were more potent inhibitors of 5HT than [norepinephrine](#) reuptake, whereas milnacipran was a more potent inhibitor of [norepinephrine](#) uptake [168][161]. [Duloxetine](#) has exhibited higher potency at both reuptake sites than milnacipran or [venlafaxine](#) [161][169][168]. In vitro, [duloxetine](#) has not shown significant affinity for [histamine](#) H1, [dopamine](#) D2, cholinergic, alpha-1 adrenergic, 5HT-1A, 5HT-1B, 5HT-1D, 5HT-2A, 5HT-2C, or opioid receptors [161][168][166].

c) The in vitro activity of antidepressants has not always been predictive of in vivo/clinical effects. Thus, the greater in vitro activity of [duloxetine](#) compared to [venlafaxine](#) may not imply greater clinical efficacy. Some in vivo data have suggested the similar potency of [duloxetine](#) in inhibiting 5HT and [norepinephrine](#) reuptake [166], which contrasts in vitro findings. Clinical comparisons of the serotonin/[norepinephrine](#) reuptake inhibitors (SNRIs) are essential to determine relevant differences.

d) [Duloxetine](#) has increased neural sphincter activity and bladder capacity in animal studies [170][171], and has been investigated in [urinary incontinence](#).

2) Review Articles

a) A review of the pharmacology, pharmacokinetic profile, and clinical efficacy of [duloxetine](#) in the treatment of depression [163].

b) Advances in the treatment of depression, including [duloxetine](#) [172][167].

c) Mechanisms, pharmacology, pharmacokinetics, and clinical efficacy of the SNRIs [161].

4.5] Therapeutic Uses

4.5.1] FDA Uses

4.5.1.A] [Duloxetine](#) Hydrochloride

4.5.1.A.1] [Diabetic peripheral neuropathy](#) - Pain

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 A

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

b) Summary:

Evidence

In a systemic review and metaanalysis of 8 trials in 2728 patients with [painful diabetic neuropathy](#), [duloxetine](#) 60 mg/day compared with placebo significantly improved the likelihood of having at least a 50% improvement in pain within 12 weeks by 73% (4 studies,

908 patients) and the likelihood of having at least a 30% improvement in pain within 12 weeks by 53% (4 studies, 799 patients). The likelihood of having at least a 50% improvement in pain within 12 weeks was also significantly greater for [duloxetine](#) 40 mg/day and 120 mg/day dosages compared with placebo, but was not significant for the 20 mg/day dosage. The risk of adverse events leading to discontinuation was increased by 95% across all neuropathic pain indications (14 studies in 4837 patients) [24].

In a randomized trial of Chinese patients, [duloxetine](#) therapy significantly improved mean 24-hour weekly pain scores at week 12 compared with placebo (11-point Likert scale; -2.4 vs -1.97). Nausea, somnolence, and asthenia occurred significantly more frequently with [duloxetine](#) [25].

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

4.5.1.A.2] [Fibromyalgia](#)

FDA Labeled Indication

a) Overview

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

Efficacy: Adult, Effective

Recommendation: Adult, Class IIa

Strength of Evidence: Adult, Category A

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

b) Summary:

Evidence

In a systemic review and metaanalysis of 6 trials in 2249 patients with [fibromyalgia](#), [duloxetine](#) 60 mg/day compared with placebo significantly improved the likelihood of having at least a 50% improvement in pain within 12 weeks by 57%, and after more than 12 weeks by 58%. The likelihood of having at least a 50% improvement in pain within or after more than 12 weeks was also significant for the 120 mg/day dosage compared with placebo, but was not significant for the 20 mg or 30 mg/day dosages. The risk of adverse events leading to discontinuation was increased by 95% across all neuropathic pain indications (14 studies in 4837 patients) [24].

Guidelines

Serotonin [norepinephrine](#) reuptake inhibitor medications, including [duloxetine](#), are recommended in the treatment of [fibromyalgia](#), based on clinical evidence of reduced pain, which was independent of effects on mood. Some clinical response was seen within 8 weeks of treatment [32].

Systematic review and expert consensus recommends that antidepressants, including [duloxetine](#), be considered for the treatment of [fibromyalgia](#), because pain and overall function have improved during treatment [33].

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

4.5.1.A.3] [Generalized anxiety disorder](#)

FDA Labeled Indication

a) Overview

FDA Approval: Adult, yes; **Pediatric, yes (7 years or older)**

Efficacy: Adult, Effective; Pediatric, Evidence favors efficacy

Recommendation: Adult, Class IIa; Pediatric, Class IIb

Strength of Evidence: Adult, Category A; Pediatric, Category B

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

b) Summary:**Evidence (Adult)**

Duloxetine 60 to 120 mg/day significantly improved symptoms, compared with placebo, in 3 double-blind trials (N=1163) of adults with [generalized anxiety disorder](#) of at least moderate severity (mean baseline Hamilton Anxiety Rating Scale (HAM-A) scores, 23 to 25) [1][7][8]. **Duloxetine** response rate (at least 50% reduction from baseline HAM-A score) was significantly better than placebo in one study (58% and 56% vs 31%) but not in another (47% vs 37%) [7]. Although **duloxetine** 120 mg once daily was effective, there was no additional benefit compared with 60 mg/day [1].

Significantly fewer patients relapsed (13.7% vs 41.8%) and significantly more maintained remission (68.1% vs 39.3%) on **duloxetine** for up to 1 year, compared with placebo, in a double-blind trial (N=405) [9].

Evidence (Geriatric)

Duloxetine significantly improved symptoms, compared with placebo, in a randomized trial (N=291) of adults 65 years or older with [generalized anxiety disorder](#) (mean baseline Hamilton Anxiety Rating Scale scores, 25). The mean **duloxetine** dosage was 51 mg/day [1].

Evidence (Pediatric)

In a randomized trial of patients 7 to 17 years old (mean baseline Pediatric Anxiety Rating Scale PARS scores of approximately 17), **duloxetine** significantly improved symptoms compared with placebo. The mean **duloxetine** dosage was 58 mg/day [1].

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

4.5.1.A.4) Major depressive disorder**FDA Labeled Indication****a) Overview**

FDA Approval: Adult, yes; **Pediatric, no**

Efficacy: Adult, Effective; Pediatric, Ineffective

Recommendation: Adult, Class IIa; **Pediatric, Class III**

Strength of Evidence: Adult, Category A; Pediatric, Category A

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

b) Summary:**Evidence (Adult)**

Duloxetine was more effective than placebo in several randomized trials [10][11][12] and was non-inferior to **paroxetine** 20 mg/day in one randomized study (N=353) [12]. There was no significant difference between **duloxetine** 60 and 120 mg in hospitalized patients (N=338) [13] and when treatment was continued for 6 months, **duloxetine** 80 and 120 mg/day demonstrated significant improvement from baseline (N=273) [10].

In a systematic review and meta-analysis of 15 randomized trials of 4588 patients aged 60 years or older with **major depressive disorder**, treatment with **duloxetine** (62%), **paroxetine** (48%), or **sertraline** (28%) significantly increased likelihood of achieving a partial response (50% or greater reduction from baseline on the Hamilton Depression Rating Scale (HAM-D) or the Montgomery-Asberg Depression Rating Scale (MADRS)) compared with placebo. **Venlafaxine**, escitalopram, **fluoxetine**, and **citalopram** were no better than placebo. **Duloxetine** had a significant 194% increased risk of dizziness compared with placebo, while nonsignificant increase in risk was seen with **sertraline** (10%) and **paroxetine** (47%) [14].

Duloxetine compared with placebo was effective in the prevention of reemergence of depressive symptoms and **relapse** following successful acute treatment of **major depressive disorder** beyond 12 weeks with continued treatment in a randomized trial (N=533; mean age, 43.4 years). **Duloxetine** was associated with significant improvements in the time-to-relapse during the continuation phase and rate of **relapse** (17.4% vs 28.5%) [15].

Duloxetine 60 mg/day significantly reduced pain and improved depression in patients with **major depression** and moderate painful physical symptoms compared with placebo in several studies [16][17][18][19].

Evidence (Pediatric)

Duloxetine was not effective in the treatment of pediatric patients, aged 7 to 17 years, in 2 randomized trials (N=337 and N=463) [20][21][22] of similar design, as measured by the mean change from baseline Children's Depression Rating Scale-Revised total scores at 10 weeks. The active control **fluoxetine**, which is approved by the US Food and Drug Administration for the treatment of **major depressive disorder** in this population, was also no better than placebo. Therefore the results with **duloxetine** were inconclusive [21][22].

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

c) Pediatric:

1) **Duloxetine** was not different from placebo, as measured by mean change from baseline Children's Depression Rating Scale-Revised (CDRS-R) total scores at week 10 (-24.3 vs -24.3 points), in a randomized, placebo- and active-controlled study (N=337) in children (mean age, 13 years; range, 7 to 17 years) with a mean baseline CDRS-R total score of 59.4. Other nonsignificant differences at week 10 included mean Clinical Global Impressions of Severity (CGI-S) score (2.7 vs 2.6) and probability of response (67% vs 62%). **Duloxetine** was flexibly dosed from 60 to 120 mg/day and **fluoxetine** was dosed at 20 or 40 mg/day [21]. Fixed-dose **duloxetine** (30 or 60 mg/day) resulted in similar clinical endpoints at week 10, without a difference from placebo (CDRS-R change, -24.6 and -23.9 vs -21.6 points; CGI-S, 3.1 for all; probability of response, 69% and 69% vs 60%), in another study of similar design (N=463) in children (mean age, 13 years; range, 7 to 17 years) with a mean baseline CDRS-R total score of 58.8 [22]. **Fluoxetine** was the active control in both studies and did not separate from placebo on any measure in either study [22][21].

4.5.1.A.5] Musculoskeletal pain, Chronic

FDA Labeled Indication

a) Overview

FDA Approval: Adult, yes; **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:

[Duloxetine](#) hydrochloride is indicated for the management of chronic musculoskeletal pain in adults [4].

In 3 double-blind, randomized, placebo-controlled studies among patients with chronic low back pain or chronic pain secondary to [osteoarthritis](#), [duloxetine](#) was associated with greater pain reduction relative to placebo [4].

In 3 randomized, double-blind trials, treatment of [osteoarthritis of the knee](#) with [duloxetine](#) demonstrated significantly greater pain relief compared with placebo [5][6][4].

Efficacy beyond 13 weeks has not been established [4].

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

c) Adult:**1) Chronic Back Pain**

a) In two 13-week, double-blind, randomized, placebo-controlled trials among adults with chronic low back pain, [duloxetine](#) treatment demonstrated significant reduction in pain relative to placebo. Patients enrolled in the studies had no history of signs of [radiculopathy](#) or [spinal stenosis](#). In the first study, patients were initiated on [duloxetine](#) 60 mg/day (n=115) or placebo (n=121). Patients who experienced less than 30% pain reduction after 7 weeks of therapy and tolerated [duloxetine](#) 60 mg dose were subsequently given a dose adjustment to 120 mg/day in a double-blinded fashion for the rest of the study. In the second trial, patients received fixed doses of [duloxetine](#) 60 mg (n=198), or placebo (n=203). At baseline, patients in both studies had a mean pain score of 6 on a scale of 0 (worst pain) to 10 (worst possible pain). At study endpoint, patients taking [duloxetine](#) reported significantly greater pain reduction compared with those taking placebo (pain score not provided) [4].

2) Osteoarthritis

a) [Duloxetine](#) treatment of geriatric patients with primary [knee osteoarthritis](#) (OA) resulted in a significantly greater proportion of patients achieving a clinical response compared with placebo (48% vs 9%) in a 16-week, single-center, randomized, double-blind trial (n=280). Eligible patients 65 years or older (mean age, 68.5 years) had American College of Rheumatology clinical and radiographic OA with knee pain (mean score above 40 [on a scale of 0 to 100] using daily ratings during the week prior to randomization) for more than 14 days/month for 3 consecutive months preceding enrollment. Exclusion criteria included BMI greater than 32 kg/m(2), [joint inflammatory disease](#), and crystal-induced [arthropathies](#). Patients (mean BMI,

26.5 kg/m(2); mean disease duration, 5.6 years) were randomized to receive either [duloxetine](#) 60 mg/day (n=144) or placebo (n=144). Concomitant stable rescue doses of [paracetamol](#) (up to 4 g/day) and NSAIDs were permitted; other antidepressants were prohibited. The mean baseline [visual analogue pain scale](#) (VAS) score (0 to 100 mm) was 58.3 and 58.5 in the [duloxetine](#) and placebo groups, respectively. In an intent-to-treat analysis at week 16, using the Osteoarthritis Research Society International (OARSI) 2004 criteria, a clinical response defined as a 20% decrease in pain or physical function score, or at least a 20-mm decrease on the pain VAS was achieved by 48% of [duloxetine](#) patients compared with 9% of placebo-treated patients (p less than 0.05). Mean self-reported Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) scores at week 16 in the [duloxetine](#) arm compared with placebo were significantly improved on the pain (score, 6 vs 8.4; p=0.05) and function subscales (score, 24.6 vs 30.3; p=0.01), but were not significantly different on the stiffness subscale (score, 6.1 vs 6.4; p=0.55). There was a significant decrease in the mean geriatric depression scale (GDS) scores in duloxetine-treated patients compared with placebo (5.2 vs 9.7; p less than 0.05). Commonly reported adverse events in the [duloxetine](#) group included constipation, nausea, [cough](#), hyperhidrosis, and palpitations [5].

b) Treatment of [osteoarthritis of the knee](#) with [duloxetine](#) plus dose-optimized NSAIDs demonstrated significantly greater pain relief compared with placebo in a 10-week, randomized, double-blind, phase 3b trial (n=524). Adults (mean age 61 years) with moderate knee pain (score of 4 or greater on a scale of 0 to 10) for at least 14 days/month despite treatment with oral NSAIDs were randomized to receive dose-optimized NSAIDs plus either placebo (n=260) or [duloxetine](#) 60 mg/120 mg daily (n=264). All patients also received [omeprazole](#) 20 mg orally once daily or a previously used proton pump inhibitor. Following a 2 week NSAID dose-optimizing phase, patients with a continued pain score of at least 4 entered a 10-week treatment phase. Duloxetine-treated patients received 30 mg/day for 1 week, 60 mg/day for 2 weeks, and if at week 3 a pain score of 4 persisted, the dose could be increased to 120 mg/day. To minimize the influence of an end-of-treatment effect, patients and investigators were told of a sham endpoint at 10 weeks, when in reality the primary endpoint was evaluated at week 8. Routine use of other analgesics, muscle relaxants, and sedative hypnotics were prohibited. At baseline, the mean daily average pain score was 6.27 in the [duloxetine](#) group and 6.36 in placebo. [Ibuprofen](#) (45.6%) and [naproxen](#) (34.2%) were the most commonly used NSAIDs. At week 8, the estimated mean change in average pain rating (primary endpoint) was -2.46 (standard error (SE) 0.11) compared with -1.55 (SE 0.11) in placebo (p less than 0.001). A significant improvement in pain was seen as early as week 1 in the [duloxetine](#) arm compared with placebo (p=0.01), and this persisted at each subsequent week (p less than 0.001). There was no difference in the frequency of use of rescue medication ([acetaminophen](#)) between treatment groups (p=0.08). Treatment-emergent adverse events occurring at least twice the frequency in the [duloxetine](#) group compared with placebo group included nausea, dry mouth, constipation, fatigue, and decreased appetite. Bleeding-related adverse events occurred in 4 duloxetine-treated patients compared with 1 patient in the placebo arm and there was a significant change in blood pressure in the [duloxetine](#) group compared with placebo (systolic: -3.2 mmHg vs 0.3 mmHg, p=0.002; diastolic: -0.5 vs 1.3 mmHg, p=0.02). The short duration of the study limits its extrapolation to long-term maintenance of [osteoarthritis](#) and bleeding-related complications [6].

c) In a 13-week, double-blind, randomized, placebo-controlled trials among adults with [idiopathic osteoarthritis](#) of the knee, [duloxetine](#) treatment demonstrated significant pain reduction relative to placebo. Patients were randomized to receive [duloxetine](#) 30 mg once daily for one week followed by a dose increase to 60 mg/day (n=128) or matching placebo (n=128). At baseline, patients in both studies had a mean pain score of 6 (scale of 0 to 10). At study endpoint, patients taking [duloxetine](#) reported significantly greater pain reduction compared with those taking placebo (pain score not provided). NSAID use did not alter treatment outcome results in subgroup analysis [4].

4.5.2] Non FDA Uses

4.5.2.A] [Duloxetine](#) Hydrochloride

4.5.2.A.1] [Cancer](#) pain

See Drug Consult reference: Management of Cancer-Related Pain in Adult Patients

4.5.2.A.2] Pain, Chemotherapy-induced - Peripheral nerve disease

a) Overview

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

Efficacy: Adult, Evidence favors efficacy

Recommendation: Adult, Class IIb

Strength of Evidence: Adult, Category B

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

b) Summary:

In a multicenter, randomized, double-blind, crossover, phase 3 trial of patients with chemotherapy-induced [neuropathy](#) (n=231), 5 weeks of [duloxetine](#) treatment resulted in a significantly greater mean reduction of average pain score compared with placebo [26].

See Drug Consult reference: Chemotherapy-Induced [Peripheral Neuropathy](#)- Guidelines

c) Adult:

1) In a multicenter, randomized, double-blind, crossover, phase 3 trial of patients with chemotherapy-induced [neuropathy](#) (n=231) [duloxetine](#) therapy in the initial 5-week treatment period resulted in a significantly greater mean decrease in average pain scores compared with placebo (-1.06 vs -0.34) using the Brief Pain Inventory Short Form scores (BPI-SF; range 0 to 10, with a 0.98 reduction considered to be the minimally clinically important difference). Included patients (mean age, 59 +/- 10.5 years) had at least grade 1 sensory pain based on the National Cancer Institute Common Terminology Criteria for Adverse Events version 3.0 grading scale, and reported at least 4 on a 10-point scale (average neuropathic pain) for 3 or more months after completing chemotherapy (40% [paclitaxel](#); 59% [oxaliplatin](#)). Patients were randomized to receive 5 weeks of treatment with either [duloxetine](#) 30 mg daily for the first week followed by [duloxetine](#) 60 mg/day for 4 weeks (n=115), or placebo for the initial 5 weeks (n=116), then, following a 2-week washout period, patients crossed-over to the alternate treatment for the next 5 weeks, for a total study period of 14

weeks. Doses of analgesics (eg, opioids, [acetaminophen](#), [aspirin](#), NSAIDs), stable for at least 2 weeks before study registration, and chemotherapy (only with [paclitaxel](#), albumin-bound [paclitaxel](#), [oxaliplatin](#), [docetaxel](#), or cisplatin) were permitted. Pain was assessed weekly via BPI-SF. In an analysis of the primary endpoint after 5 weeks, [duloxetine](#) therapy resulted in a statistically and clinically significant greater decrease in average pain (mean change score, 1.06; 95% CI, 0.72 to 1.4) compared with placebo (mean change score, 0.34; 95% CI, 0.01 to 0.66; $p=0.003$); treatment difference 0.73 (95% CI, 0.26 to 1.2). More patients who received [duloxetine](#) in the first 5 weeks (59%) reported decreased pain of any amount, compared with 38% of patients who received placebo. The relative risk of experiencing a 30% pain reduction was 1.96 (95% CI, 1.15 to 3.35), or a 50% pain reduction was 2.43 (95% CI, 1.11 to 5.3), for [duloxetine](#) compared with placebo. At the end of the initial 5-week treatment period, patients who received [duloxetine](#) reported a greater mean improvement in pain-related quality of life measured by the Functional Assessment of Cancer Treatment, Gynecologic Oncology Group Neurotoxicity (FACT/GOG-NTx) total score compared with placebo (2.44 vs 0.87; $p=0.03$). In an exploratory analysis, patients who received platinum (oxaliplatin) experienced a greater benefit from [duloxetine](#) compared with those treated with taxanes ($p=0.13$). There were more grade 3 nonhematologic adverse events reported in the [duloxetine](#) group compared with placebo (7% vs 3%) and the drop-out rate due to adverse events was 11% vs 1%, respectively, (p less than 0.001) [26].

4.5.2.A.3] Urinary incontinence

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:

Evidence

In a systematic review and meta-analysis of 7 trials that included 4900 women with [stress urinary incontinence](#), [duloxetine](#) was associated with a significantly better response rate (50% or greater reduction in frequency of incontinence episodes; 52.5% vs 33.7%) and increased average voiding interval compared with placebo. Patients also experienced a higher cure rate (absence of incontinence) with [duloxetine](#) (10.8% vs 7.8%; 3 trials with 1419 women) and significantly improved quality of life (3 studies with 1250 women). Across 9 trials, significantly more patients withdrew from [duloxetine](#) treatment because of adverse effects (17.3% vs 3%), with nausea being the most common reason [31].

[Duloxetine](#) was more effective than placebo at reducing incontinence episode frequency (-7.3 vs -5.65) in adult women with mixed [urinary incontinence](#) in an 8-week, randomized trial (N=588). Patients also experienced a significant increase in time between voids (19.7 vs 5.9 minutes) and improvement in quality of life (44.2% vs 27.3% rated condition as very much or much better) with [duloxetine](#) treatment. Treatment-emergent adverse effects with [duloxetine](#) resulted in significantly fewer patients completing the study compared with placebo (78% vs 94.8%) [27].

4.6] Comparative Efficacy / Evaluation With Other Therapies

4.6.A] Amitriptyline Hydrochloride

4.6.A.1] Diabetic peripheral neuropathy - Pain

a) There was no difference from baseline in subjective pain or sleep between treatment arms (all groups showed improvement), for patients who received [amitriptyline](#), [duloxetine](#), or pregabalin for the treatment of painful [diabetic peripheral neuropathy](#) in a randomized trial (N=83). Sleep continuity and maintenance of REM sleep was improved more with pregabalin and [amitriptyline](#) compared with [duloxetine](#); however, [duloxetine](#) and [amitriptyline](#) improved daytime function by improving reaction time and CNS arousal and processing ability. There was no difference in quality of life scores for any of the treatments. Patients who received pregabalin experienced the highest number of adverse reactions, including fatigue, somnolence, and dizziness [179].

b) In a 14-week randomized, crossover study (N=58), there was no difference in the reduction in median pain score for patients who received [duloxetine](#) or [amitriptyline](#) for the treatment of [painful diabetic neuropathy](#) (good improvement [median pain score reduction greater than 50% on 100-point visual analog scale], [amitriptyline](#), 55% vs [duloxetine](#), 59%). Additionally, no difference was found between treatments for other scales (McGill and Likert), pain relief at 6 weeks, or sleep and overall well being; both groups significantly improved from baseline. Moderate to severe adverse events were more common with [amitriptyline](#) (51% vs 24%); dry mouth was significantly more common with [amitriptyline](#) (55% vs 24%), while constipation was more common with [duloxetine](#) (37% vs 17%) [180].

4.6.B] Citalopram Hydrobromide

4.6.B.1] Major depressive disorder

a) In a systematic review and metaanalysis in 15 randomized trials of patients aged 60 years or older with [major depressive disorder](#), treatment with [duloxetine](#) (62%), [paroxetine](#) (48%), or [sertraline](#) (28%) was associated with a significantly greater likelihood of achieving a partial response (defined as 50% or greater reduction from baseline in depression score based on the Hamilton Depression Rating Scale, which is preferred, or the Montgomery-Asberg Depression Rating Scale) compared with placebo. [Venlafaxine](#) and escitalopram each had a nonsignificant 20% likelihood of a partial response, while [fluoxetine](#) (8%) and [citalopram](#) (7%) had the lowest benefit. As for dizziness, [duloxetine](#) had a significant 194% increased risk compared with placebo, while a nonsignificant risk was seen with [sertraline](#) (10% increase in risk) and [paroxetine](#) (47% increase risk) [14].

4.6.C] Escitalopram Oxalate

4.6.C.1] Major depressive disorder

a) In a systematic review and metaanalysis in 15 randomized trials of patients aged 60 years or older with [major depressive disorder](#), treatment with [duloxetine](#) (62%), [paroxetine](#) (48%), or [sertraline](#) (28%) was associated with a significantly greater likelihood of achieving a partial response (defined as 50% or greater reduction from baseline in depression score based on the Hamilton Depression Rating Scale, which is preferred, or the Montgomery-Asberg Depression Rating Scale) compared with placebo. [Venlafaxine](#) and escitalopram each had a nonsignificant 20% likelihood of a partial response, while [fluoxetine](#) (8%) and [citalopram](#) (7%) had the lowest benefit. As for dizziness, [duloxetine](#) had a significant 194% increased risk compared with placebo, while a nonsignificant risk was seen with [sertraline](#) (10% increase in risk) and [paroxetine](#) (47% increase risk) [14].

b) There was no significant difference between treatment with escitalopram 20 mg/day compared with [duloxetine](#) 60 mg/day in the time to all-cause discontinuation of therapy in patients with severe depression who failed to respond to initial 2-week treatment with escitalopram 10 mg/day according to a 12-week, randomized, double-blind, fixed-dose study (n=484). However, secondary endpoint analysis did demonstrate a significant improvement on the Montgomery-Asberg Depression Rating Scale (MADRS) in escitalopram-treated patients compared with [duloxetine](#). Outpatients (mean age, 42.4 years) with primary [major depressive disorder](#) (DSM-IV criteria) on the Mini International Neuropsychiatric Interview, a current [depressive episode](#) of at least 3-months duration, MADRS total score of 30 or greater (mean baseline score 34.7 in the escitalopram group and 34.9 in the [duloxetine](#) group), and a Clinical Global Impressions (CGI)-Severity score of at least 4 were included in the study. Patients who failed to respond to 2 weeks of escitalopram 10 mg/day (less than 50% MADRS improvement) were randomized to receive 8 weeks of either escitalopram 20 mg/day (n=229), or [duloxetine](#) 60 mg/day (n=245). Dosage adjustments were prohibited. There was no difference between the 2 treatment arms in the time to all-cause discontinuation of therapy (primary endpoint; hazard ratio escitalopram/[duloxetine](#), 0.95; 95% CI, 0.64 to 1.41; p=0.727). The change from baseline to week 8 in MADRS total score was significantly improved in the escitalopram arm compared with [duloxetine](#) (-21.86 vs -19.99; least squares mean difference (LSMD), -1.87; 95% CI, -3.6 to -0.14; p=0.034) with significance in favor of escitalopram at each visit, with the exception of week 4 (p=0.051). Remission on MADRS (score of 10 or lower) was achieved by significantly more escitalopram-treated patients compared with [duloxetine](#) (54% vs 42%; p=0.013). Self-rated Quick Inventory of Depressive Symptomatology (QID-SR) was also significantly improved in escitalopram-treated patients compared with [duloxetine](#) (LSMD escitalopram/[duloxetine](#), -1.03; 95% CI, -1.91 to -0.14; p=0.024). There was no significant difference observed between the escitalopram arm compared with [duloxetine](#) on improvement of 50% or greater on MADRS (73% vs 70%), CGI-Improvement score 2 or lower (77% vs 75%), mean change from baseline on CGI-Severity score (-2.4 +/- 0.09 vs -2.2 +/- 0.08), or any other efficacy parameter measured. Thirteen patients from each treatment group discontinued the study prematurely due to an adverse event. Limitations of the study include the short duration of the escitalopram 10 mg/day lead-in period and a 50% improvement criteria may have been too restrictive to classify patients as non-responders [182].

c) In an 8-week, randomized, double-blind, placebo- and active-comparator controlled, multicenter, noninferiority trial in adult patients (n=684) with [major depressive disorder](#) (MDD), onset of efficacy for [duloxetine](#) 60 mg daily was at least as fast as onset for escitalopram 10 mg daily, and patients in both active treatment groups were more likely to meet onset criteria than placebo patients. Patients aged 18 years or older (range, 18 to 79 years), meeting the DSM-IV criteria for MDD and with a Montgomery-Asberg Depression Rating Scale (MADRS) total score of 22 or greater and a Clinical Global Impression Scale-Severity (CGI-S) score of 4 or greater were included. Patients were randomized to receive either [duloxetine](#) 60 mg daily (n=273; mean age, 41.1 years; mean baseline Hamilton Rating Scale for Depression (HAM-D) Maier subscale score, 17.6), escitalopram 10 mg daily (n=274; mean age, 43.3 years; mean baseline HAM-D score, 17.8), or placebo (n=137; mean age, 42.5 years; mean baseline HAM-D score, 17.7) during an 8-week, acute treatment period. Onset of efficacy (primary endpoint) was defined as achieving a 20% or greater decrease in HAM-D score by week 2 that was sustained for the remainder of the acute treatment period. In the intent-to-treat analysis, the probability of meeting efficacy onset criteria was similar in the [duloxetine](#) and escitalopram groups (42.6% vs 35.2%, respectively; difference, 7.4%; 95% confidence interval (CI), -1.3% to 16.2%; p=0.097), and patients in both groups were more likely to achieve efficacy onset compared to placebo patients (21.5%; [duloxetine](#) vs placebo, p less than 0.001; escitalopram vs placebo, p=0.008). The noninferiority of [duloxetine](#) to escitalopram was maintained following a per-protocol analysis. In an analysis for the main treatment effect in which data from all visits were pooled, a significantly greater proportion of [duloxetine](#) patients achieved efficacy onset vs escitalopram patients (p=0.026), and a greater proportion of patients in both active treatment groups achieved efficacy compared to placebo patients (p less than or equal to 0.018 for both). The median time to onset was significantly

shorter among duloxetine-treated patients than both escitalopram- and placebo-treated patients (23 days vs 41 days vs 55 days, respectively; [duloxetine](#) vs escitalopram, $p=0.032$; [duloxetine](#) vs placebo, p less than 0.001), and median time to onset did not differ between escitalopram and placebo patients ($p=0.087$). The probability of achieving a treatment response (secondary endpoint) by week 8, defined as a 50% or greater improvement in HAMD total score, was similar among the [duloxetine](#) (48.7%), escitalopram (45.3%), and placebo (36.9%) groups, and the probability of remission (HAMD total score of 7 or less) also did not differ between the groups (40.1% vs 33% vs 27.7%, respectively). The 191 subjects who failed to complete the study were evenly distributed among the groups, and a similar percentage in each group discontinued due to adverse effects. Nausea more commonly caused discontinuation among [duloxetine](#) patients compared with escitalopram patients (2.9% vs 0.4%, respectively; $p=0.02$). Both nausea and dry mouth occurred more often in [duloxetine](#) patients compared to escitalopram and placebo patients and at a rate greater than 10% (nausea, 23.8% vs 12% vs 8.8%; dry mouth, 21.6% vs 10.9% vs 10.9%; p less than 0.05 for all). Although this study focused on the acute 8-week treatment period, subjects completing this trial period continued with blinded treatment for an additional 6 months [183]. During the 6-month extension phase, the [duloxetine](#) dose ranged from 60 to 120 mg/day and the escitalopram dose ranged from 10 to 20 mg/day; placebo non-responders from the acute treatment phase were assigned in a double-blind fashion to active treatment. Among the 431 patients (63%) continuing on in the extension phase, there were no significant differences in antidepressant efficacy between the [duloxetine](#) and escitalopram groups based on HAMD total scores. The probability of remission was 70% and 75% among the [duloxetine](#) and escitalopram groups, respectively ($p=0.44$). The only statistically significant difference between the groups was on the HAMD sleep subscale, where escitalopram-treated patients had greater improvement in insomnia than duloxetine-treated patients (mean change from baseline, -1.89 vs -1.55; p less than 0.05). Although discontinuation rates over the 8-month study were higher in the [duloxetine](#) group vs escitalopram (62% vs 55%; $p=0.02$), rates of discontinuation due to adverse events were similar (12.8% vs 12%, respectively) [184].

d) In a randomized, double-blind, fixed-dose, noninferiority trial ($n=294$), although [duloxetine](#) was at least as effective as escitalopram for the long term treatment of [major depressive disorder](#) (MDD), escitalopram was superior in acute treatment. The study included outpatients aged 18 to 73 years old with MDD according to the DSM-IVTR criteria, with a Montgomery-Asberg Depression Rating Scale (MADRS) total score of 26 or greater, and with a Clinical Global Impression Scale-Severity (CGI-S) score of 4 or greater were included. With the exception of [obsessive-compulsive disorder](#), [posttraumatic stress disorder](#), or [panic disorder](#), patients with a secondary, current, comorbid anxiety disorder were included. Study patients were randomized to receive either [duloxetine](#) 60 mg ($n=151$) or escitalopram 20 mg (initial dose, 10 mg/day; increased after 2 weeks; $n=143$) orally once daily for 24 weeks. At baseline, the MADRS scores were 32.1 ± 4.4 and 32.5 ± 4.3 in the [duloxetine](#) and escitalopram groups, respectively. At the end of the 24 week study, the mean change from baseline in MADRS score in the intent-to-treat population (primary endpoint) for escitalopram and [duloxetine](#) were -23.4 and -21.7, respectively ($p=0.055$). Based on a per-protocol analysis ($n=287$), the between-group difference (escitalopram minus [duloxetine](#)) in MADRS scores at 24 weeks was 0.67 (95% CI, -1.06 to 2.41; p not significant), which met the prespecified noninferiority criteria (ie, upper limit of the one-sided CI did not include 2.5). Furthermore, superiority of escitalopram was evident (ie, upper limit of the one-sided CI did not include zero) at week 8 and week 24 based on a between-group treatment differences of 2.54 (95% CI, $p=0.011$) and 2.21 ($p=0.027$), respectively, based on the per-protocol population. At 24 weeks, 81.6% ($n=115$) of escitalopram-treated patients were considered to be responders (ie, 50% or greater decrease from baseline MADRS total score) compared with 73% ($n=112$) of duloxetine-treated patients. Among secondary endpoints, escitalopram was significantly more effective than [duloxetine](#) in CGI-I ($p=0.039$) score reduction from baseline to week 8. Escitalopram also was significantly better than [duloxetine](#) in the Sheehan Disability Scale (SDS) work score reduction at week 24, and SDS total score reduction at weeks 8 and 24 (p less than 0.05 for all). Significantly more patients on [duloxetine](#) reported insomnia (12.6% vs 4.9%) and constipation (8.6% vs

2.8%) compared to escitalopram, with almost twice the withdrawal rate due to adverse events in the [duloxetine](#) group (17% vs 9%; p less than 0.05) [185].

4.6.D] [Fluoxetine Hydrochloride](#)

4.6.D.1] [Major depressive disorder](#)

a) In a systematic review and metaanalysis in 15 randomized trials of patients aged 60 years or older with [major depressive disorder](#), treatment with [duloxetine](#) (62%), [paroxetine](#) (48%), or [sertraline](#) (28%) was associated with a significantly greater likelihood of achieving a partial response (defined as 50% or greater reduction from baseline in depression score based on the Hamilton Depression Rating Scale, which is preferred, or the Montgomery-Asberg Depression Rating Scale) compared with placebo. [Venlafaxine](#) and escitalopram each had a nonsignificant 20% likelihood of a partial response, while [fluoxetine](#) (8%) and [citalopram](#) (7%) had the lowest benefit. As for dizziness, [duloxetine](#) had a significant 194% increased risk compared with placebo, while a nonsignificant risk was seen with [sertraline](#) (10% increase in risk) and [paroxetine](#) (47% increase risk) [14].

4.6.E] [Paroxetine Hydrochloride](#)

4.6.E.1] [Major depressive disorder](#)

a) In a systematic review and metaanalysis in 15 randomized trials of patients aged 60 years or older with [major depressive disorder](#), treatment with [duloxetine](#) (62%), [paroxetine](#) (48%), or [sertraline](#) (28%) was associated with a significantly greater likelihood of achieving a partial response (defined as 50% or greater reduction from baseline in depression score based on the Hamilton Depression Rating Scale, which is preferred, or the Montgomery-Asberg Depression Rating Scale) compared with placebo. [Venlafaxine](#) and escitalopram each had a nonsignificant 20% likelihood of a partial response, while [fluoxetine](#) (8%) and [citalopram](#) (7%) had the lowest benefit. As for dizziness, [duloxetine](#) had a significant 194% increased risk compared with placebo, while a nonsignificant risk was seen with [sertraline](#) (10% increase in risk) and [paroxetine](#) (47% increase risk) [14].

b) [Duloxetine](#) therapy was more effective than placebo and non-inferior to [paroxetine](#) therapy in the treatment of psychological and physical symptoms of depression. In a randomized, double-blind, placebo-controlled, multi-center study, patients ($n=353$) with [major depressive disorder](#), a Hamilton Depression Rating Scale (HAM-D) total score of at least 15, and a moderate Clinical Global Impression (CGI) Severity rating (score of at least 4) received oral [duloxetine](#) 80 milligrams (mg) daily (in divided doses), [duloxetine](#) 40 mg daily (in divided doses), [paroxetine](#) 20 mg daily, or placebo for 8 weeks. Response was defined as at least a 50% reduction from baseline in the HAM-D total score and remission was defined as a HAM-D score of 7 or less. At week 8, both the 80 and 40 mg dosing regimens of [duloxetine](#) produced significantly greater reductions in HAM-D scores from baseline as compared with placebo (mean difference, 3.62 points, 95% CI 1.38, 5.86; $p=0.002$ and 2.34 points, 95% CI 0.19, 4.66; $p=0.034$, respectively). A significantly greater reduction in HAM-D total scores was also observed with [duloxetine](#) 80 mg therapy as compared with [paroxetine](#) treatment (mean difference, 2.39 points, 95% CI 0.14, 4.65; $p=0.037$). [Paroxetine](#) therapy was not significantly different from placebo at week 8, however at weeks 2, 4, and 6; [paroxetine](#) treatment was superior to placebo. The response rate at endpoint was significantly higher in patients treated with [duloxetine](#) 80 mg as compared with placebo (51% vs 31%, $p=0.009$, respectively). Additionally, the remission rate in the [duloxetine](#) 80 mg group (50%) was significantly higher at endpoint as compared with remission rates for patients in the [duloxetine](#) 40 mg group (35%; $p=0.045$) and the placebo group (30%; $p=0.008$), but was not superior to patients in the [paroxetine](#) group (37%; $p=ns$). Significant reductions from baseline to endpoint in overall pain severity were observed in patients treated with [duloxetine](#) 80 mg (reduction from baseline, 47%; -7.5 points on VAS scale, 95%CI -25, 1; $p=0.005$), as compared with placebo, however significant reductions were not seen with [paroxetine](#) or [duloxetine](#) 40

mg therapy as compared with placebo. Both [duloxetine](#) and [paroxetine](#) were generally well tolerated and only insomnia was reported significantly more often in duloxetine-treated (80 mg) patients as compared with paroxetine-treated patients (19.8% vs 8%, respectively; $p=0.031$) [12].

4.6.F] [Paroxetine Mesylate](#)

4.6.F.1] [Major depressive disorder](#)

a) In a systematic review and metaanalysis in 15 randomized trials of patients aged 60 years or older with [major depressive disorder](#), treatment with [duloxetine](#) (62%), [paroxetine](#) (48%), or [sertraline](#) (28%) was associated with a significantly greater likelihood of achieving a partial response (defined as 50% or greater reduction from baseline in depression score based on the Hamilton Depression Rating Scale, which is preferred, or the Montgomery-Asberg Depression Rating Scale) compared with placebo. [Venlafaxine](#) and escitalopram each had a nonsignificant 20% likelihood of a partial response, while [fluoxetine](#) (8%) and [citalopram](#) (7%) had the lowest benefit. As for dizziness, [duloxetine](#) had a significant 194% increased risk compared with placebo, while a nonsignificant risk was seen with [sertraline](#) (10% increase in risk) and [paroxetine](#) (47% increase risk) [14].

4.6.G] [Pregabalin](#)

4.6.G.1] [Diabetic peripheral neuropathy - Pain](#)

a) There was no difference in pain improvement in patients who received high-dose monotherapy ([duloxetine](#) 120 mg/day or pregabalin 600 mg/day) or combination therapy ([duloxetine](#) 60 mg/day plus pregabalin 300 mg/day) in a 20-week randomized trial of patients with [painful diabetic neuropathy](#) who did not respond to standard doses of either monotherapy ($N=343$). Additionally, there was no difference with any other pain, improvement, or anxiety and depression scales, except for the Hospital Anxiety and Depression Scale, which favored combination therapy (mean difference, -0.62). Adverse events were similar among treatment groups [178].

b) There was no difference from baseline in subjective pain or sleep between treatment arms (all groups showed improvement), for patients who received [amitriptyline](#), [duloxetine](#), or pregabalin for the treatment of painful [diabetic peripheral neuropathy](#) in a randomized trial ($N=83$). Sleep continuity and maintenance of REM sleep was improved more with pregabalin and [amitriptyline](#) compared with [duloxetine](#); however, [duloxetine](#) and [amitriptyline](#) improved daytime function by improving reaction time and CNS arousal and processing ability. There was no difference in quality of life scores for any of the treatments. Patients who received pregabalin experienced the highest number of adverse reactions, including fatigue, somnolence, and dizziness [179].

4.6.H] [Sertraline Hydrochloride](#)

4.6.H.1] [Major depressive disorder](#)

a) In a systematic review and metaanalysis in 15 randomized trials of patients aged 60 years or older with [major depressive disorder](#), treatment with [duloxetine](#) (62%), [paroxetine](#) (48%), or [sertraline](#) (28%) was associated with a significantly greater likelihood of achieving a partial response (defined as 50% or greater reduction from baseline in depression score based on the Hamilton Depression Rating Scale, which is preferred, or the Montgomery-Asberg Depression Rating Scale) compared with placebo. [Venlafaxine](#) and escitalopram each had a nonsignificant 20% likelihood of a partial response, while [fluoxetine](#) (8%) and [citalopram](#) (7%) had the lowest benefit. As for dizziness, [duloxetine](#) had a significant 194% increased risk compared with placebo, while a nonsignificant risk was seen with [sertraline](#) (10% increase in risk) and [paroxetine](#) (47% increase risk) [14].

4.6.I] Venlafaxine Hydrochloride

4.6.I.1] Major depressive disorder

a) In a systematic review and metaanalysis in 15 randomized trials of patients aged 60 years or older with [major depressive disorder](#), treatment with [duloxetine](#) (62%), [paroxetine](#) (48%), or [sertraline](#) (28%) was associated with a significantly greater likelihood of achieving a partial response (defined as 50% or greater reduction from baseline in depression score based on the Hamilton Depression Rating Scale, which is preferred, or the Montgomery-Asberg Depression Rating Scale) compared with placebo. [Venlafaxine](#) and escitalopram each had a nonsignificant 20% likelihood of a partial response, while [fluoxetine](#) (8%) and [citalopram](#) (7%) had the lowest benefit. As for dizziness, [duloxetine](#) had a significant 194% increased risk compared with placebo, while a nonsignificant risk was seen with [sertraline](#) (10% increase in risk) and [paroxetine](#) (47% increase risk) [14].

b) A meta-analysis of published, peer-reviewed, randomized, placebo-controlled, double-blind trials found that [duloxetine](#) and [venlafaxine](#) extended-release (XR) are significantly superior compared to placebo in remission and response rates for [major depressive disorder](#) and although there was a trend in favor of [venlafaxine](#) XR the differences did not reach statistical significance when compared to [duloxetine](#). A systematic literature search of Cochrane, EMBASE, and MEDLINE (1996 to January 2005) was performed by two independent reviewers. Data was obtained from 8 trials to evaluate efficacy (n=1754) and discontinuation/safety (n=1791). Patients had a one week placebo lead-in period followed by either [duloxetine](#) 40 to 120 milligrams (mg) per day or [venlafaxine](#) XR 75 to 225 mg per day for a minimum of 8 weeks. The primary outcomes were remission and response rates. Remission was defined as an improvement in the Hamilton Rating Scale for Depression (HAM-D) score to less than or equal to 7 or to a Montgomery-Asberg Depression Rating Scale (MADRS) score of less than or equal to 10. Response was defined as an improvement of 50% from baseline in either the HAM-D or MADRS scores. The secondary outcomes evaluated were dropout rates and rates of adverse effects. Both remission and response rates improved for [duloxetine](#) and [venlafaxine](#) XR and were statistically significant compared to placebo (both p less than 0.001). No significant difference was found for remission and response rates when [duloxetine](#) and [venlafaxine](#) XR were compared. Patients receiving placebo had a higher dropout rate due to lack of efficacy compared to those patients receiving [duloxetine](#) or [venlafaxine](#) XR (both p less than 0.001). More patients in the active drug treatment groups dropped out due to adverse effects compared to placebo ([duloxetine](#) p=0.008; [venlafaxine](#) XR p less than 0.001). Again, when [duloxetine](#) and [venlafaxine](#) XR were compared, no statistically significant differences were found for dropout rates due to lack of efficacy or adverse drug reactions. The reported adverse events were comparable between drugs. A sensitivity analysis was also performed and included 2 additional studies, one study for [venlafaxine](#) XR dealing with patients with comorbid anxiety and one study for [duloxetine](#) dealing with patients with comorbid pain. Adding the 2 studies demonstrated similar results with both drugs having a statistically significant difference from placebo for remission and response rates [181].

Outcome	Active Drug	Active Drug vs Placebo Difference(a)	95% CI	p Value
Remission	duloxetine	0.142	0.089 to 0.195	<0.001
	venlafaxine XR	0.178	0.09 to 0.265	<0.001
Response	duloxetine	0.186	0.13 to 0.242	<0.001
	venlafaxine XR	0.244	0.15 to 0.337	<0.001
Dropout rate due to ADRs	duloxetine	0.057	0.015 to 0.1	0.008
	venlafaxine XR	0.061	0.025 to 0.097	<0.001
Dropout rate due to lack of efficacy	duloxetine	-0.111 (c)	-0.159 to -0.63	<0.001
	venlafaxine XR	-0.107	-0.151 to -0.064	<0.001

ADRs = adverse drug reactions; XR
 = extended release; CI = confidence
 interval
 (a) The rate when meta-analytic rate
 of placebo is subtracted from the
 active drug rate.
 (b) Corresponding p value of the
 difference rate calculated with a Z-
 test.
 (c) Negative difference rates indicate
 a larger effect for placebo.

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