

DRUGDEX-EV 2336

MICROMEDEX

DRUGDEX® Evaluations
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OLANZAPINE/FLUOXETINE HYDROCHLORIDE

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0.0] Overview

1] Class

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

Antidepressant
Antipsychotic

2] Dosing Information

a) Adult

1) Gradually reduce [olanzapine/fluoxetine](#) dose when discontinuing treatment to avoid withdrawal symptoms; if intolerable symptoms develop, consider resuming therapy at the previously prescribed dose and taper at a slower rate [2]

a) [Bipolar disorder](#), depressed phase

1) Initial, olanzapine 6 mg/fluoxetine 25 mg orally once daily each evening [1]

2) Usual range, olanzapine 6 to 12 mg/fluoxetine 25 to 50 mg orally once daily each evening; safety of doses greater than olanzapine 18 mg/fluoxetine 75 mg has not been established; periodically reexamine the need for continued treatment [1]

b) [Major depressive disorder](#), Treatment-resistant

1) Initial, olanzapine 6 mg/fluoxetine 25 mg orally once daily each evening [1]

2) Usual range, olanzapine 6 to 18 mg/fluoxetine 25 to 50 mg orally once daily each evening; safety of doses greater than olanzapine 18 mg/fluoxetine 75 mg has not been established; periodically reexamine the need for continued treatment [1]

b) Pediatric

1j) Gradually reduce olanzapine/fluoxetine dose when discontinuing treatment to avoid withdrawal symptoms; if intolerable symptoms develop, consider resuming therapy at the previously prescribed dose and taper at a slower rate [2]

a) Bipolar disorder, depressed phase

1j) (10 to 17 years) Initial, olanzapine 3 mg/fluoxetine 25 mg orally once daily each evening [1]

2j) (10 to 17 years) Usual range, olanzapine 6 to 12 mg/fluoxetine 25 to 50 mg orally once daily each evening; safety of doses greater than olanzapine 12 mg/fluoxetine 50 mg has not been established; periodically reexamine the need for continued treatment [1]

3j) Contraindications

a) Concomitant use with MAOIs, including linezolid or IV methylene blue, or within 14 days of MAOI discontinuation; at least 5 weeks should elapse after fluoxetine hydrochloride/olanzapine discontinuation before MAOI initiation due to increased risk of serotonin syndrome [9]

b) Concomitant use with pimozide; risk of interaction or QT-interval prolongation [9]

c) Concomitant use with thioridazine or within 5 weeks of fluoxetine hydrochloride/olanzapine discontinuation; risk of QT-interval prolongation or elevated thioridazine levels [9]

4j) Serious Adverse Effects

a) Angle-closure glaucoma

b) Cerebrovascular accident

c) Depression, Worsening

d) Diabetic ketoacidosis

e) Drug reaction with eosinophilia and systemic symptoms

f) Dyskinesia

g) Hyponatremia

h) Impaired cognition

i) Mania

j) Neuroleptic malignant syndrome

k) Prolonged QT interval

l) Pulmonary eosinophilia

m) Seizure

n) Serotonin syndrome

o) Suicidal thoughts

p) Suicide

q) [Torsades de pointes](#)

r) Violent behavior

5) Clinical Applications

a) FDA Approved Indications

1) [Bipolar disorder](#), depressed phase

2) [Major depressive disorder](#), Treatment-resistant

1.0] Dosing Information

[Drug Properties](#)

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1.1] Drug Properties

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

1.2] Storage and Stability

A) Preparation

1) Oral

a) The combination of [olanzapine/fluoxetine](#) should be administered in the evening. While food has no appreciable effect on the absorption of [olanzapine](#) and [fluoxetine](#) administered individually, the effect of food on the absorption of the combination has not been studied [2].

B) Oral route

1) Capsule

a) Store at controlled room temperature, 25 degrees C (77 degrees F); excursions permitted to 15 to 30 degrees C (59 to 86 degrees F). Protect from moisture [611].

1.3] Adult Dosage

1.3.1] Normal Dosage

1.3.1.A] Important Note

b) Discontinue MAOIs intended to treat psychiatric disorders at least 14 days prior to the administration of olanzapine/fluoxetine. Allow at least 5 weeks to elapse between discontinuation of olanzapine/fluoxetine and initiation of MAOIs intended to treat psychiatric disorders [1].

J) Do not initiate olanzapine/fluoxetine in a patient receiving linezolid or IV methylene blue. If a patient is already receiving olanzapine/fluoxetine and treatment with linezolid or IV methylene blue is unavoidable, and the potential benefit of therapy outweighs the risk for serotonin syndrome, discontinue olanzapine/fluoxetine. Monitor for symptoms of serotonin syndrome for 5 weeks or for 24 hours after the last dose of linezolid or IV methylene blue, whichever comes first. Resume olanzapine/fluoxetine therapy 24 hours after the last dose of linezolid or IV methylene blue [1].

1.3.1.B] **Bipolar disorder, depressed phase**

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

1.3.1.C] **Major depressive disorder, Treatment-resistant**

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

1.3.1.D] **Oral route**

1.3.1.D.1] **Bipolar disorder, depressed phase**

- a) Initial dosage: **Olanzapine** 6 mg/**fluoxetine** 25 mg orally once daily each evening [1]
- b) Usual dosage: **Olanzapine** 6 to 12 mg/**fluoxetine** 25 to 50 mg orally once daily each evening; periodically reexamine the need for continued treatment [1]
- c) Maximum dosage: The safety of doses greater than **olanzapine** 18 mg/**fluoxetine** 75 mg has not been established [1].

1.3.1.D.2] **Major depressive disorder, Treatment-resistant**

- a) Initial dosage: **Olanzapine** 6 mg/**fluoxetine** 25 mg orally once daily each evening [1]
- b) Usual dosage: **Olanzapine** 6 to 18 mg/**fluoxetine** 25 to 50 mg orally once daily each evening; periodically reexamine the need for continued treatment [1]
- c) Maximum dosage: The safety of doses greater than **olanzapine** 18 mg/**fluoxetine** 75 mg has not been established [1].

1.3.1.D.3] **Drug Discontinuation**

- a) Gradually reduce **olanzapine/fluoxetine** dosage when discontinuing treatment to avoid withdrawal symptoms (eg, **dysphoric mood**, irritability, agitation, dizziness, **sensory disturbances**, anxiety, confusion, headache, lethargy, emotional lability, insomnia, and **hypomania**). Monitor the patient for these signs and symptoms during treatment discontinuation. If intolerable symptoms occur following a reduction in dose or upon discontinuation of treatment, then resuming the previously prescribed dose followed by a more gradual reduction may be considered [2].

1.3.2] **Dosage in Renal Failure**

- A) Dose adjustment not required [1].

1.3.3] **Dosage in Hepatic Insufficiency**

- A) **Hepatic impairment**: Initial, **olanzapine** 3 to 6 mg/**fluoxetine** 25 mg orally once daily [1]

B) **Hepatic impairment, cirrhosis:** Use a lower or less frequent dose of the fluoxetine component of olanzapine/fluoxetine [1].

1.3.4] Dosage in Geriatric Patients

A) Initiate at the low end of the dosing range [1].

1.3.6] Dosage in Other Disease States

A) Coadministration with CYP1A2 Inhibitors

1) Consider using lower doses of the olanzapine component of olanzapine/fluoxetine [1].

B) Gender

1) Dose adjustment based solely on gender is not required [1].

C) Hypotensive Reaction, Predisposition

1) Initial, olanzapine 3 to 6 mg/fluoxetine 25 mg orally once daily [1]

D) Multiple Metabolism-Slowing Factors (Female, Geriatric, Nonsmoker)

1) Initial, olanzapine 3 to 6 mg/fluoxetine 25 mg orally once daily; escalate with caution, titrate slowly, and adjust dose as needed [1].

E) Pharmacodynamic Sensitivity to Olanzapine

1) Initial, olanzapine 3 to 6 mg/fluoxetine 25 mg orally once daily [1]

F) Race

1) Dose adjustment is not required [1].

G) Smokers

1) Dose adjustment is not routinely required [1].

H) Weight

1) Dose adjustment based on body weight is not required [1].

1.4] Pediatric Dosage

1.4.1] Normal Dosage

1.4.1.A] Important Note

J) Discontinue MAOIs intended to treat psychiatric disorders at least 14 days prior to the administration of olanzapine/fluoxetine. Allow at least 5 weeks to elapse between discontinuation of olanzapine/fluoxetine and initiation of MAOIs intended to treat psychiatric disorders [1].

J) Do not initiate olanzapine/fluoxetine in a patient receiving linezolid or IV methylene blue. If a patient is already receiving olanzapine/fluoxetine and treatment with linezolid or IV methylene blue is unavoidable, and the potential benefit of therapy outweighs the risk for serotonin syndrome, discontinue olanzapine/fluoxetine. Monitor for symptoms of serotonin syndrome for 5 weeks or for 24 hours after the last dose of linezolid or IV methylene blue, whichever comes first. Resume olanzapine/fluoxetine therapy 24 hours after the last dose of linezolid or IV methylene blue [1].

1.4.1.B] Bipolar disorder, depressed phase

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

1.4.1.C] Oral route**1.4.1.C.1] Bipolar disorder, depressed phase****a)] 10 to 17 Years**

- 1)] Initial dosage: **Olanzapine** 3 mg/**fluoxetine** 25 mg orally once daily each evening [1]
- 2)] Usual dosage: **Olanzapine** 6 to 12 mg/**fluoxetine** 25 to 50 mg orally once daily each evening; periodically reexamine the need for continued treatment [1]
- 3)] Maximum dosage: The safety of doses greater than **olanzapine** 12 mg/**fluoxetine** 50 mg has not been established [1].

1.4.1.C.2)] Drug Discontinuation

- a)] Gradually reduce **olanzapine/fluoxetine** dosage when discontinuing treatment to avoid withdrawal symptoms (eg, **dysphoric mood**, irritability, agitation, dizziness, **sensory disturbances**, anxiety, confusion, headache, lethargy, emotional lability, insomnia, and **hypomania**). Monitor the patient for these signs and symptoms during treatment discontinuation. If intolerable symptoms occur following a reduction in dose or upon discontinuation of treatment, then resuming the previously prescribed dose followed by a more gradual reduction may be considered [2].

1.4.2] Dosage in Renal Failure

A)] Dose adjustment not required [1].

1.4.5] Dosage in Other Disease States

A)] Coadministration with CYP1A2 Inhibitors

- 1)] Consider using lower doses of the **olanzapine** component of **olanzapine/fluoxetine** [1].

2.0] Pharmacokinetics**Drug Concentration Levels****ADME****2.2] Drug Concentration Levels**

A)] Peak Concentration

- 1)] Oral, single-dose, **fluoxetine** 60 mg/**olanzapine** 5 mg: 16% increase of **olanzapine** C_{max} [2]
 - a)] Administration of **fluoxetine** 60 mg (as a single dose or daily administration for 8 days) and a single dose of **olanzapine** 5 mg caused a 16% increase in the mean **olanzapine** C_{max}, a 17% increase in the mean **olanzapine** AUC, and a 16% decrease in apparent clearance of **olanzapine** compared with administration of **olanzapine** alone. These small changes are not considered to be clinically

significant; therefore, the pharmacokinetics of the individual components is expected to reasonably characterize the overall pharmacokinetics of the combination product [2].

2) Oral, single-dose, **fluoxetine** 40 mg: 15 to 55 nanograms/mL (48 to 178 nanomol/L) [2]

a) After a single, oral dose of **fluoxetine** 40 mg, C_{max} of 15 to 55 nanograms/milliliter (ng/mL; 48 to 178 nanomol/L) occurred in 6 to 8 hours [2].

3) Oral, multiple-dose, **fluoxetine** 40 mg/day: 91 to 302 nanograms/mL (294 to 976 nanomol/L) [2]

a) After **fluoxetine** dosing at 40 mg/day for 30 days, **fluoxetine** plasma concentrations ranged from 91 to 302 ng/mL (294 to 976 nanomol/L) and norfluoxetine concentrations ranged from 72 to 258 ng/mL (244 to 874 nanomol/L). The metabolism of **fluoxetine** is not proportional to dose, but the pharmacokinetics of norfluoxetine appear linear [2].

4) **Olanzapine/fluoxetine**, pediatric patients less than 50 kg: **fluoxetine** plasma concentrations 76% higher than 50 kg or more [2]

a) In pediatric patients, 10 to 17 years old, who weighed less than 50 kg and received **olanzapine/fluoxetine** in the 8-week, randomized, double-blind, placebo-controlled study (n=255), **fluoxetine** plasma concentrations were about 76% higher and norfluoxetine concentrations were about 38% higher compared with patients who weighed 50 kg or more [2].

5) **Olanzapine/fluoxetine**, pediatric patients less than 50 kg: **olanzapine** plasma concentrations 31% higher than 50 kg or more [2]

a) In pediatric patients 10 to 17 years old who weighed less than 50 kg and received **olanzapine/fluoxetine** in the 8-week, randomized, double-blind, placebo-controlled study (n=255), **olanzapine** plasma concentrations were about 31% higher compared with patients who weighed 50 kg or more [2].

B) Time to Peak Concentration

1) Oral, single-dose: **olanzapine**, 4 hours; **fluoxetine**, 6 hours [2].

a) Following a single oral dose of **olanzapine** 12 mg/**fluoxetine** 50 mg, T_{max} for **olanzapine** and **fluoxetine** occurred at approximately 4 and 6 hours, respectively [2].

C) Area Under the Curve

1) Oral, single-dose, **fluoxetine** 60 mg/**olanzapine** 5 mg: 17% increase of **olanzapine** AUC [2]

a) Administration of **fluoxetine** 60 mg (as a single dose or daily administration for 8 days) and a single dose of **olanzapine** 5 mg caused a 16% increase in the mean **olanzapine** C_{max}, a 17% increase in the mean **olanzapine** AUC, and a 16% decrease in apparent clearance of **olanzapine** compared with administration of **olanzapine** alone. These small changes are not considered to be clinically significant; therefore, the pharmacokinetics of the individual components is expected to reasonably characterize the overall pharmacokinetics of the combination product [2].

2.3] ADME

2.3.1] Absorption

A) Bioavailability

1) Olanzapine, well absorbed [2]

a) Olanzapine is well absorbed [2].

B) Effects of Food

1) No effect [2]

a) The effect of food on the absorption and bioavailability of the combination of olanzapine and fluoxetine has not been evaluated. The bioavailability of olanzapine and fluoxetine administered separately was not affected by food, but food may delay absorption of fluoxetine by 1 to 2 hours, which is likely not clinically relevant. It is unlikely that there would be a significant food effect on the bioavailability of the combination [2].

2.3.2] Distribution

A) Distribution Sites

1) Protein Binding

a) Olanzapine, 93%; fluoxetine 94.5% [2]

1) Olanzapine is 93% bound to plasma proteins over the concentration range of 7 to 1100 nanograms/milliliter (22 to 3500 nanomol/L), binding primarily to albumin and alpha-1-acid glycoprotein [2].

2) Over the concentration range from 200 to 1000 nanogram/milliliter (600 to 3000 nanomol/L), approximately 94.5% of fluoxetine is bound in vitro to human serum proteins, including albumin and alpha-1-glycoprotein [2][603][604].

B) Distribution Kinetics

1) Volume of Distribution

a) Olanzapine, 1000 L [2]; fluoxetine, 1000 to 7200 L [604].

1) The Vd of olanzapine was approximately 1000 L [2]

2) The Vd of fluoxetine ranged from 1000 to 7200 L, and the corresponding Vd of norfluoxetine ranged from 700 to 5700 L. No relationship between the Vd of fluoxetine or its metabolite and renal function has been observed [604].

2.3.3] Metabolism

A) Metabolism Sites and Kinetics

1) Liver, extensive [2].

a) Olanzapine is eliminated extensively by first-pass metabolism, with approximately 40% of the dose metabolized before reaching the systemic circulation. The primary metabolic pathways are direct glucuronidation and CYP450-mediated oxidation; CYP2D6-mediated oxidation is a minor metabolic pathway, as clearance is not reduced with **enzyme deficiency**. **Fluoxetine** is extensively metabolized in the liver via CYP2D6 to the active metabolite, norfluoxetine [2].

B) Metabolites**1) Olanzapine, 10-N-glucuronide: inactive [2]**

a) 10-N-glucuronide was present at steady state at 44% of the **olanzapine** concentration [2].

2) Olanzapine, 4'-N-desmethyl olanzapine: inactive [2]

a) 4'-N-desmethyl olanzapine was present at steady state at 31% of the **olanzapine** concentration [2].

3) Fluoxetine, norfluoxetine: active [2]

a) Fluoxetine is extensively metabolized via the CYP2D6 pathway to its only identified active metabolite, norfluoxetine [2].

b) Fluoxetine is metabolized primarily via N-demethylation to the active metabolite, norfluoxetine [603][604]. Glucuronide conjugates are also found but in small quantities [603].

c) Extensive metabolizers with respect to cytochrome CYP2C19 showed lower maximum levels of **fluoxetine** (p less than 0.001) and higher levels of norfluoxetine (p less than 0.001) after a 40-mg dose of **fluoxetine** than did poor metabolizers with the CYP2C19*2 or CYP2C19*3 mutation. Oral clearance by poor metabolizers was 55% lower than oral clearance by extensive metabolizers (p less than 0.001) [605].

C) Other**1) Metabolic Enzymes and Transporters**

a) Olanzapine is a Substrate of CYP1A2 and CYP2D6

1) The administration of carbamazepine, a potent CYP1A2 inducer, with olanzapine increased the clearance of olanzapine by approximately 50%. Fluvoxamine, an inhibitor of CYP1A2, increased olanzapine C_{max} by 54% and AUC by 52% in female nonsmokers and C_{max} by 77% and AUC by 108% in male smokers. Agents that induce CYP1A2 may cause an increase in olanzapine clearance [2].

2) A single dose of fluoxetine 60 mg coadministered with olanzapine 5 mg increased the mean C_{max} of olanzapine by 16%, the mean AUC by 17%, and the mean apparent clearance by 16%. In another study, the concomitant administration of fluoxetine 25 mg or more with olanzapine 6 or 12 mg decreased the apparent clearance of olanzapine by 14%. The small change in olanzapine clearance, not deemed clinically

significant, was attributed to the inhibition of CYP2D6, a minor metabolic pathway for olanzapine, by fluoxetine, a potent CYP2D6 inhibitor [2].

b) Fluoxetine is a CYP2D6 Inhibitor

1) Fluoxetine is a potent CYP2D6 inhibitor. Concomitant administration of fluoxetine with alprazolam, clozapine, haloperidol, and phenytoin has resulted in increased blood concentrations, and concomitant administration with diazepam may prolong $t(1/2)$ in some patients. Concomitant administration of fluoxetine with imipramine and desipramine increased stable plasma levels more than 2- to 10-fold, and the increase may persist for 3 weeks or longer after fluoxetine discontinuation [2].

c) Fluoxetine is a Substrate of CYP2D6

1) Fluoxetine is extensively metabolized in the liver via the CYP2D6 pathway [2].

2.3.4] Excretion

A) Kidney

1) Renal Excretion (%)

a) Olanzapine, 57% (7% unchanged) [2]; **fluoxetine**, 60% (2.5% to 5% unchanged) [603]

1) Approximately 57% of a single oral dose of radiolabeled olanzapine was recovered in the urine, and 7% was unchanged drug [603].

2) The primary route of fluoxetine elimination appears to be hepatic metabolism to inactive metabolites excreted by the kidney [606]

3) About 60% of an oral fluoxetine dose was excreted in the urine [603]. Only 2.5% to 5% of an oral fluoxetine dose is recovered as unchanged drug; 10% is excreted as free norfluoxetine [603][604]. Conjugated metabolites, fluoxetine glucuronide and norfluoxetine glucuronide, represent 5.2% and 9.5% of a dose, respectively [603].

B) Feces

1) Olanzapine, 30% [2]; **fluoxetine**, 12% [603]

a) Approximately 30% of a single oral dose of radiolabeled olanzapine was recovered in feces [2].

b) About 12% of a fluoxetine dose was recovered in feces [603].

C) Total Body Clearance

1) Olanzapine, 25 L/hr [2]

a) The mean apparent plasma clearance of olanzapine was 25 L/hr and ranged from 12 L/hr (5th percentile) to 47 L/hr (95th percentile) [2].

b) Administration of fluoxetine 60 mg (as a single dose or daily administration for 8 days) and a single dose of olanzapine 5 mg caused a 16% increase in the mean olanzapine C_{max}, a 17% increase in the mean olanzapine AUC, and a 16% decrease in apparent clearance of olanzapine compared with administration of olanzapine alone. These small changes are not considered to be clinically significant; therefore, the pharmacokinetics of the individual components is expected to reasonably characterize the overall pharmacokinetics of the combination product [2].

2) Olanzapine, women: 30% lower than men [2]

a) The clearance of olanzapine is about 30% lower in women compared with men [2].

3) Olanzapine, smokers: 50% higher than nonsmokers [2]

a) The clearance of olanzapine is about 40% higher in smokers compared with nonsmokers [2].

2.3.5] Elimination Half-life

A) Parent Compound

1) Olanzapine, 30 hours; fluoxetine, 4 to 6 days (chronic administration) [2]

a) The mean olanzapine t_(1/2) was 30 hours and ranged from 21 hours (5th percentile) to 54 hours (95th percentile) [2].

b) The t_(1/2) of fluoxetine was 1 to 3 days after acute administration and 4 to 6 days after chronic administration [2].

c) The mean t_(1/2) of fluoxetine among extensive metabolizers with respect to CYP2C19 was about 28 hours; among poor metabolizers with the CYP2C19*2 or CYP2C19*3 mutation, mean t_(1/2) was 62 hours [605].

2) Olanzapine, elderly: 1.5 times longer than nonelderly [2]

a) The mean t_(1/2) was about 1.5 times longer in subjects 65 years and older compared with those younger than 65 years in a study of healthy subjects (n=24) [2].

3) Olanzapine, cirrhosis: 7.6 days [2]

a) In a study of patients with cirrhosis, the mean t_(1/2) of fluoxetine in patients with cirrhosis was 7.6 days compared with 2 to 3 days for normal subjects [2].

B) Metabolites

1) Norfluoxetine: 9.3 days [2]

a) The mean t_(1/2) of norfluoxetine after multiple doses of fluoxetine 40 mg/day was 9.3 days. After a single dose, mean t_(1/2) was 8.6 days [2].

2) Norfluoxetine, cirrhosis: 12 days [2]

a) In a study of patients with [cirrhosis](#), the mean $t(1/2)$ of norfluoxetine in patients with [cirrhosis](#) was 12 days compared with 7 to 9 days for normal subjects [2].

2.3.6] Extracorporeal Elimination

A) [Hemodialysis](#)

1) Dialyzable: [Olanzapine](#), no[2]

a) [Olanzapine](#) is not removed by dialysis. In a study of depressed patients on dialysis (n=12), [fluoxetine](#) 20 mg once daily for 2 months yielded steady-state [fluoxetine](#) and norfluoxetine plasma concentrations similar to concentrations in patients with normal renal function [2].

B) [Peritoneal](#)

1) Dialyzable: [Olanzapine](#), no[2]

a) [Olanzapine](#) is not removed by dialysis. In a study of depressed patients on dialysis (n=12), [fluoxetine](#) 20 mg once daily for 2 months yielded steady-state [fluoxetine](#) and norfluoxetine plasma concentrations similar to concentrations in patients with normal renal function [2].

3.0] Cautions

[Contraindications](#)

[Precautions](#)

[Adverse Reactions](#)

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

[Drug Interactions](#)

3.0.A] Black Box WARNING

Oral (Capsule)

Suicidal Thoughts And Behaviors; And Increased Mortality In Elderly Patients With Dementia-Related Psychosis

Suicidal Thoughts and Behaviors: Antidepressants increased the risk of suicidal thoughts 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 and older. In patients of all ages who are started on antidepressant therapy, monitor closely for worsening and emergence of suicidal thoughts and behaviors. Advise families and caregivers of the need for close observation and communication with the prescriber. Fluoxetine hydrochloride/olanzapine is not approved for use in children less than 10 years of age.

Increased Mortality in Elderly Patients with Dementia-Related Psychosis: Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death. Fluoxetine hydrochloride/olanzapine is not approved for the treatment of patients with dementia-related psychosis [1].

3.1] Contraindications

A)] Concomitant use with MAOIs, including [linezolid](#) or IV methylene blue, or within 14 days of MAOI discontinuation; at least 5 weeks should elapse after [fluoxetine](#) hydrochloride/[olanzapine](#) discontinuation before MAOI initiation due to increased risk of [serotonin syndrome](#) [9]

B)] Concomitant use with [pimozide](#); risk of interaction or QT-interval prolongation [9]

C)] Concomitant use with [thioridazine](#) or within 5 weeks of [fluoxetine](#) hydrochloride/[olanzapine](#) discontinuation; risk of QT-interval prolongation or elevated [thioridazine](#) levels [9]

3.2] Precautions

A)] Black box warning: Increased risk of suicidality or worsening depression with antidepressant therapy, especially in children, adolescents, and young adults during the first few months of therapy or following dose adjustments; monitoring recommended and discontinuation may be required [9]

B)] Black box warning: Increased risk of death with antipsychotic treatment in elderly patients with dementia-related [psychosis](#) (unapproved use) [9]

C)] Anticholinergic effects: Cholinergic antagonism may worsen clinically significant [prostatic hypertrophy](#), [narrow-angle glaucoma](#), [paralytic ileus](#), or related conditions [9].

D)] Cardiovascular: QT-interval prolongation, [ventricular arrhythmia](#), and [torsades de pointes](#) have been reported; baseline assessment and ongoing monitoring recommended; consider discontinuation if conditions occur [9].

E)] Cardiovascular: Orthostatic hypotension progressing to syncope may occur, especially during initial dose titration [9].

F)] Cardiovascular: Cerebrovascular events (eg, [stroke](#), TIA), including fatalities, have occurred in elderly patients with dementia-related [psychosis](#) (unapproved use) [9].

G)] Concomitant use: Avoid concomitant use with drugs known to prolong the QT interval [9].

H)] Concomitant use: Concurrent use of CYP2D6 inhibitors or highly protein-bound agents increases risk of QT-interval prolongation [9].

I)] Endocrine and metabolic: Patients with [diabetes mellitus](#) or with borderline blood glucose level elevations (fasting 100 to 126 mg/dL [6 to 6.99 mmol/L], nonfasting 140 to 200 mg/dL [7.8 to 10 mmol/L]) at increased risk for [hyperglycemia](#) that may not resolve upon discontinuation; monitoring recommended [9]

J)] Endocrine and metabolic: [Hyperglycemia](#), including cases associated with [ketoacidosis](#), [hyperosmolar coma](#), or death, has been reported; baseline screening and monitoring recommended; discontinuation may be warranted [9].

K)] Endocrine and metabolic: [Hyperlipidemia](#) (ie, total cholesterol, [triglycerides](#)) has been reported, with higher incidence among children and adolescents; monitoring recommended [9].

L)] Endocrine and metabolic: Clinically significant weight gain has been reported, with higher incidence among children and adolescents; monitoring recommended [9].

M)] Endocrine and metabolic: Thermoregulation disruption has occurred with use of antipsychotics [9].

N)] Endocrine and metabolic: [Hyponatremia](#) and SIADH have occurred; consider discontinuation if symptomatic [hyponatremia](#) occurs [9].

O)] Endocrine and metabolic: [Hyperprolactinemia](#), with higher incidence among children and adolescents, has been reported, which may result in [galactorrhea](#), [amenorrhea](#), [gynecomastia](#), impotence, [hypogonadism](#), and decreased bone density [9].

P)] Gastrointestinal: [Esophageal dysmotility](#) and aspiration have been reported with antipsychotic use [9].

Q)] Hematologic: Life-threatening hemorrhages and other abnormal bleeding has been reported with [fluoxetine](#) use [9].

R)] Hematologic: [Cytopenias](#) (ie, [agranulocytosis](#), [leukopenia](#), [neutropenia](#)) have been reported with antipsychotic treatment; monitoring recommended and discontinuation may be required [9].

S)] Hepatic: Reduce dose in patients with [cirrhosis](#) [9].

T)) Immunologic: Drug reaction with [eosinophilia](#) and systemic symptoms (DRESS), a rare and potentially fatal severe skin reaction, has been reported with [olanzapine](#); discontinue if suspected [10].

U)) Immunologic: Serious [allergic reactions](#), including [anaphylaxis](#), rash, [urticaria](#), and life-threatening systemic reactions possibly related to [vasculitis](#), have been reported; discontinue if conditions occur [9].

V)) Neurologic: Life-threatening [neuroleptic malignant syndrome](#) has been reported in association with [olanzapine](#) therapy; immediate treatment interruption required; careful monitoring recommended with therapy restart [9].

W)) Neurologic: Use caution in patients with a history of seizure disorder or conditions that lower seizure threshold (eg, [Alzheimer disease](#); unapproved use) [9].

X)) Neurologic: Potentially irreversible [tardive dyskinesia](#) may occur with antipsychotic treatment; discontinuation may be warranted [9].

Y)) Neurologic: Sedation-related cognitive and motor impairment has been reported [9].

Z)) Neurologic: Increased risk of [tardive dyskinesia](#) with long-term therapy or higher cumulative doses; monitoring recommended [9]

AA)) Ophthalmic: [Angle-closure glaucoma](#) may occur in patients with anatomically narrow angles and without a patent [iridectomy](#) [9].

AB)) Psychiatric: Antidepressants may trigger a mixed or [manic episode](#) in patients with underlying [bipolar disorder](#); baseline screening and monitoring recommended [9].

AC)) Respiratory: Pulmonary reactions have occurred, which may be preceded by dyspnea [9].

AD)) Serotonin syndrome: Life-threatening [serotonin syndrome](#) has been reported, often with concurrent use with other serotonergic drugs (eg, triptans, tricyclic antidepressants, [fentanyl](#), [lithium](#), [tramadol](#), [buspirone](#), tryptophan, St John's wort), MAOIs (including methylene blue IV and [linezolid](#)), and other drugs that impair serotonin metabolism; monitoring recommended; discontinue use if suspected [9].

AE)) Withdrawal: Avoid abrupt withdrawal, as serious withdrawal symptoms have been reported; monitoring recommended [9].

3.3] Adverse Reactions

3.3.1] Cardiovascular Effects

3.3.1.A] [Bradycardia](#)

1)) In a clinical pharmacology study of [olanzapine/fluoxetine](#), 3 healthy subjects were discontinued from the trial after experiencing severe, but self-limited, hypotension and bradycardia that occurred 2 to 9 hours following a single 12-mg/50-mg dose of [olanzapine/fluoxetine](#). Reactions consisting of this combination of hypotension and bradycardia (and also accompanied by [sinus pause](#)) have been observed in at least three other healthy subjects treated with various formulations of [olanzapine](#) (one oral, two intramuscular) [12].

3.3.1.B] [Edema](#)

1)) Incidence: 15% [2]

2)) Edema, including peripheral edema, pitting edema, [generalized edema](#), eyelid edema, face edema, gravitational edema, localized edema, periorbital edema, swelling, joint swelling, swelling face, and eye swelling, occurred in 15% of adult patients who received [fluoxetine](#) and [olanzapine](#) (n=771) compared with 2% of patients who received placebo (n=477) in controlled clinical studies including [depressive episodes](#) associated with bipolar I disorder and treatment resistant depression [2].

3.3.1.C] [Orthostatic hypotension](#)

1)) Incidence: 4% [12]

2)) In the [olanzapine/fluoxetine](#)-controlled clinical studies across all indications, there were no significant differences between orthostatic changes in the group receiving combination therapy compared with

olanzapine, fluoxetine, and placebo groups. Orthostatic systolic blood pressure decreases of at least 30 mmHg occurred in 4% (28/705), 2.3% (19/831), 4.5% (18/399), and 1.8% (8/442) of the olanzapine/fluoxetine, olanzapine, fluoxetine, and placebo groups, respectively. In controlled clinical studies, the incidence of patients with a decrease in orthostatic pulse of 20 beats per minute (bpm) or greater concomitantly with a decrease in orthostatic systolic blood pressure of 20 mmHg or greater was 0.3% (2/706) in the olanzapine/fluoxetine group, 0.7% (6/837) in the olanzapine group, 0% in the fluoxetine group, and 0.2% (1/445) in the placebo group. The incidence of syncope in olanzapine/fluoxetine-treated patients was 0.4% (3/771) compared with placebo (0.2%, 1/477)[12].

3J) In a clinical pharmacology study of olanzapine/fluoxetine, 3 healthy subjects were discontinued from the trial after experiencing severe, but self-limited, hypotension and bradycardia that occurred 2 to 9 hours following a single 12-mg/50-mg dose of olanzapine/fluoxetine. Reactions consisting of this combination of hypotension and bradycardia (and also accompanied by sinus pause) have been observed in at least three other healthy subjects treated with various formulations of olanzapine (one oral, two intramuscular) [12].

3.3.1.D] Prolonged QT interval

1J) QT interval prolongation and ventricular arrhythmia, including torsade de pointes, have been reported with postmarketing use of fluoxetine. Use caution when administering the olanzapine and fluoxetine combination to patients with congenital long QT syndrome, a history of QT prolongation, a family history of long QT syndrome or sudden cardiac death, and other conditions predisposing them to QT prolongation and ventricular arrhythmia. Consider monitoring patients at risk for QT prolongation or ventricular arrhythmia at baseline and periodically with ECG assessments. If patients develop signs or symptoms consistent with ventricular arrhythmia, consider discontinuing the combination treatment [2].

2J) The mean increase in QTc interval for adult patients treated with the olanzapine and fluoxetine combination (4.4 msec) in clinical studies was significantly greater than that for placebo-treated (-0.8 msec), olanzapine-treated patients (-0.3 msec), and fluoxetine-treated patients (1.7 msec). There were no significant differences between patients treated with olanzapine and fluoxetine, placebo, olanzapine, or fluoxetine in the incidence of QTc outliers of greater than 500 msec [2].

3J) The mean change in QTc interval (from baseline to endpoint) for patients 10 to 17 years of age treated with the olanzapine and fluoxetine combination was 8.2 msec (95% CI, 6.2 to 10.2 msec) and was statistically significant greater than that for patients treated with placebo in an 8-week, randomized, double-blind clinical trial for acute treatment of depressive episodes associated with bipolar I disorder. No patient had QTc increases of 60 msec or greater or an overall QTc of 480 msec or greater in this study [2].

3.3.1.E] Tachycardia

1J) Tachycardia has occurred in olanzapine/fluoxetine-treated patients in premarketing clinical studies [12].

3.3.1.F] Torsades de pointes

1J) QT interval prolongation and ventricular arrhythmia, including torsade de pointes, have been reported with postmarketing use of fluoxetine. Use caution when administering the olanzapine and fluoxetine combination to patients with congenital long QT syndrome, a history of QT prolongation, a family history of long QT syndrome or sudden cardiac death, and other conditions predisposing them to QT prolongation and ventricular arrhythmia. Consider monitoring patients at risk for QT prolongation or ventricular arrhythmia at baseline and periodically with ECG assessments. If patients develop signs or symptoms consistent with ventricular arrhythmia, consider discontinuing the combination treatment [2].

3.3.2] Dermatologic Effects

3.3.2.A] Erythema multiforme

1)) [Erythema multiforme](#) has been reported with [olanzapine](#) or [fluoxetine](#) monotherapy, but was not observed in [olanzapine/fluoxetine](#) treated patients during premarketing clinical studies [12].

3.3.3] Endocrine/Metabolic Effects

3.3.3.A] Bicarbonate level - finding

1)) Incidence: 14.1% [14]

2)) In [olanzapine/fluoxetine](#) clinical studies (including treatment resistant depression, [depressive episodes](#) associated with Bipolar I Disorder, [major depressive disorder](#) with [psychosis](#), or sexual dysfunction), low bicarbonate level occurred at a greater frequency (statistically significant) in the [olanzapine/fluoxetine](#)-treated patients compared with placebo (14.1% vs 8.8%) [14].

3.3.3.B] [Diabetes mellitus](#)

1)) Summary

a)) As with other atypical antipsychotics, [hyperglycemia](#) has been reported in patients on [olanzapine](#). The mean increase of serum glucose, fasting and nonfasting levels, from baseline to the average of the 2 highest serum concentrations was 15 mg/dL (0.83 mmol/L), during Clinical Antipsychotic Trials of Intervention Effectiveness in patients treated for a median olanzapine-exposure duration of 9.2 months. [Olanzapine](#) is implicated in glucose abnormalities; however, it is difficult to assess the relationship because of an increased risk of [diabetes mellitus](#) in patients with [schizophrenia](#) and the increasing incidence of [diabetes mellitus](#) in the general population. In general, epidemiological studies show that atypical antipsychotics increase the risk of treatment-emergent [hyperglycemia](#). [Olanzapine](#) appears to have a greater risk of glucose abnormalities compared with other atypical antipsychotics [14].

b)) The risks and benefits of [olanzapine/fluoxetine](#) hydrochloride should be considered prior to prescribing in patients with an established diagnosis of [diabetes mellitus](#) or in patients with borderline increased blood glucose levels (fasting 100 to 126 mg/dL [6 to 6.99 mmol/L] or nonfasting 140 to 200 mg/dL [7.8 to 10 mmol/L]). Regular monitoring of blood glucose is recommended. For patients with risk factors for [diabetes mellitus](#), fasting blood glucose should be monitored prior to initiation and periodically during [olanzapine/fluoxetine](#) therapy. All patients should be monitored for signs and symptoms of [hyperglycemia](#) (polydipsia, polyuria, [polyphagia](#), and weakness). Fasting blood glucose should be tested if symptoms of [hyperglycemia](#) develop. [Hyperglycemia](#) may resolve upon discontinuation of [olanzapine/fluoxetine](#); however, some patients may continue to need antidiabetic therapy despite discontinuation of [olanzapine](#) [14].

2)) New onset [diabetes mellitus](#) (DM) has been reported with the administration of [olanzapine](#). At least 25 fatalities have been reported in association with olanzapine-induced [diabetic ketoacidosis](#) [17][18][19].

3)) A 51-year-old woman with [schizoaffective disorder](#) and [type 2 diabetes](#) (stabilized on [metformin](#) 1 gram twice daily and [gliclazide](#) 160 mg twice daily) developed [hyperglycemia](#), without weight gain, when an episode of elevated mood and [psychosis](#) was treated with [olanzapine](#). She was initially treated with [risperidone](#) for 4 weeks but did not respond. [Chlorpromazine](#) also was not effective. [Olanzapine](#), titrated to 30 mg at night, brought full remission of psychotic symptoms. Her blood glucose then began to increase, although her diet was controlled by the hospital. Oral hypoglycemic medications were increased to the maximum and she was started on actrapid [insulin](#). Glucose levels remained unstable until [olanzapine](#) was tapered and discontinued, at which time her hypoglycemic medications were reduced to previous levels and actrapid [insulin](#) was discontinued. Zuclopenthixol was subsequently used to treat her [schizoaffective](#)

disorder. The patient showed no significant weight gain during treatment with [olanzapine](#), which suggests that [olanzapine](#) can have a direct effect on glucose regulation [20].

4) A 27-year-old man developed signs of [diabetes mellitus](#) (polydipsia, [polyphagia](#), nausea and vomiting, [hyperglycemia](#), ketonuria) 2 years after starting [olanzapine](#) for treatment of [schizophrenia](#). He was treated with [insulin](#), and his dose of [olanzapine](#) was increased from 10 mg/day to 15 mg/day to replace [valproic acid](#), which he had taken for 3 years. After 3 months, [insulin](#) therapy was replaced by [pioglitazone](#) 30 mg/day, resulting in relatively good glycemic control. [Olanzapine](#) therapy was not discontinued because of the risk of psychotic worsening [21].

5) A 45-year-old obese man developed elevated fasting glucose 1 year after his treatment for [schizophrenia](#) was changed from [risperidone](#) to [olanzapine](#) (20 to 25 mg/day). Six months later, he was treated with [glyburide](#) 1.25 mg/day. Over the next 6 months, glycosylated [hemoglobin](#) levels remained stable, but his weight began to increase. Five months later, he complained of diarrhea and weight loss. His [glyburide](#) dose was increased to 1.88 mg/day. With further symptoms (polyuria, polydipsia, and diaphoresis), his [glyburide](#) dosage was increased to 10 mg twice daily, [insulin](#) treatment was started, and [olanzapine](#) was replaced by [risperidone](#). Six weeks after discontinuation of [olanzapine](#), the patient's glycosylated [hemoglobin](#) had dropped to 6%. [Insulin](#) was discontinued, [glyburide](#) was reduced to 1.25 mg/day, and his weight stabilized. Five months later, his [diabetes](#) was well-controlled [22].

6) Olanzapine-induced glucose dysregulation has been reported as an adverse effect, possibly due to drug-induced weight gain. [Olanzapine](#) was associated with a severe exacerbation of [type 2 diabetes](#) in a 51-year-old woman with a [major depressive disorder](#) and substance abuse. Initially, the patient was treated with [sertraline](#) and [haloperidol](#) decanoate. After 4 weeks, [sertraline](#) was replaced by [fluoxetine](#) due to continued severe depressive symptoms. At week 18, [haloperidol](#) was replaced by [olanzapine](#) due to persistent auditory and visual hallucinations. Prior to initiation of [olanzapine](#) therapy, the patient's [diabetes](#) was well-controlled by diet (glycosylated [hemoglobin](#) 6.5%, baseline fasting blood glucose 89 to 132 mg/dL or 4.94 to 7.33 mmol/L). Twelve days after [olanzapine](#) initiation, glucose control diminished and continued to worsen despite treatment with [glipizide](#), [metformin](#), and diet. At week 26, [fluoxetine](#) therapy was replaced by [venlafaxine](#) due to inadequate antidepressant response. At week 35 (fasting blood glucose 120 to 461 mg/dL (6.7 to 25.59 mmol/L), glycosylated [hemoglobin](#) 12.5%), [insulin](#) therapy (NPH 70/30) was initiated and titrated to 70 units per day. [Olanzapine](#) was tapered during weeks 39 and 40 and discontinued. Two weeks after all antipsychotic therapy was stopped, the patient's fasting blood glucose levels had decreased to within 85 and 163 mg/dL (4.72 and 9.05 mmol/L). By the time of discharge, the [insulin](#) dose had been reduced to 45 units/day NPH 70/30 [23].

7) Cases of new-onset [diabetes mellitus](#) (DM) were reported that developed after initiation of [olanzapine](#) treatment. The DM began between 5 weeks and 17 months (mean 26 weeks; median 20 weeks) after [olanzapine](#) initiation. Two cases presented with [diabetic ketoacidosis](#). Four patients had a family history of DM and 4 patients experienced weight gain while on [olanzapine](#). [Olanzapine](#) was eventually discontinued in all cases but in 4 out of 7 cases, medical treatment for DM was still required [18].

3.3.3.C] [Diabetic ketoacidosis](#)

1) Summary

a) As with other atypical antipsychotics, [diabetic ketoacidosis](#) or [hyperosmolar coma](#), including death, has been reported in patients on [olanzapine](#). [Olanzapine](#) is implicated in glucose abnormalities; however, it is difficult to assess the relationship because of an increased risk of [diabetes mellitus](#) in patients with [schizophrenia](#) and the increasing incidence of [diabetes mellitus](#) in the general population. In general, epidemiological studies show that atypical antipsychotics increase the risk of treatment-emergent [hyperglycemia](#). [Olanzapine](#) appears to have a greater risk of glucose abnormalities compared with other atypical antipsychotics [14].

b)) The risks and benefits of [olanzapine/fluoxetine](#) hydrochloride should be considered prior to prescribing in patients with an established diagnosis of [diabetes mellitus](#) or in patients with borderline increased blood glucose levels (fasting 100 to 126 mg/dL [6 to 6.99 mmol/L] or nonfasting 140 to 200 mg/dL [7.7 to 10 mmol/L]). Regular monitoring of blood glucose is recommended. For patients with risk factors for [diabetes mellitus](#), fasting blood glucose should be monitored prior to initiation and periodically during [olanzapine/fluoxetine](#) therapy. All patients should be monitored for signs and symptoms of [hyperglycemia](#) (polydipsia, polyuria, [polyphagia](#), and weakness). Fasting blood glucose should be tested if symptoms of [hyperglycemia](#) develop. [Hyperglycemia](#) may resolve upon discontinuation of [olanzapine/fluoxetine](#); however, some patients may continue to need antidiabetic therapy despite discontinuation of [olanzapine](#) [14].

2)) [Diabetic coma](#) has been reported with [olanzapine](#) or [fluoxetine](#) monotherapy, but was not observed in [olanzapine/fluoxetine](#) treated patients during premarketing clinical studies [14].

3)) Olanzapine-induced [ketoacidosis](#) has been reported, including one near-fatal case in a 44-year-old African American woman. In the near-fatal case, the patient had taken [olanzapine](#) 25 mg/day for approximately 1 month [15].

4)) [Diabetic ketoacidosis](#) following 3 months of [olanzapine](#) therapy was reported in a 31-year-old man with no familial or personal history of [diabetes](#). The patient was started on [insulin](#) and [olanzapine](#) was discontinued. Fifteen days later his [insulin](#) requirements decreased and then stopped. Eight months later the patient has remained metabolically stable, free of diabetic symptoms [16].

5)) [Diabetic ketoacidosis](#) has been reported with the administration of [olanzapine](#). At least 25 fatalities have been reported in association with olanzapine-induced [diabetic ketoacidosis](#) [17][18][19].

6)) A 50-year-old African American man developed [diabetic ketoacidosis](#) after receiving 8 months of [olanzapine](#) therapy. At the time, he was receiving [olanzapine](#) 30 mg daily with [divalproex](#) 750 mg twice daily. He began [insulin](#) therapy but after the [olanzapine](#) was discontinued, his blood sugar returned to normal [19].

7)) A 39-year-old man developed [diabetic ketoacidosis](#) after receiving [olanzapine](#) 10 mg for a treatment-refractory disorder. He had no family history or previous laboratory evidence of [diabetes](#). His body mass index was high at 40 kg/m(2). He was admitted with asthenia, polyuria, dehydration, severe [hyperglycemia](#) (6 mmol/L), and [acidosis](#). His [HbA1c](#) was 14.7%. He was maintained on [insulin](#) 3 times daily. When [olanzapine](#) was discontinued, [insulin](#) requirements decreased after 15 days. His blood glucose and [HbA1c](#) became normal [16].

3.3.3.D] Hypercholesterolemia

1)) Summary

a)) Significant increases in total cholesterol have been observed during treatment with [olanzapine/fluoxetine](#) hydrochloride. The mean increase in random total cholesterol from baseline was 12.1 mg/dL in [olanzapine/fluoxetine](#)-treated patients compared with 4.8 mg/dL in [olanzapine](#) monotherapy-treated patients and a decrease of 5.5 mg/dL in placebo-treated patients (statistically significant), in an analysis of 7 placebo-controlled studies of up to 12 weeks duration. Baseline and follow-up lipid monitoring of lipids is recommended in patients on [olanzapine](#) [14].

2)) Incidence: adults, 8.2% to 36.2%; pediatrics, 12.3% to 75% [2]

3)) Adults

a)) In an analysis of 7 placebo-controlled monotherapy studies of up to 12 weeks duration, the mean increase in random total cholesterol from baseline was 12.1 mg/dL (0.313 mmol/L) in [olanzapine/fluoxetine](#)-treated patients compared with 4.8 mg/dL (0.12 mmol/L) in [olanzapine](#) monotherapy-treated patients and a decrease of 5.5 mg/dL (0.142 mmol/L) in placebo-treated

patients. The table below provides the frequency and degree of increase of nonfasting cholesterol in adults from controlled clinical studies with treatment up to 12 weeks[14]:

Nonfasting Total Cholesterol In
Adults With Treatment Up to 12
weeks

Change from Baseline	Treatment Arm	N	Portion of Patients
Increase by 40 mg/dL (1 mmol/L) or more	olanzapine/fluoxetine	685	35% *
olanzapine	749	22.7%	
placebo	390	9%	
Normal to High	olanzapine/fluoxetine	256	8.2% *
olanzapine	279	2.9%	
placebo	175	1.7%	
Borderline to High	olanzapine/fluoxetine	213	36.2% *
olanzapine	261	27.6%	
placebo	111	9.9%	

KEY: mg/dL = milligrams/deciliter; Normal = less than 200 mg/dL (5 mmol/L); Borderline = 200 mg/dL (5 mmol/L) to less than 240 mg/dL (6.2 mmol/L); High = 240 mg/dL (6.2 mmol/L) or greater; * = statistically significant compared with placebo and olanzapine

b) In long-term [olanzapine/fluoxetine](#) studies of at least 48 weeks, changes in nonfasting total cholesterol from normal at baseline to high occurred in 12% (n=150) and changes from borderline to high occurred in 56.6% (n=143) of patients. The mean change in nonfasting total cholesterol was 11.3 mg/dL (n=426) [14].

c) In an analysis of 5 placebo-controlled monotherapy studies of up to 12 weeks duration, olanzapine-treated patients had increases from baseline in mean fasting total cholesterol of 5.3 mg/dL (0.137 mmol/L) compared with decreases from baseline of 6.1 mg/dL (0.158 mmol/L) for placebo-treated patients. In long-term [olanzapine](#) studies of at least 48 weeks, patients had increases from baseline in mean fasting total cholesterol of 5.6 mg/dL (0.145 mmol/L). In an analysis of patients who completed 12 months of therapy, the mean nonfasting total cholesterol did not increase further after approximately 4 to 6 months. The tables below provide the frequency and degree of increase of fasting cholesterol and [LDL cholesterol](#) [14]:

Fasting Total Cholesterol In
Adults

	Up to 12 weeks exposure	At least 48 weeks exposure			
Change from Baseline	Treatment Arm	N	Portion of Patients	N	Portion of Patients
Increase by 40 mg/dL (1 mmol/L) or more	olanzapine	745	21.6%	489	32.9%
placebo	402	9.5%	NA	NA	
Normal to High	olanzapine	392	2.8%	283	14.8%
placebo	207	2.4%	NA	NA	
Borderline to High	olanzapine	222	23%	125	55.2%
placebo	112	12.5%	NA	NA	

KEY: mg/dL = milligrams/deciliter; mmol/L =

millimole/liter; Normal
= less than 200 mg/dL (5
mmol/L); Borderline = 200
mg/dL (5 mmol/L) to less
than 240 mg/dL (6.2 mmol/
L); High = 240 mg/dL (6.2
mmol/L) or greater; NA =
Not Applicable

Fasting Low-Density-
Lipoprotein Cholesterol In
Adults

	Up to 12 weeks exposure	At least 48 weeks exposure			
Change from Baseline	Treatment Arm	N	Portion of Patients	N	Portion of Patients
Increase by 30 mg/dL (0.8 mmol/L) or more	olanzapine	536	23.7% *	483	39.8%
placebo	304	14.1%	NA	NA	
Normal to High	olanzapine	154	0%	123	7.3%
placebo	82	1.2%	NA	NA	
Borderline to High	olanzapine	302	10.6%	284	31%
placebo	173	8.1%	NA	NA	

KEY: mg/dL = milligrams/
deciliter; mmol/L =
millimole/liter; Normal
= less than 100 mg/dL (3
mmol/L); Borderline = 100
mg/dL (3 mmol/L) to less
than 160 mg/dL (4.1 mmol/
L); High = 160 mg/dL (4.1
mmol/L) or greater; NA =
Not Applicable

1j) Children and Adolescents

a) The mean changes in fasting total and LDL cholesterol levels for patients 10 to 17 years of age treated with the olanzapine and fluoxetine combination was an increase of 16.3 mg/dL (0.422 mmol/L) and 9.7 mg/dL (0.251 mmol/L), respectively, compared with a total decrease of 4.3 mg/dL (0.111 mmol/L) and LDL decrease of 3.5 mg/dL (0.091 mmol/L) for patients treated with placebo in an 8-week, randomized, double-blind clinical trial for acute treatment of depressive episodes associated with bipolar I disorder. The table below provides the frequency and degree of increase of fasting total cholesterol and LDL cholesterol in this study[2]:

Fasting Total Cholesterol In Children and Adolescents

Category Change from Baseline	Treatment Arm	N	Portion of Patients
Increase by 40 mg/dL or more	OFC	158	52.5%
placebo	81	8.6%	
Normal to High	OFC	81	12.3%
placebo	44	4.5%	
Borderline to High	OFC	22	72.7%
placebo	11	24.3%	
Normal/borderline to High	OFC	126	32.5%
placebo	67	10.4%	
Normal to Borderline/high	OFC	81	58%

placebo	44	31.8%
KEY: mg/dL = milligrams/deciliter; OFC = olanzapine + fluoxetine combination; Normal = less than 170 mg/dL; Borderline = 170 mg/dL to less than 200 mg/dL; High = 200 mg/dL or greater ; NA = Not Applicable		
Fasting LDL Cholesterol In Children and Adolescents		
Category Change from Baseline	Treatment Arm	N
Increase by 30 mg/dL (0.8 mmol/L) or more	OFC	158
placebo	81	23.5%
Normal to High	OFC	112
placebo	62	6.5%
Borderline to High	OFC	12
placebo	3	0%
Normal/borderline to High	OFC	138
placebo	77	7.8%
Normal to Borderline/high	OFC	112
placebo	62	14.5%
KEY: mg/dL = milligrams/deciliter; mmol/L = millimole/liter; OFC = olanzapine + fluoxetine combination; Normal = less than 110 mg/dL (2.8 mmol/L); Borderline = 110 mg/dL (2.8 mmol/L) to less than 130 mg/ dL (3.4 mmol/L); High = 130 mg/dL (3.4 mmol/L) or greater; NA = Not Applicable		

d) In an analysis of 3 placebo-controlled monotherapy studies of up to 6 weeks duration in adolescents, olanzapine-treated adolescents had increases from baseline in mean fasting total cholesterol of 12.9 mg/dL (0.334 mmol/L) and **LDL cholesterol** compared with increases from baseline in mean fasting total cholesterol and **LDL cholesterol** of 1.3 mg/dL (0.034 mmol/L) and 1 mg/dL (0.03 mmol/L) for placebo-treated patients, respectively. In long-term **olanzapine** studies of at least 24 weeks, adolescents had increases from baseline in mean fasting total cholesterol and **LDL cholesterol** of 5.5 mg/dL (0.14 mmol/L) and 5.4 mg/dL (0.139 mmol/L), respectively, and a mean decrease in fasting **HDL cholesterol** of 4.5 mg/dL (0.116 mmol/L). The tables below provide the frequency and degree of increase of fasting total cholesterol and **LDL cholesterol** [14]:

Fasting Total Cholesterol In
Adolescents

Category Change from Baseline	Up to 6 weeks exposure Treatment Arm	At least 24 weeks exposure N	Portion of Patients	N	Porti
Increase by 40 mg/dL (1.03 mmol/L) or more	olanzapine	138	14.5%	122	14.8%
placebo	66	4.5%	NA	NA	
Normal to High	olanzapine	87	6.9%	78	7.7%
placebo	43	2.3%	NA	NA	
Borderline to High	olanzapine	36	38.9%	33	57.6%

placebo	13	7.7%	NA	NA	
KEY: mg/dL = milligrams/deciliter; mmol/L = millimole/liter; Normal = less than 170 mg/dL (4.4 mmol/L); Borderline = 170 mg/dL (4.4 mmol/L) to less than 200 mg/dL (5 mmol/L); High = 200 mg/dL (5 mmol/L) or greater; NA = Not Applicable					
Fasting Low-Density-Lipoprotein Cholesterol In Adolescents					
Category Change from Baseline	Up to 6 weeks exposure Treatment Arm	At least 24 weeks exposure N	Portion of Patients	N	Portion of Patients
Increase by 30 mg/dL or more	olanzapine	137	17.5%	121	22.3%
placebo	63	11.1%	NA	NA	
Normal to High	olanzapine	98	5.1%	92	10.9%
placebo	44	4.5%	NA	NA	
Borderline to High	olanzapine	29	48.3% *	21	47.6%
placebo	9	0%	NA	NA	
KEY: mg/dL = milligrams/deciliter; mmol/L = millimole/liter; Normal = less than 110 mg/dL (2.8 mmol/L); Borderline = 110 mg/dL (2.8 mmol/L) to less than 130 mg/dL (3.4 mmol/L); High = 130 mg/dL (3.4 mmol/L) or greater; NA = Not Applicable					

3.3.3.E] Hyperglycemia

1) Summary

a) As with other atypical antipsychotics, [hyperglycemia](#) has been reported in patients on [olanzapine](#). In an analysis of 7 controlled clinical studies, 2 of which were placebo-controlled, with treatment duration up to 12 weeks, [olanzapine/fluoxetine](#) was associated with greater mean change in random glucose compared with placebo (8.65 mg/dL [0.4802 mmol/L] vs -3.86 mg/dL [0.2143 mmol/L]). The mean increase of serum glucose (fasting and nonfasting levels) from baseline to the average of the 2 highest serum concentrations was 15 mg/dL (0.83 mmol/L), during Clinical Antipsychotic Trials of Intervention Effectiveness in patients treated for a median olanzapine-exposure duration of 9.2 months. [Olanzapine](#) is implicated in glucose abnormalities; however, it is difficult to assess the relationship because of an increased risk of [diabetes mellitus](#) in patients with [schizophrenia](#) and the increasing incidence of [diabetes mellitus](#) in the general population. In general, epidemiological studies show that atypical antipsychotics increase the risk of treatment-emergent [hyperglycemia](#). [Olanzapine](#) appears to have a greater risk of glucose abnormalities compared with other atypical antipsychotics [14].

b) The risks and benefits of olanzapine/fluoxetine hydrochloride should be considered prior to prescribing in patients with an established diagnosis of diabetes mellitus or in patients with borderline increased blood glucose levels (fasting 100 to 126 mg/dL [6 to 6.99 mmol/L] or nonfasting 140 to 200 mg/dL [7.8 to 10 mmol/L]). Regular monitoring of blood glucose is recommended. For patients with risk factors for diabetes mellitus, fasting blood glucose should be monitored prior to initiation and periodically during olanzapine/fluoxetine therapy. All patients should be monitored for signs and symptoms of hyperglycemia (polydipsia, polyuria, polyphagia, and weakness). Fasting blood glucose should be tested if symptoms of hyperglycemia develop. Hyperglycemia may resolve upon discontinuation of olanzapine/fluoxetine; however, some patients may continue to need antidiabetic therapy despite discontinuation of olanzapine [14].

2) Incidence: adults, baseline normal, 2.3%; baseline borderline-normal, 34.1%; pediatrics, baseline normal, 4.8%; baseline borderline-normal, 14.3%[2]

3) Adults

a) The mean changes in random glucose concentrations were an increase of 8.65 mg/dL (0.48016 mmol/L) in olanzapine/fluoxetine-treated adults compared with a decrease of 3.86 mg/dL (0.214 mmol/L; statistically significant), in an analysis of 7 controlled clinical studies, 2 of which were placebo-controlled, with treatment duration up to 12 weeks. In patients with normal random glucose levels (less than 140 mg/dL [7.8 mmol/L]) and baseline borderline random glucose levels (140 mg/dL [7.7 mmol/L] and greater but less than 200 mg/dL [10 mmol/L]) treated with olanzapine/fluoxetine, 2.3% and 34.1% (statistically significant compared with placebo), respectively, had glucose levels of 200 mg/dL (10 mmol/L) or greater. In comparison, 0.3% and 3.6%, respectively, of the placebo-treated patients had high glucose levels. Patients at greatest risk of glucose concentration increases were patients with glucose dysregulation at baseline defined as: diagnosis with diabetes mellitus or related adverse events, treated with antidiabetic agents, or baseline random glucose concentrations of 200 mg/dL (10 mmol/L) or greater, and/or a baseline fasting glucose level of 126 mg/dL (6.99 mmol/L) or greater. These patients had a greater mean increase in glycosylated hemoglobin [14].

b) In a study of healthy volunteers, patients who received olanzapine (n=22) for 3 weeks had a mean increase in fasting blood glucose of 2.3 mg/dL (0.128 mmol/L) compared with baseline. Placebo-treated patients (n=19) had a mean increase in fasting blood glucose compared with baseline of 0.34 mg/dL (0.0189 mmol/L) [14].

c) Data for fasting glucose are limited for olanzapine/fluoxetine. However for olanzapine monotherapy the mean increases in fasting glucose levels were 2.76 mg/dL (0.1532 mmol/L) in olanzapine-treated adults compared with 0.17 mg/dL (9.4 mcmmol/L) in placebo-treated patients, in an analysis of 5 placebo-controlled trials of adults treated for up to 12 weeks [14].

d) The mean change in fasting glucose for olanzapine-treated patients was 4.2 mg/dL (0.233 mmol/L; n=487), and mean change in nonfasting glucose in patients exposed at least 48 weeks was 5.9 mg/dL (0.328 mmol/L; n=425). In analyses of patients who completed 9 to 12 months of olanzapine therapy, mean change in fasting and nonfasting glucose levels continue to increase over time [14].

4) Children and Adolescents

a) There were no clinically meaning differences in mean change of fasting glucose levels in patients 10 to 17 years of age treated with the olanzapine and fluoxetine combination compared with patients treated with placebo in an 8-week, randomized, double-blind clinical trial for acute treatment of depressive episodes associated with bipolar I disorder. Of patients with normal fasting

glucose levels (less than 100 mg/dL [6 mmol/L]) treated with [olanzapine](#) and [fluoxetine](#) (n=125), 4.8% had high glucose levels of 126 mg/dL (6.99 mmol/L) or greater compared with 1.5% of the placebo-treated patients (n=65) [2].

b)) The mean changes in fasting glucose levels were an increase of 2.68 mg/dL (0.1488 mmol/L) in olanzapine-treated adolescents compared with a decrease of 2.59 mg/dL (0.1438 mmol/L) in placebo-treated adolescents (statistically significant), in an analysis of 3 placebo-controlled trials of adolescents treated with [olanzapine](#) monotherapy for a duration of 6 weeks in [schizophrenia](#) trials or 3 weeks in [bipolar disorder](#) trials. The mean change in fasting glucose for adolescents exposed at least 24 weeks was 3.1 mg/dL (0.172 mmol/L). In adolescents with normal fasting glucose levels (less than 100 mg/dL [6 mmol/L]) and baseline borderline fasting glucose levels (100 mg/dL [6 mmol/L] to less than 126 mg/dL [6.99 mmol/L]) treated with [olanzapine](#), 0% (0 out of 124) and 14.3% (2 out of 14), respectively, had high glucose levels of 126 mg/dL (6.99 mmol/L) or greater. In comparison, 1.9% (1 out of 53) and 0% (0 out of 13), respectively, of the placebo-treated patients had high glucose levels [2].

3.3.3.F] [Hyperprolactinemia](#)

1)) Incidence: adults, 28% ; pediatrics, 85%[2]

2)) [Olanzapine](#) and [fluoxetine](#) elevates prolactin levels as with other drugs that antagonize [dopamine](#) D2 receptors. Clinically related events such as [galactorrhea](#), [amenorrhea](#), [gynecomastia](#) and impotence have been reported in patients receiving prolactin-elevating compounds. In clinical studies of [olanzapine](#) and [fluoxetine](#), elevated plasma prolactin concentrations were observed in 28% of the adults treated with the [olanzapine](#) and [fluoxetine](#) combination compared with 5% of patients who received placebo. In a pooled analysis of 2929 adults who received [olanzapine](#) and [fluoxetine](#) in clinical studies, menstrual changes were noted in 1% of females (20/1946) and breast-related events (ie, [gynecomastia](#), [galactorrhea](#)) were reported in 0.8% of females (16/1946) and 0.2% of males (2/983) [2].

3)) The mean change in prolactin levels (from baseline) for patients 10 to 17 years of age treated with the [olanzapine](#) and [fluoxetine](#) combination was 8.7 mcg/L and was statistically significant greater than that for patients treated with placebo (0.7 mcg/L) in an 8-week, randomized, double-blind clinical trial for acute treatment of [depressive episodes](#) associated with bipolar I disorder. Elevated prolactin levels (from normal or low at baseline to abnormal at any time during the trial) were reported in 85% of patients treated with [olanzapine](#) and [fluoxetine](#) compared with 36% of patients who received placebo. Although elevated prolactin concentrations were very commonly reported (occurring at an incidence of greater than 10%) in both the [olanzapine/fluoxetine](#) and placebo groups of this study, these elevations occurred in more than twice as many patients treated with the [olanzapine](#) and [fluoxetine](#) combination compared with placebo-treated patients. Adverse events potentially associated with elevated prolactin, including [dysmenorrhea](#), [galactorrhea](#), and ovulation disorder, were reported in 5 patients [2].

4)) In placebo-controlled clinical studies of [olanzapine](#) monotherapy up to 12 weeks in duration, elevated plasma prolactin concentrations were reported in 30% of adults treated with [olanzapine](#) compared with 10.5% of placebo-treated patients [14].

5)) In a single 8-week randomized, double-blind, fixed-dose study comparing [olanzapine](#) 10 mg/day (n=199), 20 mg/day (n=200), and 40 mg/day (n=200), incidence of treatment-emergent prolactin elevation greater than 24.2 ng/mL (24.2 mcg/L) in females or greater than 18.77 ng/mL (18.77 mcg/L) in males at any time during the trial were 31.2% at 10 mg, 42.7% at 20 mg, and 61.1% at 40 mg per day [14].

6)) In placebo-controlled [olanzapine](#) monotherapy studies up to 6 weeks in adolescent patients with [schizophrenia](#) or [bipolar disorder](#), elevated prolactin concentrations compared with baseline occurred in 47% of the adolescents treated with [olanzapine](#) compared with 7% of placebo. In long-term clinical trials of [olanzapine](#) in adolescents, breast-related events (ie, [gynecomastia](#), [galactorrhea](#)) occurred in 2% of males (7/286) and 2% of females (3/168) [14].

3.3.3.G] Hypoalbuminemia

- 1) Incidence: 2.7% [14]
- 2) In [olanzapine/fluoxetine](#) clinical studies (including treatment resistant depression, [depressive episodes](#) associated with Bipolar I Disorder, [major depressive disorder](#) with [psychosis](#), or sexual dysfunction), low albumin level occurred at a greater frequency (statistically significant) in the [olanzapine/fluoxetine](#)-treated patients compared with placebo (2.7% vs 0.3%) [14].

3.3.3.H] Hyponatremia

- 1) [Hyponatremia](#) (headache, difficulty concentrating, [memory impairment](#), confusion, weakness, and unsteadiness) has occurred with [olanzapine/fluoxetine](#) use, with some serious or acute cases resulting in hallucination, syncope, seizure, coma, respiratory arrest, and death. Cases of serum sodium lower than 110 mmol/L, which was reversible upon discontinuation, have been reported with [olanzapine/fluoxetine](#). The syndrome of [inappropriate antidiuretic hormone secretion](#) may have been one possible etiology. Older patients and patients taking diuretics or who were otherwise volume-depleted may be at greater risk for [hyponatremia](#). Drug discontinuation is recommended in patients who develop symptomatic [hyponatremia](#) [14].

3.3.3.I] Hypophosphatemia

- 1) Incidence: 1.9% [14]
- 2) In [olanzapine/fluoxetine](#) clinical studies (including treatment resistant depression, [depressive episodes](#) associated with Bipolar I Disorder, [major depressive disorder](#) with [psychosis](#), or sexual dysfunction), low inorganic phosphorus level occurred at a greater frequency (statistically significant) in the [olanzapine/fluoxetine](#)-treated patients compared with placebo (1.9% vs 0.3%) [14].

3.3.3.J] Increased body temperature

- 1) Disruption of the body's ability to reduce core body temperature has been attributed to antipsychotic drugs. Appropriate care is advised when prescribing [olanzapine/fluoxetine](#) for patients who will be experiencing conditions which may contribute to an elevation in core body temperature (eg, exercising strenuously, exposure to extreme heat, receiving concomitant medication with anticholinergic activity, or being subject to dehydration) [14].

3.3.3.K] Serum [triglycerides](#) raised

- 1) Summary
- a) Elevations in serum [triglycerides](#) have been observed, at times a greater than 500 mg/dL (6 mmol/L) increase, during treatment with [olanzapine/fluoxetine](#) hydrochloride. Baseline and follow-up lipid monitoring of lipids is recommended in patients on [olanzapine/fluoxetine](#) [14].
- 2) Incidence: adult, up to 67.8%; pediatric, up to 84.6% [2]
- 3) Adults
- a) The table below provides the frequency and degree of increase of nonfasting [triglycerides](#) in adults on [olanzapine/fluoxetine](#) from controlled clinical studies of up to 12 weeks[14]:

Nonfasting Triglycerides In Adults on Olanzapine/Fluoxetine			
Category	Change from Baseline	Treatment Arm	N
			Portion of Patient

Increase by 50 mg/dL (0.6 mmol/L) or more	olanzapine/fluoxetine	174	67.8%
olanzapine	172	72.7%	
Normal to High	olanzapine/fluoxetine	57	0%
olanzapine	58	0%	
Borderline to High	olanzapine/fluoxetine	106	15.1%
olanzapine	103	8.7%	
KEY: mg/dL = milligrams/deciliter; mmol/L = millimole/liter; Normal = less than 150 mg/dL (1.7 mmol/L); borderline = 150 mg/dL (1.7 mmol/L) to less than 500 mg/dL (6 mmol/L); High = 500 mg/dL (6 mmol/L) or greater			

b) In an analysis of 5 placebo-controlled olanzapine monotherapy studies of up to 12 weeks duration, the mean fasting triglycerides increased from baseline by 20.8 mg/dL (0.235 mmol/L) in olanzapine-treated patients compared with decreases from baseline of 10.7 mg/dL (0.121 mmol/L) for placebo-treated patients. In long-term olanzapine studies of at least 48 weeks, patients had increases from baseline in mean fasting triglycerides of 18.7 mg/dL (0.211 mmol/L). The proportion of olanzapine-treated patients who had at least one change in triglycerides from normal or borderline to high was greater in long-term studies as compared with short-term studies. Over a median exposure of 9.2 months in phase 1 of the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE), the mean increase in triglycerides in olanzapine-treated patients was 40.5 mg/dL (0.457 mmol/L). The table below provides the frequency and degree of increase of fasting triglycerides in adults[14]:

Fasting Triglycerides In
Adults on Olanzapine-
Monotherapy

Category Change from Baseline	Up to 12 weeks exposure Treatment Arm	At least 48 weeks exposure N	Portion of Patients	N	Portion
Increase by 50 mg/dL (0.6 mmol/L) or more	olanzapine	745	39.6%	487	61.4%
placebo	402	26.1%	NA	NA	
Normal to High	olanzapine	457	9.2%	293	32.4%
placebo	251	4.4%	NA	NA	
Borderline to High	olanzapine	135	39.3%	75	70.7%
placebo	65	20%	NA	NA	
Increase by 40 mg/dL (0.5 mmol/L) or more	olanzapine	745	21.6%	489	32.9%
placebo	402	9.5%	NA	NA	
KEY: mg/dL = milligrams/deciliter; mmol/L = millimole/liter; Normal = less than 150 mg/dL (1.7 mmol/L); Borderline = 150 mg/dL (1.7 mmol/L) to less than 200 mg/dL (2 mmol/L); High = 200 mg/dL (2 mmol/L) or greater; NA = Not Applicable					

c) Random [triglyceride](#) levels of 1000 mg/dL (10 mmol/L) or more have been reported during postmarketing reports with [olanzapine](#) or [fluoxetine](#) monotherapy [14].

d) Patients (n=25) receiving [olanzapine](#) were found to have increases in body weight and serum [triglycerides](#) [27]. In an open study, patients receiving [olanzapine](#) (mean dose 13.8 mg) had their weight, cholesterol, and [triglycerides](#) measured at baseline and after 12 weeks. Weight increased by a mean of 5.4 kg. Cholesterol levels increased by only 3 mg/dL (0.08 mmol/L) while [triglyceride](#) levels increased by 60 mg/dL (0.7 mmol/L). The [triglyceride](#) change was highly associated with weight change (p less than 0.02).

e) After an average of 16 months of [olanzapine](#) therapy, 9 patients had marked increases in [triglyceride](#) levels [28]. [Triglyceride](#) levels increased from a mean of 170 mg/dL (1.9 mmol/L) to a mean of 240 mg/dL (2.7 mmol/L). Five patients had at least a 50% increase in levels. Cholesterol levels remained essentially unchanged. The patients had a mean weight gain of 10 kg.

4) Children and Adolescents

a) The mean change in fasting [triglyceride](#) levels for patients 10 to 17 years of age treated with the [olanzapine](#) and [fluoxetine](#) combination was an increase of 35.4 mg/dL (0.4 mmol/L) compared with a decrease of 3.5 mg/dL (0.04 mmol/L) for patients treated with placebo in an 8-week, randomized, double-blind clinical trial for acute treatment of [depressive episodes](#) associated with bipolar I disorder. The table below provides the frequency and degree of increase of fasting [triglycerides](#) in this study[2]:

Fasting Triglycerides In Children and Adolescents

Category Change from Baseline	Treatment Arm	N	Portion of Patients
Increase by 50 mg/dL (0.6 mmol/L) or more	OFC	158	70.3%
placebo	81	38.3%	
Normal to High	OFC	71	39.4%
placebo	31	19.4%	
Borderline to High	OFC	13	84.6%
placebo	12	33.3%	
Normal/borderline to High	OFC	106	52.8%
placebo	56	25%	
Normal to Borderline/high	OFC	71	73.2%
placebo	31	41.9%	
Normal/borderline/high to Very High	OFC	158	2.5%
placebo	81	1.2%	

KEY: mg/dL = milligrams/deciliter; mmol/L = millimole/liter; OFC = olanzapine + fluoxetine combination; Normal = Normal = less than 90 mg/dL (1 mmol/L); Borderline = 90 mg/dL (1 mmol/L) to less than 130 mg/dL (1.5 mmol/L); High = 130 mg/dL (1.5 mmol/L) or greater; Very high = 500 mg/dL or greater (6 mmol/L); NA = Not Applicable

b) In an analysis of 3 placebo-controlled [olanzapine](#) monotherapy studies of up to 6 weeks duration in adolescents, the olanzapine-treated adolescents had increases from baseline in mean

fasting [triglycerides](#) of 28.4 mg/dL (0.321 mmol/L) compared with a decrease of 1.1 mg/dL (0.012 mmol/L) for placebo-treated adolescents. . In long-term [olanzapine](#) studies of at least 24 weeks, adolescents had increases from baseline in mean fasting [triglycerides](#) of 20.5 mg/dL (0.231 mmol/L). The table below provides the frequency and degree of increase of fasting [triglycerides](#)[2]:

Fasting Triglycerides In
Adolescents

Category Change from Baseline	Up to 6 weeks exposure Treatment Arm	At least 24 weeks exposure N	Portion of Patients	N	Portion of Patients
Increase by 50 mg/dL (0.6 mmol/L) or more	olanzapine	138	37%	122	45.9%
placebo	66	15.2%	NA	NA	
Normal to High	olanzapine	67	26.9%	66	36.4%
placebo	28	10.7%	NA	NA	
Borderline to High	olanzapine	37	59.5%	31	64.5%
placebo	17	35.3%	NA	NA	

KEY: mg/dL = milligrams/
deciliter; mmol/L =
millimole/liter; Normal =
less than 90 mg/dL (1 mmol/
L); Borderline = 90 mg/dL
(1 mmol/L) to less than 130
mg/dL (1.5 mmol/L); High
= 130 mg/dL (1.5 mmol/
L) or greater; NA = Not
Applicable

3.3.3.L] Weight increased

1) Summary

a) Weight gain is associated with [olanzapine](#) use. Increased weight occurred in 25% of adult patients who received [fluoxetine](#) and [olanzapine](#) (n=771) compared with 3% of patients who received placebo (n=477) in controlled clinical studies including [depressive episodes](#) associated with bipolar I disorder and treatment resistant depression. Increased weight was reported in 20% of patients 10 to 17 years of age treated with the [olanzapine](#) and [fluoxetine](#) combination (n=170) compared with 1% of patients treated with placebo (n=85) in an 8-week, randomized, double-blind clinical trial for acute treatment of [depressive episodes](#) associated with bipolar I disorder. Clinically significant weight gain was more common in children and adolescents treated with the [olanzapine](#) and [fluoxetine](#) combination compared with adults in short-term study data. Regular monitoring of weight should be performed. Before initiating [olanzapine](#) and [fluoxetine](#), consideration should be made to the potential consequences of weight gain [2].

2) Incidence: adult, 3% to 66%; pediatric, up to 54.7% [2]

3) Adults

a) In long-term clinical trials, weight gain (greater than 7% of their baseline weight) occurred in 66% of patients treated with [olanzapine/fluoxetine](#) (median days of exposure, 448; n=431) with the mean weight gain of 6.7 kg. Discontinuation due to weight gain in long-term exposure (48 weeks or more) occurred in 1.2% of [olanzapine/fluoxetine](#)-treated patients. In long-term [olanzapine](#) monotherapy studies, the mean weight gain was 5.6 kg (median days of exposure, 573) with 64% of patients who gaining at least 7% of their baseline weight. Discontinuation due to weight

gain occurred in 0.4% of olanzapine-treated patients in these long-term [olanzapine](#) monotherapy studies [14].

b) The mean weight changes were +4 kg and -0.3 kg for [olanzapine/fluoxetine](#) and placebo-treated patients, respectively, in an analysis of 7 short-term controlled clinical studies (2 of which were placebo-controlled). After a median duration of 6 weeks, 22% of [olanzapine/fluoxetine](#)-treated compared with 1.8% of placebo-treated patients (statistically significant) gained at least 7% of their baseline weight. After a median duration of 8 weeks, 3% of [olanzapine/fluoxetine](#)-treated compared with 0% of placebo-treated patients (statistically significant) gained at least 15% of their baseline weight. Baseline body mass index did not make a difference in the amount gained. The discontinuation rate due to weight gain was 2.5% and 0% in the [olanzapine/fluoxetine](#) and placebo treated patients, respectively [14].

c) In a single 8-week randomized, double-blind, fixed-dose study comparing [olanzapine](#) 10 mg/day (n=199), 20 mg/day (n=200), and 40 mg/day (n=200), mean baseline to endpoint increase in weight was 1.9 kg, 2.3 kg, and 3 kg, respectively, with significant differences between 10 vs 40 mg/day [14].

d) The table below provides the adult weight gain observed in [olanzapine](#) treated patients from 86 clinical olanzapine-trials [14] :

Olanzapine-Monotherapy Trials in Adults

Amount Gained	6 weeks	6 months	12 months	24 months
n=7465	n=4162	n=1345	n=474	n=147
0 kg gain or loss of weight	26.2%	24.3%	20.8%	23.2%
0 to 5 kg (0 to 11 lb)	57%	36%	26%	23.4%
greater than 5 to 10 kg (11 to 22 lb)	14.9%	24.6%	24.2%	24.1%
greater than 10 to 15 kg (22 to 33 lb)	1.8%	10.9%	14.9%	11.4%
greater than 15 to 20 kg (33 to 44 lb)	0.1%	3.1%	8.6%	9.3%
greater than 20 to 25 kg (44 to 55 lb)	0%	0.9%	3.3%	5.1%
greater than 25 to 30 kg (55 to 66 lb)	0%	0.2%	1.4%	2.3%
greater than 30 kg (greater than 66 lb)	0%	0.1%	0.8%	1.2%

Key: kg = kilograms; lb = pounds

e) Weight gain (39.8%) and increased appetite (32%) were reported following the administration of [olanzapine/fluoxetine](#) combination at mean doses of 7.5 and 46.1 mg/day, respectively [13].

f) Excessive appetite was seen more commonly with [olanzapine](#) therapy than with [haloperidol](#) (24% versus 12.4%, p less than 0.05). [Olanzapine](#) therapy was also associated with a clinically significant greater increase in weight over [haloperidol](#) therapy (p less than 0.001). However, a post hoc analysis revealed that body mass index was the predominant predictor of weight gain. Patients with a low prestudy body mass index were more likely to gain weight during [olanzapine](#) treatment. Treatment effect on weight change was consistent between male and female patients [24].

g) A prospective, multicenter, observational study showed that [olanzapine](#) treatment of outpatients (n=2128) with [schizophrenia](#) was safer than in a control group of patients (n=821) receiving a variety of other [antipsychotic drug therapies](#). Drugs used in the control group included [risperidone](#), [haloperidol](#), sertindole, zuclopenthixol, [fluphenazine](#), [thioridazine](#), [perphenazine](#), [pimozide](#), [clozapine](#), pipotiazine, sulpiride, [chlorpromazine](#), levomepromazine, clothiapine, and [lorazepam](#). Overall, [olanzapine](#) had a significantly lower incidence of adverse events than the control group (48% versus 64%, p less than 0.001). Somnolence and weight gain occurred significantly more frequently in olanzapine-treated patients. [Akathisia](#), [dystonia](#), extrapyramidal

syndrome, hypertonia, and tremor were significantly higher in the control group. Abnormal ejaculation and impotence occurred significantly more frequently in men in the control group. Over a 6-month period, fewer olanzapine-treated patients received a concomitant anticholinergic medication in comparison to patients in the control group (36% versus 58%, p less than 0.001) [25].

4) Children and Adolescents

a) The mean changes in weight for patients 10 to 17 years of age treated with the [olanzapine](#) and [fluoxetine](#) combination was an increase of 4.4 kg compared with an increase of 0.5 kg for patients treated with placebo in an 8-week, randomized, double-blind clinical trial for acute treatment of [depressive episodes](#) associated with bipolar I disorder. With 8-week exposure to combination [olanzapine](#) and [fluoxetine](#), the proportions of children and adolescents who gained at least 7%, 15%, or 25% of their baseline body weight were 52%, 14%, and 1%, respectively. The table below provides the frequency and degree of weight gain in this study [2]:

Weight Gain in Children and Adolescents from a Single Study of
Olanzapine and Fluoxetine in Bipolar Depression

Amount Gained n=170	Up to 8 weeks
0 kg gain or loss of weight	7.1%
0 to 5 kg (0 to 11 lb)	54.7%
greater than 5 to 10 kg (11 to 22 lb)	31.2%
greater than 10 to 15 kg (22 to 33 lb)	7.1%
greater than 15 to 20 kg (33 to 44 lb)	0%
greater than 20 to 25 kg (44 to 55 lb)	0%
greater than 25 to 30 kg (55 to 66 lb)	0%
greater than 30 kg (greater than 66 lb)	0%

Key: kg = kilograms; lb = pounds

b) An average weight gain of 4.6 kg in olanzapine-treated adolescents and 0.3 kg in placebo-treated adolescents was observed in an analysis of 4 placebo-controlled trials of adolescents (under the age of 18 years) treated with monotherapy [olanzapine](#) for a median duration of 3 weeks. After a median duration of 4 weeks, 40.6% of olanzapine-treated compared with 9.8% of placebo-treated patients gained at least 7% of their baseline weight. After a median duration of 19 weeks, 7.1% of olanzapine-treated compared with 2.7% of placebo-treated patients gained at least 15% of their baseline weight. The discontinuation rate due to weight gain was 1% and 0% in the [olanzapine](#) and placebo treated patients, respectively [14].

c) In long-term (24 weeks or more) [olanzapine](#) studies, 89% of adolescents gained at least 7% of their baseline weight (median days of exposure, 201) with the mean weight gain of 11.2 kg. Baseline body mass index (BMI) did not affect the amount gained. Discontinuation due to weight gain in long-term exposure occurred in 2.2% of olanzapine-treated patients[14].

d) The table below provides the adolescent weight gain with [olanzapine](#) treated patients from 6 clinical olanzapine-trials [14] :

Olanzapine-Monotherapy Trials in Adolescents

Amount Gained n=243	6 weeks n=191	6 months
0 kg gain or loss of weight	2.9%	2.1%
0 to 5 kg (0 to 11 lb)	47.3%	24.6%
greater than 5 to 10 kg (11 to 22 lb)	42.4%	26.7%
greater than 10 to 15 kg (22 to 33 lb)	5.8%	22%

greater than 15 to 20 kg (33 to 44 lb)	0.8%	12.6%
greater than 20 to 25 kg (44 to 55 lb)	0.8%	9.4%
greater than 25 to 30 kg (55 to 66 lb)	0%	2.1%
greater than 30 to 35 kg (66 to 77 lb)	0%	0%
greater than 35 to 40 kg (77 to 88 lb)	0%	0%
greater than 40 kg (greater than 88 lb)	0%	0.5%
Key: kg = kilograms; lb = pounds		

e) Adolescent patients taking [olanzapine](#) experienced greater weight gain and increased in body mass index (BMI) than patients taking [quetiapine](#) in a retrospective study involving 103 patients younger than 18 years of age. Patients received [olanzapine](#) (n=50, mean daily dose 13.9 mg) or [quetiapine](#) (n=53, mean daily dose 510.9 mg) for at least 2 weeks. Weight and height were measured at baseline and 14 or more days after baseline. Average weight gain from baseline in the [olanzapine](#) group was 3.8 kg (p less than 0.001) compared with 0.03 kg in the [quetiapine](#) group. Both the [olanzapine](#) and [quetiapine](#) groups showed slight, but significant, increases in height from baseline (0.006 meters, p=0.042 and 0.006 meters, p less than 0.001, respectively). After controlling for baseline differences, the mean weight change between groups was significant (3.4 kg, p less than 0.001). BMI increased by an average of 1.3 kg/m(2) in the [olanzapine](#) group (p less than 0.001) compared with a decreased of 0.2 kg/m(2) in the [quetiapine](#) group. After controlling for baseline differences, the mean difference in change in BMI was significant (0.9 kg/m(2), p=0.008) [26].

3.3.4] Gastrointestinal Effects

3.3.4.A] Abdominal distension

- 1) Incidence: 2% [12]
- 2) In short-term, controlled studies including [depressive episodes](#) associated with Bipolar I Disorder and treatment resistant depression, abdominal distension occurred in 2% of patients who received [fluoxetine/olanzapine](#) (n=771) compared with 0% of patients who received placebo (n=477) [12].

3.3.4.B] Constipation

- 1) Constipation was associated with [olanzapine/fluoxetine](#) in premarketing clinical studies [12].

3.3.4.C] Diarrhea

- 1) Incidence: 12.5% [13]
- 2) Dry mouth (37.1%), nausea (15.7%), and diarrhea (12.5%) have occurred following the administration of [olanzapine/fluoxetine](#) combination at mean doses of 7.5 and 46.1 milligrams/day, respectively [13].

3.3.4.D] Dysphagia

- 1) Antipsychotic drug use has been associated with [esophageal dysmotility](#) and aspiration. [Olanzapine/fluoxetine](#) is not approved for patients with [Alzheimer's disease](#) due to the risk of [aspiration pneumonia](#), a common cause of morbidity and mortality in these patients with advanced disease [12].

3.3.4.E] Flatulence

- 1) Incidence: 3% [12]
- 2) In short-term, controlled studies including [depressive episodes](#) associated with Bipolar I Disorder and treatment resistant depression, flatulence occurred in 3% of patients who received [fluoxetine/olanzapine](#) (n=771) compared with 1% of patients who received placebo (n=477) [12].

3.3.4.F] Gastrointestinal hemorrhage

1) Serotonin [norepinephrine](#) reuptake inhibitors (SNRIs) and SSRIs, including [fluoxetine](#), may increase the risk of bleeding reactions and concurrent use of [aspirin](#), NSAIDs, [warfarin](#) and other anticoagulants may increase this risk. Case reports and epidemiological studies, both of the case-control and cohort design, have demonstrated an association between use of drugs that interfere with serotonin reuptake and the occurrence of [gastrointestinal bleeding](#). Altered anticoagulant effects, including increased bleeding, have been reported with SNRIs or SSRIs when given concomitantly with [warfarin](#); however, single dose of [warfarin](#) 20 mg did not affect [olanzapine](#) pharmacokinetics. Likewise, single doses of [olanzapine](#) did not affect the pharmacokinetics of [warfarin](#). Bleeding reactions associated with SNRIs and SSRIs use have ranged from ecchymoses, [hematomas](#), [epistaxis](#) and [petechiae](#) to life-threatening hemorrhages. Patients receiving [warfarin](#) therapy should be carefully monitored when [olanzapine/fluoxetine](#) is initiated or discontinued [12].

2) Case reports have documented the occurrence of bleeding episodes in patients treated with psychotropic drugs that interfere with serotonin reuptake. Subsequent epidemiological studies, both of the case-control and cohort design, have demonstrated an association between use of psychotropic drugs that interfere with serotonin reuptake and the occurrence of [upper gastrointestinal bleeding](#). The same epidemiological studies also showed that concurrent use of an NSAID or [aspirin](#) potentiated the risk of bleeding. Patients should be cautioned regarding the risk of bleeding associated with the concomitant use of [olanzapine/fluoxetine](#) with NSAIDs, [aspirin](#), or other drugs that affect coagulation [12].

3.3.4.G] Increased appetite

1) Incidence: adult, 20%; pediatric, 17% [2]

2) In short-term, controlled studies including [depressive episodes](#) associated with bipolar I disorder and treatment resistant depression, increased appetite occurred in 20% of adult patients who received [fluoxetine/olanzapine](#) (n=771) compared with 4% of adult patients who received placebo (n=477) [2].

3) Increased appetite was reported in 17% of patients 10 to 17 years of age treated with the [olanzapine](#) and [fluoxetine](#) combination (n=170) compared with 1% of patients treated with placebo (n=85) in an 8-week, randomized, double-blind clinical trial for acute treatment of [depressive episodes](#) associated with bipolar I disorder [2].

3.3.4.H] Indigestion

1) Incidence: pediatric, 3% [2]

2) [Dyspepsia](#) was reported in 3% of patients 10 to 17 years of age treated with the [olanzapine](#) and [fluoxetine](#) combination (n=170) compared with 1% of patients treated with placebo (n=85) in an 8-week, randomized, double-blind clinical trial for acute treatment of [depressive episodes](#) associated with bipolar I disorder [2].

3.3.4.I] Nausea

1) Incidence: 15.7% [13]

2) Dry mouth (37.1%), nausea (15.7%), and diarrhea (12.5%) have occurred following the administration of [olanzapine/fluoxetine](#) combination at mean doses of 7.5 and 46.1 milligrams/day, respectively [13].

3.3.4.J] Xerostomia

1) Incidence: 15% to 37.1%[12][13]

2) In short-term, controlled studies including [depressive episodes](#) associated with Bipolar I Disorder and treatment resistant depression, dry mouth occurred in 15% of patients who received [fluoxetine/olanzapine](#) (n=771) compared with 6% of patients who received placebo (n=477) [12].

3J) Dry mouth (37.1%), nausea (15.7%), and diarrhea (12.5%) have occurred following the administration of [olanzapine/fluoxetine](#) combination at mean doses of 7.5 and 46.1 milligrams/day, respectively [13].

3.3.5] Hematologic Effects

3.3.5.A] Agranulocytosis

1J) [Agranulocytosis](#) has been reported with antipsychotic drugs, including [olanzapine](#), during clinical trials and postmarketing surveillance [11].

3.3.5.B] Aplastic anemia

1J) [Aplastic anemia](#) has been reported with [olanzapine](#) or [fluoxetine](#) monotherapy, but was not observed in [olanzapine/fluoxetine](#) treated patients during premarketing clinical studies [11].

3.3.5.C] Hemoglobin low

1J) Incidence: 2.6% [11]

2J) In [olanzapine/fluoxetine](#) clinical studies (including treatment resistant depression, [depressive episodes](#) associated with Bipolar I Disorder, [major depressive disorder](#) with [psychosis](#), or sexual dysfunction), low [hemoglobin](#) level occurred at a greater frequency (statistically significant) in the [olanzapine/fluoxetine](#)-treated patients compared with placebo (2.6% vs 0%) [11].

3.3.5.D] Leukopenia

1J) [Leukopenia/neutropenia](#) events have been reported with antipsychotic drugs, including [olanzapine](#), during clinical trials and postmarketing surveillance. Patients with preexisting low WBC count or history of drug-induced [leukopenia/neutropenia](#) may have an increased risk of a [leukopenia](#) or [neutropenia](#) event. If signs and symptoms of [leukopenia](#) occur, discontinuation of [olanzapine](#) may be necessary [11].

3.3.5.E] Lymphocytopenia

1J) Incidence: 1.9% [11]

2J) In [olanzapine/fluoxetine](#) clinical studies (including treatment resistant depression, [depressive episodes](#) associated with Bipolar I Disorder, [major depressive disorder](#) with [psychosis](#), or sexual dysfunction), low [lymphocytes](#) level occurred at a greater frequency (statistically significant) in the [olanzapine/fluoxetine](#)-treated patients compared with placebo (1.9% vs 0%) [11].

3.3.5.F] Neutropenia

1J) [Neutropenia](#) has been reported with [olanzapine](#) monotherapy, but was not observed in [olanzapine/fluoxetine](#) treated patients during premarketing clinical studies. [Neutropenia/leukopenia](#) events have been reported with antipsychotic drugs, including [olanzapine](#), during clinical trials and postmarketing surveillance. Patients with preexisting low WBC count or history of drug-induced [leukopenia/neutropenia](#) may have an increased risk of a [leukopenia](#) or [neutropenia](#) event. If signs and symptoms of [neutropenia](#) occur, discontinuation of [olanzapine](#) may be necessary. In patients who develop severe [neutropenia](#) (ANC less than 1000/mm(3)), [olanzapine](#) should be discontinued and WBC monitored until recovery [11].

3.3.5.G] Summary

1J) Decreased [hemoglobin](#) and low [lymphocyte](#) levels have been reported in clinical studies of [fluoxetine/olanzapine](#). [Aplastic anemia](#) has been reported with [fluoxetine](#) or [olanzapine](#) monotherapy but

not with the combination. [Neutropenia/leukopenia](#) events and [agranulocytosis](#) have been reported with antipsychotic drugs, including [olanzapine](#), during clinical trials and postmarketing surveillance. Patients with preexisting low WBC count or history of drug-induced [leukopenia/neutropenia](#) may have an increased risk of a [leukopenia](#) or [neutropenia](#) event. If signs and symptoms of [neutropenia](#) occur, discontinuation of [olanzapine](#) may be necessary. In patients who develop severe [neutropenia](#) (ANC less than 1000/mm(3)), [olanzapine](#) should be discontinued and WBC monitored until recovery [11].

3.3.6] Hepatic Effects

3.3.6.A] [ALT/SGPT](#) level raised

1) Incidence: adults, 5%; pediatrics, 45.9% [2]

2) As with [olanzapine](#), asymptomatic elevations of hepatic transaminases ([ALT](#) (SGPT), [AST](#) (SGOT), and [gamma-glutamyltransferase \(GGT\)](#)) and [alkaline phosphatase](#) have been observed with [olanzapine](#) and [fluoxetine](#) combination. In the [olanzapine](#) and [fluoxetine](#)-controlled database, [ALT](#) (SGPT) elevations (greater than or equal to 3 times the upper limit of the normal range) were observed in 5% (38/698) of patients exposed to [olanzapine](#) and [fluoxetine](#) compared with 0.5% (2/378) of the placebo patients and 4% (33/751) of [olanzapine](#)-treated patients. [ALT](#) (SGPT) elevations 5 or more times the upper limit of normal were found in 2% (11/701) of patients treated with [olanzapine](#) and [fluoxetine](#) compared with 0.3% (1/379) of placebo-treated patients and 1% (11/760) of [olanzapine](#)-treated patients. At last follow-up, elevated [ALT](#) (SGPT) values had decreased or returned to normal range in most patients who either stopped or remained on [olanzapine](#) and [fluoxetine](#) therapy. There were no incidents of [jaundice](#), [liver failure](#), or events meeting Hy's rule criteria among patients with elevated [ALT](#) (SGPT) values [2].

3) Elevated [ALT](#) (from normal or low at baseline to abnormal at any time during the study) was reported in 45.9% of patients 10 to 17 years of age treated with the [olanzapine](#) and [fluoxetine](#) combination (n=170) compared with 2.5% of patients treated with placebo (n=85) in an 8-week, randomized, double-blind clinical trial for acute treatment of [depressive episodes](#) associated with bipolar I disorder [2].

3.3.6.B] [AST/SGOT](#) level raised

1) Incidence: pediatric, 33.7% [2]

2) Elevated [AST](#) (from normal or low at baseline to abnormal at any time during the study) was reported in 33.7% of patients 10 to 17 years of age treated with the [olanzapine](#) and [fluoxetine](#) combination (n=170) compared with 7.6% of patients treated with placebo (n=85) in an 8-week, randomized, double-blind clinical trial for acute treatment of [depressive episodes](#) associated with bipolar I disorder [2].

3.3.6.C] [Cholestatic hepatitis](#)

1) In the postmarketing period, there have been rare reports of [hepatitis](#) and very rare cases of [cholestatic](#) or mixed [liver injury](#) [4].

2) [Jaundice](#) and [cholestatic jaundice](#) have been reported with [olanzapine](#) or [fluoxetine](#) monotherapy, but was not observed in [olanzapine/fluoxetine](#) treated patients during premarketing clinical studies [4].

3.3.6.D] Decreased [bilirubin](#) level

1) Incidence: 15% [4]

2) In [olanzapine/fluoxetine](#) clinical studies (including treatment resistant depression, [depressive episodes](#) associated with Bipolar I Disorder, [major depressive disorder](#) with [psychosis](#), or sexual dysfunction), low [total bilirubin](#) level occurred at a greater frequency (statistically significant) in the [olanzapine/fluoxetine](#)-treated patients compared with placebo (15% vs 4%) [4].

3.3.6.E] Hepatitis

1) In the postmarketing period, there have been rare reports of [hepatitis](#) and very rare cases of cholestatic or mixed [liver injury](#) [4].

3.3.6.F] Increased liver function test

1) Incidence: pediatrics, 9% [2]

2) As with [olanzapine](#), asymptomatic elevations of hepatic transaminases ([ALT](#) (SGPT), [AST](#) (SGOT), and [gamma-glutamyltransferase](#) ([GGT](#))) and [alkaline phosphatase](#) have been observed with [olanzapine](#) and [fluoxetine](#) combination. In the [olanzapine](#) and fluoxetine-controlled database, [ALT](#) (SGPT) elevations (greater than or equal to 3 times the upper limit of the normal range) were observed in 5% (38/698) of patients exposed to [olanzapine](#) and [fluoxetine](#) compared with 0.5% (2/378) of the placebo patients and 4% (33/751) of olanzapine-treated patients. [ALT](#) (SGPT) elevations 5 or more times the upper limit of normal were found in 2% (11/701) of patients treated with [olanzapine](#) and [fluoxetine](#) compared with 0.3% (1/379) of placebo-treated patients and 1% (11/760) of olanzapine-treated patients. At last follow-up, elevated [ALT](#) (SGPT) values had decreased or returned to normal range in most patients who either stopped or remained on [olanzapine](#) and [fluoxetine](#) therapy. There were no incidents of [jaundice](#), [liver failure](#), or events meeting Hy's rule criteria among patients with elevated [ALT](#) (SGPT) values [2].

3) Increased hepatic enzymes, including increased [alanine aminotransferase](#), increased [AST](#), [abnormal liver function](#) test, increased [gamma-glutamyltransferase](#), and increased [transaminases](#), were reported in 9% of patients 10 to 17 years of age treated with the [olanzapine](#) and [fluoxetine](#) combination (n=170) compared with 1% of patients treated with placebo (n=85) in an 8-week, randomized, double-blind clinical trial for acute treatment of [depressive episodes](#) associated with bipolar I disorder [2].

3.3.7] Immunologic Effects**3.3.7.A] Drug reaction with [eosinophilia](#) and systemic symptoms****1) General Information**

a) Drug reaction with [eosinophilia](#) and systemic symptoms (DRESS), a rare and potentially fatal severe skin reaction, has been reported with [olanzapine](#) [10].

b) Presentation generally includes 3 or more of the following: A cutaneous reaction (eg, rash, [exfoliative dermatitis](#)), [eosinophilia](#), fever, and [lymphadenopathy](#) with a systemic complication of [hepatitis](#), [myocarditis](#), [pericarditis](#), [nephritis](#), [pancreatitis](#), or [pneumonitis](#) [10].

c) Potentially fatal drug reaction with a mortality rate of up to 10% [10].

2) Management

a) Immediately discontinue treatment if DRESS is suspected [10].

b) Consider treatment with systemic corticosteroids in cases with extensive organ involvement [10].

3) Adult Case Reports

a) Since marketing approval of the first [olanzapine](#) product in 1996, 23 case reports of DRESS have been identified by the US Food and Drug Administration, including one fatality. Median time to onset was 19 days after [olanzapine](#) initiation, and median duration of [olanzapine](#) treatment was 2 months. The median [olanzapine](#) dose was 20 mg/day, but DRESS was reported at doses as low as 5 mg/day. Among the 22 serious, nonfatal cases, 18 patients required hospitalization.

Symptoms completely resolved after [olanzapine](#) discontinuation in 9 patients, and laboratory confirmation for an [olanzapine allergic reaction](#) was obtained for 6 patients [10].

b) Olanzapine-induced hypersensitivity syndrome, consisting of fever, rash, [eosinophilia](#) and [toxic hepatitis](#), has been reported in a 34-year-old man 60 days after initiation of [olanzapine](#) therapy. Symptoms resolved following the discontinuation of [olanzapine](#). Skin and liver biopsies confirmed drug-induced hypersensitivity syndrome [29].

3.3.7.B] Hypersensitivity reaction

1) In premarketing controlled clinical studies, the overall incidence of rash or allergic events in treated patients (4.6% (26/571)) was similar to that of placebo (5.2% (25/477)). The majority of the cases of rash and/or [urticaria](#) were mild; however, three patients discontinued (one due to rash, which was moderate in severity, and two due to allergic events, one of which included face edema). In [fluoxetine](#) US clinical studies, 7% of 10,782 fluoxetine-treated patients developed various types of rashes and/or [urticaria](#) [12].

2) Among the cases of rash and/or [urticaria](#) reported in premarketing clinical studies, almost a third were withdrawn from treatment because of the rash and/or systemic signs or symptoms associated with the rash. Clinical findings reported in association with rash include fever, [leukocytosis](#), arthralgias, edema, [carpal tunnel syndrome](#), respiratory distress, [lymphadenopathy](#), [proteinuria](#), and mild transaminase elevation. Most patients improved promptly with discontinuation of [fluoxetine](#) and/or adjunctive treatment with antihistamines or steroids, and all patients experiencing these events were reported to recover completely [12].

3) In [fluoxetine](#) premarketing clinical studies, 2 patients are known to have developed a serious cutaneous systemic illness. In neither patient was there an unequivocal diagnosis, but 1 was considered to have a [leukocytoclastic vasculitis](#), and the other, a severe desquamating syndrome that was considered variously to be a [vasculitis](#) or [erythema multiforme](#). Other patients have had systemic syndromes suggestive of [serum sickness](#). Since the introduction of [fluoxetine](#), systemic events, possibly related to [vasculitis](#), have developed in patients with rash. Although these events are rare, they may be serious, involving the lung, kidney, or liver. Death has been reported to occur in association with these systemic events [12].

4) Anaphylactoid events, including [bronchospasm](#), [angioedema](#), and [urticaria](#) alone and in combination, have been reported. Pulmonary events, including inflammatory processes of varying histopathology and/or fibrosis, have been reported rarely. These events have occurred with dyspnea as the only preceding symptom. Whether these systemic events and rash have a common underlying cause or are due to different etiologies or pathogenic processes is not known. Furthermore, a specific underlying immunologic basis for these events has not been identified. Upon the appearance of rash or of other possible allergic phenomena for which an alternative etiology cannot be identified, the drug should be discontinued [12].

3.3.8] Musculoskeletal Effects

3.3.8.A] Arthralgia

1) Incidence: 4% [12]

2) In short-term, controlled studies including [depressive episodes](#) associated with Bipolar I Disorder and treatment resistant depression, arthralgia occurred in 4% of patients who received [fluoxetine/olanzapine](#) (n=771) compared with 1% of patients who received placebo (n=477) [12].

3.3.8.B] Muscle rigidity

1) Incidence: 2% [12]

2)) In short-term, controlled studies including [depressive episodes](#) associated with Bipolar I Disorder and treatment resistant depression, musculoskeletal stiffness occurred in 2% of patients who received [fluoxetine/olanzapine](#) (n=771) compared with 1% of patients who received placebo (n=477) [12].

3.3.8.C) Pain, Extremity

1)) Incidence: 3% [12]

2)) In short-term, controlled studies including [depressive episodes](#) associated with Bipolar I Disorder and treatment resistant depression, pain in extremity occurred in 3% of patients who received [fluoxetine/olanzapine](#) (n=771) compared with 1% of patients who received placebo (n=477) [12].

3.3.9) Neurologic Effects

3.3.9.A) Asthenia

1)) Incidence: 3% to 19.3% [12][13]

2)) In short-term, controlled studies including [depressive episodes](#) associated with Bipolar I Disorder and treatment resistant depression, asthenia occurred in 3% of patients who received [fluoxetine/olanzapine](#) (n=771) compared with 1% of patients who received placebo (n=477) [12].

3)) Asthenia was reported in 19.3% of patients following the administration of [olanzapine/fluoxetine](#) combination at mean doses of 7.5 and 46.1 mg/day, respectively, in a 76-week, open-label study of patients with [major depressive disorder](#) (n=560) [13].

3.3.9.B) Cerebrovascular accident

1)) In trials of [olanzapine](#) in elderly patients with dementia-related [psychosis](#), cerebrovascular adverse events, such as [stroke](#), and [transient ischemic attack](#), including fatalities were reported. In placebo-controlled trials, the incidence of cerebrovascular adverse events was significantly higher in patients treated with [olanzapine](#) compared with patients treated with placebo [12].

3.3.9.C) Dizziness

1)) Incidence: 1.6% to 12.5% [12][13]

2)) In a single 8-week randomized, double-blind, fixed-dose study comparing [olanzapine](#) 10 mg/day (n=199), 20 mg/day (n=200), and 40 mg/day (n=200), dizziness was reported at 2.6%, 1.6%, and 6.6%, respectively, with significant differences between 20 vs 40 mg/day [12].

3)) Dizziness was reported in 12.5% of patients following the administration of [olanzapine/fluoxetine](#) combination at mean doses of 7.5 and 46.1 milligrams/day, respectively, in a 76-week, open-label study of patients with [major depressive disorder](#) (n=560) [13]

3.3.9.D) Dyskinesia

1)) A syndrome of potentially irreversible, involuntary, dyskinetic movements ([tardive dyskinesia](#)) may develop in patients treated with antipsychotic drugs. Although the prevalence of the syndrome appears to be highest among the elderly, especially elderly women, it is impossible to rely upon prevalence estimates to predict, at the inception of antipsychotic treatment, which patients are likely to develop the syndrome. Whether antipsychotic drug products differ in their potential to cause [tardive dyskinesia](#) is unknown. The risk of developing [tardive dyskinesia](#) and the likelihood that it will become irreversible are believed to increase as the duration of treatment and the total cumulative dose of antipsychotic drugs administered to the patient increase. However, the syndrome can develop, although much less commonly, after relatively brief treatment periods at low doses or may even arise after discontinuation of treatment [12].

2) The incidence of dyskinetic movement in olanzapine/fluoxetine-treated patients was infrequent. The mean score on the Abnormal Involuntary Movement Scale (AIMS) across clinical studies involving olanzapine/fluoxetine-treated patients decreased from baseline. Nonetheless, olanzapine/fluoxetine should be prescribed in a manner that is most likely to minimize the risk of tardive dyskinesia. If signs and symptoms of tardive dyskinesia appear in a patient on olanzapine/fluoxetine, drug discontinuation should be considered. However, some patients may require treatment with olanzapine/fluoxetine despite the presence of the syndrome. The need for continued treatment should be reassessed periodically [12].

3) Dyskinesia has been reported with olanzapine or fluoxetine monotherapy, but was not observed in olanzapine/fluoxetine treated patients during premarketing clinical studies [12].

3.3.9.E] Headache

1) Incidence: up to 23.3% [13]

2) Headache was reported in 23.3% of patients following the administration of olanzapine/fluoxetine combination at mean doses of 7.5 and 46.1 mg/day, respectively, in a 76-week, open-label study of patients with major depressive disorder (n=560) [13].

3.3.9.F] Impaired cognition

1) Sedation-related adverse events were commonly reported with olanzapine and fluoxetine treatment, occurring at an incidence of 26.6% in adult patients treated with olanzapine and fluoxetine compared with 10.9% in placebo-treated patients. Sedation-related adverse events (somnolence, hypersomnia, and lethargy) led to discontinuation in 2% (15/771) of patients during controlled clinical studies. As with any CNS-active drug, the olanzapine and fluoxetine combination has the potential to impair judgment, thinking, or motor skills. Patients should be cautioned about operating hazardous machinery, including automobiles, until they are reasonably certain that olanzapine/fluoxetine therapy does not affect them adversely [2].

2) Somnolence-related adverse events was reported in 24% of patients 10 to 17 years of age treated with the olanzapine and fluoxetine combination (n=170) compared with 2% of patients treated with placebo (n=85) in an 8-week, randomized, double-blind clinical trial for acute treatment of depressive episodes associated with bipolar I disorder. Somnolence-related adverse events, including sedation and hypersomnia, led to discontinuation in 1.2% (2 of 170) of patients treated with olanzapine and fluoxetine in this study [2].

3.3.9.G] Insomnia

1) Incidence: up to 11.8% [13]

2) Insomnia was reported in 11.8% of patients following the administration of olanzapine/fluoxetine combination at mean doses of 7.5 and 46.1 mg/day, respectively, in a 76-week, open-label study of patients with major depressive disorder (n=560) [13].

3.3.9.H] Seizure

1) Incidence: 0.2% [12]

2) Seizures occurred in 0.2% (4/2547) of olanzapine/fluoxetine-treated patients during open-label clinical studies. No seizures occurred in the controlled olanzapine/fluoxetine studies. Seizures have also been reported with both olanzapine and fluoxetine monotherapy. Therefore, olanzapine/fluoxetine should be used cautiously in patients with a history of seizures or with conditions that potentially lower the seizure threshold. Conditions that lower the seizure threshold may be more prevalent in a population of greater than or equal to 65 years of age [12].

3J) There have been rare reports of prolonged seizures in patients on [fluoxetine](#) receiving [electroconvulsive therapy](#) (ECT), even though there are no clinical studies establishing the benefit of the combined use of ECT and [fluoxetine](#) [12].

3.3.9.I] Somnolence

1J) Incidence: adult, 27%; pediatric, 24% [2]

2J) Somnolence, including sedation, hypersomnia, and lethargy, occurred in 27% of patients who received [fluoxetine](#) and [olanzapine](#) (n=771) compared with 11% of patients who received placebo (n=477) in controlled clinical studies including [depressive episodes](#) associated with bipolar I disorder and treatment resistant depression [2].

3J) Somnolence, including sedation and hypersomnia, was reported in 24% of patients 10 to 17 years of age treated with the [olanzapine](#) and [fluoxetine](#) combination (n=170) compared with 2% of patients treated with placebo (n=85) in an 8-week, randomized, double-blind clinical trial for acute treatment of [depressive episodes](#) associated with bipolar I disorder [2].

3.3.9.J] Tremor

1J) Incidence: 9% [2]

2J) In short-term, controlled studies including [depressive episodes](#) associated with Bipolar I Disorder and treatment resistant depression, tremor occurred in 9% of patients who received [fluoxetine/olanzapine](#) (n=771) compared with 3% of patients who received placebo (n=477) [12].

3J) Tremor was reported in 9% of patients 10 to 17 years of age treated with the [olanzapine](#) and [fluoxetine](#) combination (n=170) compared with 1% of patients treated with placebo (n=85) in an 8-week, randomized, double-blind clinical trial for acute treatment of [depressive episodes](#) associated with bipolar I disorder [2].

3.3.10] Ophthalmic Effects

3.3.10.A] Angle-closure glaucoma

1J) General Information

aJ) May occur with antidepressant treatment in patients with anatomically narrow angles without patent [iridectomy](#) [9]

3.3.10.B] Blurred vision

1J) Incidence: 5% [12]

2J) In short-term, controlled studies including [depressive episodes](#) associated with Bipolar I Disorder and treatment resistant depression, blurred vision occurred in 5% of patients who received [fluoxetine/olanzapine](#) (n=771) compared with 2% of patients who received placebo (n=477) [12].

3.3.12] Psychiatric Effects

3.3.12.A] Anxiety

1J) Incidence: adult, 13.9% [13]; pediatric, 3% [2]

2J) Anxiety was reported in 13.9% of adult patients following the administration of [olanzapine/fluoxetine](#) combination at mean doses of 7.5 and 46.1 mg/day, respectively, in a 76-week, open-label study of patients with [major depressive disorder](#) (n=560) [13].

3J) Anxiety was reported in 3% of patients 10 to 17 years of age treated with the [olanzapine](#) and [fluoxetine](#) combination (n=170) compared with 1% of patients treated with placebo (n=85) in an 8-week, randomized, double-blind clinical trial for acute treatment of [depressive episodes](#) associated with bipolar I disorder [2].

3.3.12.B] Depression, Worsening

1) All patients being treated with antidepressants for any indication should be monitored appropriately and observed closely for clinical worsening, suicidality and unusual changes in behavior, in particular during the first few months or at times of dose increase or decrease [2].

2) Adult and pediatric patients who experience symptoms of anxiety, agitation, panic attacks, insomnia, irritability, hostility (aggressiveness), impulsivity, [akathisia](#) (psychomotor restlessness), [hypomania](#), or mania may be at risk of worsening of their depression. This same concern applies to treating patients with other psychiatric and nonpsychiatric disorders. If these symptoms are observed, therapy should be reevaluated and it may be necessary to discontinue medications when symptoms are severe, sudden in onset, or were not part of the patient's initial symptoms [32].

3.3.12.C] Disturbance in thinking

1) Incidence: 2% [12]

2) In short-term, controlled studies including [depressive episodes](#) associated with Bipolar I Disorder and treatment resistant depression, abnormal thinking occurred in 2% of patients who received [fluoxetine/olanzapine](#) (n=771) compared with 1% of patients who received placebo (n=477) [12].

3.3.12.D] Disturbance of attention

1) Incidence: 5% [12]

2) In short-term, controlled studies including [depressive episodes](#) associated with Bipolar I Disorder and treatment resistant depression, disturbance in attention occurred in 5% of patients who received [fluoxetine/olanzapine](#) (n=771) compared with 1% of patients who received placebo (n=477) [12].

3.3.12.E] Feeling nervous

1) Incidence: 2% to 11.6% [12][13]

2) In short-term, controlled studies including [depressive episodes](#) associated with Bipolar I Disorder and treatment resistant depression, nervousness occurred in 2% of patients who received [fluoxetine/olanzapine](#) (n=771) compared with 1% of patients who received placebo (n=477) [12].

3) Nervousness was reported in 11.6% of patients following the administration of [olanzapine/fluoxetine](#) combination at mean doses of 7.5 and 46.1 milligrams/day, respectively, in a 76-week, open-label study of patients with [major depressive disorder](#) (n=560) [13]

3.3.12.F] Mania

1) In the 3 [bipolar depression](#) studies, there was no statistically significant difference in the incidence of manic events (manic reaction or manic depressive reaction) for patients who received the [olanzapine](#) and [fluoxetine](#) combination compared with placebo-treated patients. In one of the studies in adults, the incidence of manic events was 7% (3 of 43) in patients treated with [olanzapine](#) and fluoxetine-compared with 3% (5 of 184) placebo-treated patients. In the other adult study, the incidence of manic events was 2% (1 of 43) of patients treated with [olanzapine](#) and [fluoxetine](#) compared with 8% (15 of 193) of placebo-treated patients. The incidence of manic reactions for patients 10 to 17 years of age treated with the [olanzapine](#) and [fluoxetine](#) combination was 1% (2 of 170) compared with 0% of patients treated with placebo (n=84) in an 8-week, randomized, double-blind clinical trial for acute treatment of [depressive episodes](#) associated with bipolar I disorder. Because of the cyclical nature of [bipolar disorder](#), patients should be monitored closely for the development of symptoms of mania/[hypomania](#) during treatment with [olanzapine/fluoxetine](#) [2].

3.3.12.G] Restlessness

1) Incidence: adult, 4%; pediatric, 3% [2]

2) In short-term, controlled studies including depressive episodes associated with Bipolar I Disorder and treatment resistant depression, restlessness occurred in 4% of patients who received fluoxetine/olanzapine (n=771) compared with 1% of patients who received placebo (n=477) [2].

3) Restlessness was reported in 3% of patients 10 to 17 years of age treated with the olanzapine and fluoxetine combination (n=170) compared with 1% of patients treated with placebo (n=85) in an 8-week, randomized, double-blind clinical trial for acute treatment of depressive episodes associated with bipolar I disorder [2].

3.3.12.H] Suicidal thoughts

1) Incidence: pediatric, 2% [2]

2) Adults

a) No clinically significant differences in the risk of suicide and suicide attempts were observed across antidepressant agents and antidepressant classes in a 9-year, population-based cohort study consisting 287,543 adults. Based on the health care utilization data, the overall combined event rates of suicide death or hospitalization due to self harm ranged from 4.41 to 9.09 per 1000 person years. Among patients who received fluoxetine (n=22,207; 10,872 person-years), suicide occurred at an event rate of 0.92/1000 person-years (95% confidence interval (CI), 0.44 to 1.69) and suicide attempts occurred at a rate of 6.35/1000 person-years (95% CI, 4.94 to 8.03). Based on data among treatment-naïve patients alone (no antidepressant use in the past 3 years; n=10,953; 5728 person-years), suicide occurred at a rate of 1.05/1000 person-years (95% CI, 0.38 to 2.28) and suicide attempts occurred at a rate of 4.89/1000 person-years (95% CI, 3.25 to 7.06). Most events were reported within the first 6 months after start of therapy [30].

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

3) Pediatrics

a) A causal role for antidepressants in inducing suicidality has been established in pediatric patients. While the fluoxetine and olanzapine combination is not approved for use in children less than 10 years of age [2], anyone considering the use of antidepressants in a child or adolescent must balance this risk with the clinical need. In pooled analyses of 24 short-term, placebo-controlled trials of nine antidepressants (citalopram, fluoxetine, fluvoxamine, paroxetine, sertraline, bupropion, mirtazapine, nefazodone, and venlafaxine extended-release) including over 4400 pediatric patients with major depressive disorder (MDD), obsessive compulsive disorder (OCD), or other psychiatric disorders, a greater risk of suicidal behavior or ideation during the first few months of therapy was demonstrated in patients receiving antidepressants as compared with placebo (4% vs 2%). The risk of suicidality was most consistently observed in the trials that included patients with MDD, but there were signs of risk emerging from trials in other psychiatric indications, such as obsessive compulsive disorder and social anxiety disorder. No

suicides occurred in these trials. The risk of suicidality during longer-term use (ie, beyond several months) in pediatric patients is not known [31].

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

c) [Suicidal ideation](#) was reported in 2% of patients 10 to 17 years of age treated with the [olanzapine](#) and [fluoxetine](#) combination (n=170) compared with 1% of patients treated with placebo (n=85) in an 8-week, randomized, double-blind clinical trial for acute treatment of [depressive episodes](#) associated with bipolar I disorder [2].

4) Management

a) Adult and pediatric patients being treated with antidepressants for [major depressive disorder](#) who experience symptoms of anxiety, agitation, panic attacks, insomnia, irritability, hostility (aggressiveness), impulsivity, [akathisia](#) (psychomotor restlessness), [hypomania](#), or mania may be at risk of [suicidal ideation](#) and behavior (suicidality). This same concern applies to treating patients with other psychiatric and nonpsychiatric disorders. If these symptoms are observed, therapy should be reevaluated and it may be necessary to discontinue medications when symptoms are severe, sudden in onset, or were not part of the patient's initial symptoms. Closely monitor patients especially during the initial few months of therapy or at times of dose changes [32].

3.3.12.I] Suicide

1) The possibility of a suicide attempt is inherent in [bipolar disorder](#) and may persist until significant remission occurs. Close supervision of high-risk patients should accompany drug therapy. Prescriptions for [olanzapine/fluoxetine](#) should be written for the smallest quantity consistent with good patient management in order to reduce the risk of overdose. There were reports of suicides during clinical trials in adults, but the number was not sufficient to reach any conclusion about drug effect on suicide [12].

2) No clinically significant differences in the risk of suicide and suicide attempts were observed across antidepressant agents and antidepressant classes in a 9-year, population-based cohort study consisting 287,543 adults. Based on the health care utilization data, the overall combined event rates of suicide death or hospitalization due to self harm ranged from 4.41 to 9.09 per 1000 person years. Among patients who received [fluvoxamine](#) (n=9690; 4182 person-years), suicide occurred at an event rate of 0.95/1000 person-years (95% confidence interval (CI), 0.26 to 2.44) and suicide attempts occurred at a rate of 8.37/1000 person-years (95% CI, 5.83 to 11.64). Based on data among treatment-naïve patients alone (no antidepressant use in the past 3 years; n=4032; 1858 person-years), suicide occurred at a rate of 1.08/1000 person-years (95% CI, 0.13 to 3.88) and suicide attempts occurred at a rate of 5.92/1000 person-years (95% CI, 2.96 to 10.59). Following an extensive propensity score adjustment in comparison with [fluoxetine](#) hydrochloride, [fluvoxamine](#) had an overall hazard ratio of 1.35 (95% CI, 0.55 to 3.35). Most events were reported within the first 6 months after start of therapy [30].

3.3.12.J] Violent behavior

1) Violent behaviors have been reported with [olanzapine](#) or [fluoxetine](#) monotherapy, but was not observed in [olanzapine/fluoxetine](#) treated patients during premarketing clinical studies [12].

3.3.13] Renal Effects

3.3.13.A] Glycosuria

1) Incidence: 4.4% [12]

2) In an analysis of 6 controlled clinical studies, glycosuria were reported at 4.4% in patients treated with [olanzapine/fluoxetine](#) compared with 1.4% in patients receiving placebo [12].

3.3.13.B] Increased uric acid level

1) Incidence: 2.9% [12]

2) In [olanzapine/fluoxetine](#) clinical studies (including treatment resistant depression, [depressive episodes](#) associated with Bipolar I Disorder, [major depressive disorder](#) with [psychosis](#), or sexual dysfunction), elevated uric acid level occurred at a greater frequency (statistically significant) in the [olanzapine/fluoxetine](#)-treated patients compared with placebo (2.9% vs 0.5%) [12].

3.3.13.C] Serum [blood urea nitrogen](#) raised

1) Incidence: 2.8% [12]

2) In [olanzapine/fluoxetine](#) clinical studies (including treatment resistant depression, [depressive episodes](#) associated with Bipolar I Disorder, [major depressive disorder](#) with [psychosis](#), or sexual dysfunction), elevated urea nitrogen level occurred at a greater frequency (statistically significant) in the [olanzapine/fluoxetine](#)-treated patients compared with placebo (2.8% vs 0.8%) [12].

3.3.14] Reproductive Effects

3.3.14.A] [Dysmenorrhea](#)

1) Incidence: pediatric, 2% [2]

2) [Dysmenorrhea](#) was reported in 2% of patients 10 to 17 years of age treated with the [olanzapine](#) and [fluoxetine](#) combination (n=170) compared with 0% of patients treated with placebo (n=85) in an 8-week, randomized, double-blind clinical trial for acute treatment of [depressive episodes](#) associated with bipolar I disorder [2].

3.3.14.B] [Erectile dysfunction](#)

1) Incidence: 2% [4]

2) In short-term, controlled studies including [depressive episodes](#) associated with Bipolar I Disorder and treatment resistant depression, [erectile dysfunction](#) occurred in 2% of patients who received [fluoxetine/olanzapine](#) (n=771) compared with 1% of patients who received placebo (n=477) [4].

3.3.14.C] [Sexual dysfunction](#)

1) In the pool of controlled [olanzapine/fluoxetine](#) studies, there were higher rates of treatment-emergent adverse events such as decreased libido, [anorgasmia](#), impotence and abnormal ejaculation in the [olanzapine/fluoxetine](#) group than in the placebo group. One case of decreased libido led to discontinuation in the [olanzapine/fluoxetine](#) group. In the controlled studies that contained a [fluoxetine](#) arm, the rates of decreased libido and abnormal ejaculation in the [olanzapine/fluoxetine](#) group were less than the rates in the [fluoxetine](#) group. None of the differences were statistically significant [4]. In a large study (n=560), decreased libido occurred in 11.4% of patients following the administration of [olanzapine/fluoxetine](#) combination at mean doses of 7.5 and 46.1 mg/day, respectively [13].

2) Sexual dysfunction, including [priapism](#), has been reported with all SSRIs. While it is difficult to know the precise risk of sexual dysfunction associated with the use of SSRIs, physicians should routinely inquire about such possible side effects [4].

3.3.15] Respiratory Effects

3.3.15.A] Pulmonary eosinophilia

1) [Eosinophilic pneumonia](#) has been reported with [olanzapine](#) or [fluoxetine](#) monotherapy, but was not observed in [olanzapine/fluoxetine](#) treated patients during premarketing clinical studies [12].

3.3.15.B] Sinusitis

1) Incidence: 2% [12]

2) In short-term, controlled studies including [depressive episodes](#) associated with Bipolar I Disorder and treatment resistant depression, [sinusitis](#) occurred in 2% of patients who received [fluoxetine/olanzapine](#) (n=771) compared with 1% of patients who received placebo (n=477) [12].

3.3.16] Other

3.3.16.A] Death

1) In [olanzapine](#) placebo-controlled clinical trials of elderly patients with dementia-related [psychosis](#), the incidence of death in the [olanzapine](#) group was significantly higher than the placebo group (3.5% vs 1.5%, respectively). Combination [olanzapine/fluoxetine](#) therapy is not approved for the treatment of dementia-related [psychosis](#) [4].

2) Sudden unexpected death has been reported with [olanzapine](#) or [fluoxetine](#) monotherapy, but was not observed in [olanzapine/fluoxetine](#) treated patients during premarketing clinical studies [4].

3) Results of a population-based, retrospective cohort study demonstrated that the use of conventional antipsychotics was associated with an even greater risk for death than atypical antipsychotics when administered to elderly patients (aged 66 years and older) with [dementia](#). Atypical versus no antipsychotic use and conventional versus atypical antipsychotic use pairwise comparisons were made. A total of 27,259 matched pairs were identified and the [dementia](#) cohort was stratified based on place of residence (community versus long-term care facilities). In order to adjust for difference in baseline health status, propensity score matching was used. The primary outcome of the study was all-cause mortality. The risk for death was evaluated at 30, 60, 120, and 180 days after the antipsychotic medications were initially dispensed. There was a statistically significant increase in the risk for death at 30 days associated with new use of atypical antipsychotic medications compared with nonuse in both the community-dwelling cohort (adjusted hazard ratio (HR), 1.31 (95% confidence interval (CI), 1.02 to 1.70); absolute risk difference, 0.2 percentage point) and long-term care cohort (adjusted HR, 1.55 (95% CI, 1.15 to 2.07); absolute risk difference, 1.2 percentage points). For both cohorts, the risk associated with atypical antipsychotics appeared to persist to 180 days. The risk for death associated with conventional antipsychotics was even greater than the risk identified with atypical antipsychotics. At 30 days, the adjusted HR for the community-dwelling cohort was 1.55 (95% CI, 1.19 to 2.02) and 1.26 (95% CI, 1.04 to 1.53) for the long-term care cohort (adjusted risk difference for both was 1.1 percentage points). The risk appeared to persist to 180 days for both groups. Some important limitations to the study include unknown or unmeasured confounders may influence the results and cause of death could not be examined [33].

4) Results of a population-based, retrospective cohort study demonstrated comparable to possibly greater risk of death associated with the use of conventional antipsychotic medications in the elderly (aged 65 years and older) compared with atypical antipsychotic medications. The analysis excluded patients with [cancer](#) and included only new users of antipsychotic medications. The primary study outcome was 180-

day all-cause mortality. A set of potential confounders was measured based on healthcare utilization data within 6 months before the initiation of antipsychotic medications. Of the 37,241 elderly patients identified, 12,882 and 24,359 received conventional and atypical antipsychotic medications, respectively. The risk of death in the conventional drug group within the first 180 days was 14.1% compared with 9.6% in the atypical drug group (unadjusted mortality ratio, 1.47; 95% confidence interval (CI), 1.39 to 1.56). In the multivariable analysis which controlled for potential confounders, the adjusted mortality ratio for the risk of death within 180 days for conventional versus atypical drug therapy was 1.32 (95% CI, 1.23 to 1.42). When the most frequently prescribed conventional antipsychotic drugs were compared with [risperidone](#), the mortality ratio associated with [haloperidol](#) was 2.14 (95% CI, 1.86 to 2.45) and [loxapine](#) was 1.29 (95% CI, 1.19 to 1.40), while there was no difference associated with [olanzapine](#). The increased mortality risk for conventional versus atypical drug therapy was greatest when doses higher (above median) doses were used (mortality ratio 1.67; 95% CI, 1.5 to 1.86) and also during the first 40 days of therapy (mortality ratio 1.6; 95% CI, 1.42 to 1.8). Confirmatory analyses consisting of multivariable Cox regression, propensity score, and instrumental variable estimation confirmed the results of the study [34].

3.3.16.B] Drug overdose

- 1) Incidence: pediatric, 3% [2]
- 2) Accidental overdose was reported in 3% of patients 10 to 17 years of age treated with the [olanzapine](#) and [fluoxetine](#) combination (n=170) compared with 1% of patients treated with placebo (n=85) in an 8-week, randomized, double-blind clinical trial for acute treatment of [depressive episodes](#) associated with bipolar I disorder [2].

3.3.16.C] Fatigue

- 1) Incidence: up to 12% [4]
- 2) In short-term, controlled studies including [depressive episodes](#) associated with Bipolar I Disorder and treatment resistant depression, fatigue occurred in 12% of patients who received [fluoxetine/olanzapine](#) (n=771) compared with 2% of patients who received placebo (n=477) [4].
- 3) In a single 8-week randomized, double-blind, fixed-dose study comparing [olanzapine](#) 10 mg/day (n=199), 20 mg/day (n=200), and 40 mg/day (n=200), fatigue was reported at 1.5%, 2.1%, and 6.6%, respectively, with significant differences between 10 vs 40 and 20 vs 40 mg/day [4].

3.3.16.D] Fever

- 1) Incidence: 2% [4]
- 2) In short-term, controlled studies including [depressive episodes](#) associated with Bipolar I Disorder and treatment resistant depression, pyrexia occurred in 2% of patients who received [fluoxetine/olanzapine](#) (n=771) compared with 1% of patients who received placebo (n=477) [4].

3.3.16.E] Neuroleptic malignant syndrome

- 1) [Neuroleptic malignant syndrome](#) (NMS) has been reported in association with administration of antipsychotic drugs, including [olanzapine](#). Clinical manifestations of NMS are [hyperpyrexia](#), muscle rigidity, altered mental status, and evidence of autonomic instability (irregular pulse or blood pressure, [tachycardia](#), diaphoresis, and [cardiac dysrhythmia](#)). Additional signs may include elevated [creatinine phosphokinase](#), myoglobinuria ([rhabdomyolysis](#)), and [acute renal failure](#). Management of NMS should include immediate discontinuation of antipsychotic drugs and other drugs not essential to concurrently therapy, intensive symptomatic treatment and medical monitoring, and treatment of any concomitant serious medical problems for which specific treatments are available. There is no general agreement about specific [pharmacological treatment](#) regimens for NMS [4].

3.3.16.F] Pain

1) Incidence: 2% [4]

2) In short-term, controlled studies including [depressive episodes](#) associated with Bipolar I Disorder and treatment resistant depression, pain occurred in 2% of patients who received [fluoxetine/olanzapine](#) (n=771) compared with 1% of patients who received placebo (n=477) [4].

3.3.16.G] Serotonin syndrome

1) The development of a potentially life-threatening [serotonin syndrome](#) or [neuroleptic malignant syndrome](#) (NMS)-like reactions have been reported with serotonin [norepinephrine](#) reuptake inhibitor (SNRIs) and SSRIs alone but particularly with concomitant use of serotonergic drugs (including triptans), with drugs which impair metabolism of serotonin (including MAOIs), or with antipsychotics or other [dopamine](#) antagonists. [Serotonin syndrome](#) 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). [Serotonin syndrome](#), in its most severe form can resemble NMS, which includes [hyperthermia](#), muscle rigidity, autonomic instability with possible rapid fluctuation of vital signs, and mental status changes. Patients should be monitored for the emergence of [serotonin syndrome](#) or NMS-like signs and symptoms. The concomitant use of [olanzapine/fluoxetine](#) with MAOIs for depression is contraindicated. Further, concomitant use of [olanzapine/fluoxetine](#) with 5-hydroxytryptamine receptor agonist (triptans) is clinically warranted, and its use is not recommended with SNRIs, SSRIs, or tryptophan. Treatment with [olanzapine/fluoxetine](#) and any concomitant serotonergic or antidopaminergic agents, including antipsychotics, should be discontinued immediately, if the above reactions occur, and supportive symptomatic treatment should be initiated [4].

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](#).

See Drug Consult reference: PREGNANCY RISK CATEGORIES

2) Crosses Placenta: Yes

3) Clinical Management

a) There are no adequate and well-controlled studies of [fluoxetine/olanzapine](#) use in pregnant women; however, third-trimester antipsychotic drug exposure has been associated with extrapyramidal and/or withdrawal symptoms in neonates. Epidemiologic studies showed an increased risk of [persistent pulmonary hypertension of the newborn](#) (PPHN) with prenatal exposure to [fluoxetine](#) and other SSRIs during pregnancy, a condition associated with considerable neonatal morbidity and mortality. Yet, discontinuation of antidepressant medication in women with a history of [major depression](#) who were euthymic at the start of pregnancy placed them at a higher risk for [relapse of major depression](#) compared with women who continued antidepressant medication. In animal studies, there was no evidence of [teratogenicity](#) in pregnant rats or rabbits administered oral [olanzapine](#) and [fluoxetine](#) at doses up to 9 and 2 times the maximum recommended human

dose, respectively. The combination [olanzapine/fluoxetine](#) should be given during pregnancy only if the maternal risk of untreated bipolar I depression or treatment-resistant depression outweighs the potential fetal risk [600].

4) Literature Reports

a) There are no adequate and well-controlled studies of [fluoxetine](#) and [olanzapine](#) use in combination or as single agents in pregnant women. Maternal use of antipsychotic drugs during the third trimester of pregnancy has been associated with an increased risk of neonatal extrapyramidal and/or withdrawal symptoms (eg, agitation, hypertonia, hypotonia, tremor, somnolence, respiratory distress, and feeding disorder) following delivery. Severity of these adverse effects have ranged from cases that are self-limiting to cases that required prolonged periods of hospitalization and ICU care [600].

b) In a prospective longitudinal study (n=201), discontinuation of antidepressant medication in women with a history of [major depression](#) and who were euthymic at the start of pregnancy increased the chance for [relapse of major depression](#) compared with women who continued antidepressant medication. However, neonatal exposure, particularly in the third trimester, to [fluoxetine](#) and other SSRIs or serotonin and [norepinephrine](#) reuptake inhibitors (SNRIs) has led to complications requiring prolonged hospitalization, respiratory support, and tube feeding. Clinical findings have included cyanosis, [apnea](#), seizures, temperature instability, feeding difficulty, vomiting, [hypoglycemia](#), hypotonia, hypertonia, hyperreflexia, tremor, jitteriness, irritability, and constant crying; a clinical scenario reflective of SSRI or SNRI toxicity, a drug discontinuation syndrome, or [serotonin syndrome](#) in some cases. Epidemiologic studies showed an increased risk of [persistent pulmonary hypertension of the newborn](#) (PPHN) with prenatal exposure to [fluoxetine](#) and other SSRIs during pregnancy, a condition associated with considerable neonatal morbidity and mortality [600].

c) Risk assessment studies of [fluoxetine](#) exposure during the first trimester have yielded inconsistent results. There was no evidence of an increased risk for congenital anomalies in more than 10 cohort and case-control studies. In a prospective, cohort study conducted by the European Network of Teratology Information Service, however, there was an increased risk of cardiovascular anomalies in infants following maternal first trimester [fluoxetine](#) exposure (n=253) compared with infants of mothers who had no [fluoxetine](#) exposure (n=1359). The cardiovascular malformations followed no specific pattern and causality to [fluoxetine](#) could not be established [601].

d) A case-control study found that the use of SSRIs after 20 weeks of gestation was associated with an increased risk of [persistent pulmonary hypertension of the newborn](#) (PPHN). [Fluoxetine](#), [paroxetine](#), and [sertraline](#) were the specific SSRIs studied to carry this increased risk. A total of 377 women who had infants with PPHN were matched to 836 women and their infants. Assessment of exposure was determined by telephone interview within 6 months of birth. After adjusting for other covariates, SSRI use after 20 weeks of gestation was associated with an odds ratio of 6.1 (95% confidence interval, 2.2 to 16.8; p=0.001) of delivering an infant with PPHN relative to no use during the pregnancy. SSRI use before 20 weeks of gestation and non-SSRI antidepressant use at any gestation time was not associated with increased risk of PPHN development. The incidence of PPHN in the general population is about 0.1% to 0.2%. According to this study, infants exposed to SSRIs after 20 weeks of gestation have a PPHN incidence of 0.6% to 1.2% [602].

e) In animal reproduction studies, no evidence of [teratogenicity](#) was noted when oral [olanzapine](#) and [fluoxetine](#) were administered individually and in combination at doses up to 2 and 1 times

the maximum recommended human dose (MRHD) on a mg/m(2) basis, respectively, in rats; and at doses up to 9 and 2 times the MRHD on a mg/m(2) basis, respectively, in rabbits. However, the highest combination doses studied were associated with maternal toxicity (decreases in fetal weight in the rabbits and rats, and retarded skeletal ossification in the rabbits). Marked elevations in early offspring mortality (69% per litter survival through postnatal day 4) and [growth retardation](#) (approximately 8% reduced body weight in females) were noted in another study of rats administered [olanzapine](#) and [fluoxetine](#) combinations at doses up to 1 and 0.5 times the MRHD, respectively, on a mg/m(2) basis; no effect was noted with the low-dose combination equivalent to 0.25 and 0.13 times the MRHD, respectively, on a mg/m(2) basis. Surviving offspring showed no defects at any dose in reproductive performance or in physical or neurobehavioral development [601].

f) No evidence of [teratogenicity](#) was observed in rats and rabbits administered [olanzapine](#) in doses 9 and 30 times the maximum recommended human dose (MRHD), respectively, on a mg/m(2) basis; however, an earlier rat study showed early resorptions and greater numbers of nonviable fetuses with [olanzapine](#) doses 9 times the MRHD on a mg/m(2) basis, while rabbits developed fetal toxicity (ie, increased resorptions, decreased fetal weight) with [olanzapine](#) doses 30 times the MRHD on a mg/m(2) basis. [Prolonged gestation](#) in rats occurred at doses 5 times the MRHD on a mg/m(2) basis [601].

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) [Olanzapine](#) and [fluoxetine](#) are excreted in human breast milk. Due to the potential of serious adverse reactions in nursing infants, a decision should be made to discontinue breastfeeding or discontinue [fluoxetine/olanzapine](#), considering the importance of the drug to the mother. Breastfeeding is not recommended in women who are receiving [fluoxetine/olanzapine](#) [601].

3) Literature Reports

a) In an oral [olanzapine](#) study of healthy, nursing women, [olanzapine](#) was excreted in breast milk. The estimated mean infant dose at steady state was 1.8% of the maternal [olanzapine](#) dose [601].

b) The manufacturer reported a maternal plasma concentration of 295 nanograms (ng)/mL of [fluoxetine](#) plus norfluoxetine, with a corresponding breast milk concentration of 70.4 ng/mL. No adverse effects in the nursing infant were reported. In another case, a nursing infant's plasma drug levels were 340 ng/mL of [fluoxetine](#) and 208 ng/mL of norfluoxetine on the second day of breastfeeding. The mother's daily dose of [fluoxetine](#) was not reported. The infant developed crying, sleep disturbance, vomiting, and watery stools [601].

3.5] Drug Interactions

3.5.1] Drug-Drug Combinations

3.5.1.A] Abciximab

- 1) Interaction Effect: increased risk of bleeding
- 2) Summary: Exercise caution when coadministering a SSRI and an antiplatelet agent or anticoagulant as this may increase the risk of bleeding events[272][173][385].
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Use caution with concomitant use of [fluoxetine](#) with anticoagulants or antiplatelet agents, as coadministration may increase bleeding risk[272][173][385].
- 7) Probable Mechanism: altered anticoagulant effects
- 8) Literature Reports

a) In a retrospective study of patients over 50 years of age with the diagnosis of acute [myocardial infarction](#) (N=27,058), SSRI use with any antiplatelet therapy significantly increased the risk of bleeding by 1.42-fold compared with [aspirin](#) use alone. Therapy with [aspirin](#), [clopidogrel](#), and an SSRI significantly increased risk by 2.35-fold compared with [aspirin](#) use alone and by 1.57-fold compared with [clopidogrel](#) and [aspirin](#) combination therapy [385].

b) In a systematic review and meta-analysis of 22 observational studies, SSRI use was associated with a significant 1.55 fold increase in risk of [upper gastrointestinal bleeding](#) (UGIB). Concomitant use of SSRIs and antiplatelet drugs was associated with a 2.48-fold increase in risk of UGIB (3 studies) [272].

3.5.1.B] Abiraterone

- 1) Interaction Effect: elevated [fluoxetine](#) plasma concentrations and increased risk of QT-interval prolongation
- 2) Summary: Concomitant treatment of [fluoxetine](#) with other CYP2D6 inhibitors can increase [fluoxetine](#) plasma concentrations and increase the risk of adverse effects, including episodes of QT-interval prolongation, [ventricular arrhythmia](#), and [torsade de pointes](#). Use caution in coadministration of these drugs[173]. If concomitant use is required, initiate [fluoxetine](#) at the lowest dose possible and titrate dose carefully based on patient response [540].
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Use caution with coadministration of [fluoxetine](#) and CYP2D6 inhibitors, as increased [fluoxetine](#) plasma concentrations may increase the risk of adverse effects, including episodes of QT-interval prolongation, [ventricular arrhythmia](#), and [torsade de pointes](#)[173]. If concomitant use is required, initiate [fluoxetine](#) at the lowest dose possible and titrate dose carefully based on patient response [540].
- 7) Probable Mechanism: inhibition of CYP2D6-mediated [fluoxetine](#) metabolism

3.5.1.C] Acecainide

- 1) Interaction Effect: an increased risk of [cardiotoxicity](#) (QT prolongation, [torsades de pointes](#), [cardiac arrest](#))
- 2) Summary: Even though no formal drug interaction studies have been done, the coadministration of Class III antiarrhythmics and other drugs known to prolong the QTc interval is not recommended[300]

[301][302]. [Fluoxetine](#) has been shown to prolong the QTc interval at the recommended therapeutic dose [303].

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

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

7) Probable Mechanism: additive effects on QT prolongation

3.5.1.D) Aceclofenac

1) Interaction Effect: an increased risk of bleeding

2) Summary: Caution is recommended with the concomitant use of NSAIDs and antidepressants, including SSRIs due to an increased risk of [intracranial hemorrhage](#)[529] and [gastrointestinal bleeding](#) [533][534][530][531]. Bleeding events have included [epistaxis](#), ecchymosis, [hematoma](#), [petechiae](#), and life-threatening hemorrhages [536][535][537][538]. When an SSRI and an NSAID are given concurrently, monitor the patient for signs of increased bleeding.

3) Severity: major

4) Onset: unspecified

5) Substantiation: established

6) Clinical Management: Use caution if NSAIDs and SSRIs are coadministered. Concomitant use of NSAIDs and SSRIs may cause an increased risk of [intracranial hemorrhage](#)[529] and [gastrointestinal bleeding](#) [530][531]. When an SSRI and an NSAID are given concurrently, monitor the patient for signs of increased bleeding.

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

8) Literature Reports

a) Concomitant use of NSAIDs and antidepressants, including tricyclic antidepressants, SSRIs, serotonin-norepinephrine reuptake inhibitors, and MAOIs, resulted in a 60% increased risk of [intracranial hemorrhage](#) within 30 days of concomitant use compared with antidepressant use alone. There was no significant difference between the antidepressant drug classes and the increased risk; however, there was an increased risk associated with male patients compared with female patients [529].

b) SSRIs increase the risk of upper gastrointestinal (GI) bleeding, and this effect is potentiated by concurrent use of NSAIDs or low-dose [aspirin](#). Hospitalizations for [upper GI bleeding](#) were searched among 26,005 users of antidepressant medications and compared with the number of hospitalizations in those patients who did not receive prescriptions for antidepressants. The amount of [upper GI bleeding](#) episodes was 3.6 times more than expected. Combined use of an SSRI and NSAIDs or low-dose [aspirin](#) increased the risk to 12.2 and 5.2 times, respectively. The findings of this study demonstrate an increased risk of [upper GI bleeding](#) during the use of SSRIs. Combined use of SSRIs and NSAIDs or low-dose [aspirin](#) increased the risk even further [532].

c) Two metaanalyses of incidents of upper GI bleed due to SSRIs, NSAIDs, and their combination found that SSRIs increased the risk by 1.73 [533] to 2.36 times [534], NSAIDs by 2.55 times [533], and the combination of SSRIs and NSAIDs by 4.02 [533] to 6.33 times [534].

d) The release of serotonin by [platelets](#) is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs and NSAIDs have been associated with an increased risk of bleeding [535].

3.5.1.E] Acemetacin

- 1) Interaction Effect: an increased risk of bleeding
- 2) Summary: Caution is recommended with the concomitant use of NSAIDs and antidepressants, including SSRIs due to an increased risk of [intracranial hemorrhage](#)[529] and [gastrointestinal bleeding](#) [533][534][530][531]. Bleeding events have included [epistaxis](#), ecchymosis, [hematoma](#), [petechiae](#), and life-threatening hemorrhages [536][535][537][538]. When an SSRI and an NSAID are given concurrently, monitor the patient for signs of increased bleeding.
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: established
- 6) Clinical Management: Use caution if NSAIDs and SSRIs are coadministered. Concomitant use of NSAIDs and SSRIs may cause an increased risk of [intracranial hemorrhage](#)[529] and [gastrointestinal bleeding](#) [530][531]. When an SSRI and an NSAID are given concurrently, monitor the patient for signs of increased bleeding.
- 7) Probable Mechanism: depletion of [platelet](#) serotonin by SSRI; additive effects
- 8) Literature Reports

a) Concomitant use of NSAIDs and antidepressants, including tricyclic antidepressants, SSRIs, serotonin-norepinephrine reuptake inhibitors, and MAOIs, resulted in a 60% increased risk of [intracranial hemorrhage](#) within 30 days of concomitant use compared with antidepressant use alone. There was no significant difference between the antidepressant drug classes and the increased risk; however, there was an increased risk associated with male patients compared with female patients [529].

b) SSRIs increase the risk of upper gastrointestinal (GI) bleeding, and this effect is potentiated by concurrent use of NSAIDs or low-dose [aspirin](#). Hospitalizations for [upper GI bleeding](#) were searched among 26,005 users of antidepressant medications and compared with the number of hospitalizations in those patients who did not receive prescriptions for antidepressants. The amount of [upper GI bleeding](#) episodes was 3.6 times more than expected. Combined use of an SSRI and NSAIDs or low-dose [aspirin](#) increased the risk to 12.2 and 5.2 times, respectively. The findings of this study demonstrate an increased risk of [upper GI bleeding](#) during the use of SSRIs. Combined use of SSRIs and NSAIDs or low-dose [aspirin](#) increased the risk even further [532].

c) Two metaanalyses of incidents of upper GI bleed due to SSRIs, NSAIDs, and their combination found that SSRIs increased the risk by 1.73 [533] to 2.36 times [534], NSAIDs by 2.55 times [533], and the combination of SSRIs and NSAIDs by 4.02 [533] to 6.33 times [534].

d) The release of serotonin by [platelets](#) is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs and NSAIDs have been associated with an increased risk of bleeding [535].

3.5.1.F] Acenocoumarol

- 1) Interaction Effect: an increased risk of bleeding
- 2) Summary: The release of serotonin by [platelets](#) is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs and anticoagulants has been associated with an increased risk of bleeding[458][457]. Bleeding events reported have included [epistaxis](#), ecchymosis, [hematoma](#), [petechiae](#), and life-threatening hemorrhages. Altered anticoagulant effects (including increased bleeding) have been reported with the coadministration of SSRIs with anticoagulants [457].

- 3) Severity: major
- 4) Onset: delayed
- 5) Substantiation: probable
- 6) Clinical Management: When [fluoxetine](#) and an anticoagulant are given concurrently, monitor patient for signs of increased bleeding. Patients who are taking an anticoagulant should be monitored closely for altered anticoagulant effects, including increased bleeding, when [fluoxetine](#) therapy is initiated or discontinued[457].
- 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 a significant 1.7-fold increased risk for hospitalization for nongastrointestinal bleeding; however, the rate of [gastrointestinal bleeding](#) was not significantly different [458].

3.5.1.G] Activated Charcoal

- 1) Interaction Effect: decreased bioavailability of [olanzapine](#)
- 2) Summary: Activated charcoal reduces the maximum concentration and area under the concentration-time curve (AUC) by approximately 60%[130]. This drug interaction may make activated charcoal useful in cases of [olanzapine](#) overdose.
- 3) Severity: minor
- 4) Onset: rapid
- 5) Substantiation: theoretical
- 6) Clinical Management: Do not administer activated charcoal and [olanzapine](#) concomitantly.
- 7) Probable Mechanism: binding of [olanzapine](#) in the gut

3.5.1.H] Ajmaline

- 1) Interaction Effect: an increased risk of [cardiotoxicity](#) (QT prolongation, [torsades de pointes](#), [cardiac arrest](#))
- 2) Summary: Even though no formal drug interaction studies have been done, the coadministration of Class Ia antiarrhythmics and other drugs known to prolong the QTc interval is not recommended[343]. [Fluoxetine](#) has demonstrated QT prolongation at therapeutic doses [344].
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: The concurrent administration of class Ia antiarrhythmic agents and agents that prolong the QT interval, such as [fluoxetine](#), is not recommended.
- 7) Probable Mechanism: additive effects on QT prolongation

3.5.1.I] Alfentanil

- 1) Interaction Effect: increased risk of CNS depression (ie, [respiratory depression](#), profound sedation, coma)
- 2) Summary: The concomitant use of [alfentanil](#) with other CNS depressants may result in profound sedation, [respiratory depression](#), coma, and/or death. Reserve concomitant use to clinical settings where

alternative treatment options are inadequate. If combination therapy is required, reduce the initial dose of the newly prescribed medication and titrate to clinical response while monitoring for [respiratory depression](#) and sedation[78].

3J) Severity: major

4J) Onset: unspecified

5J) Substantiation: theoretical

6J) Clinical Management: Reserve concomitant use of [alfentanil](#) with other CNS depressants to clinical settings where alternative treatment options are inadequate. If combination therapy is required, reduce the initial dose of the newly prescribed medication and titrate to clinical response while monitoring for [respiratory depression](#) and sedation[78].

7J) Probable Mechanism: additive CNS depression

3.5.1.J] [Almotriptan](#)

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

2J) Summary: Concomitant use of triptans and selective serotonin reuptake inhibitors (SSRI's) has been associated with [serotonin syndrome](#), some of which life-threatening[354]. Symptoms of [serotonin syndrome](#) may include restlessness, hallucinations, loss of coordination, fast heart beat, rapid changes in blood pressure, increased body temperature, overreactive reflexes, nausea, vomiting, and diarrhea. Clinicians should be aware that triptans may be commonly used intermittently and that either the triptan or the SSRI may be prescribed by a different physician. Discuss the risks of [serotonin syndrome](#) with patients who are prescribed this combination and monitor them closely for symptoms of [serotonin syndrome](#) [199].

3J) Severity: major

4J) Onset: delayed

5J) Substantiation: theoretical

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

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

8J) Literature Reports

aJ) Concomitant administration of [fluoxetine](#) and [almotriptan](#) is well tolerated and [fluoxetine](#) has only a modest effect on [almotriptan](#) maximum plasma concentration (C_{max}). Other [almotriptan](#) pharmacokinetics are not significantly affected. A randomized, open-label, two-way crossover study involving 14 healthy volunteers has been conducted. Subjects received each of the following treatments with a minimum 3-week washout between periods: (1) three 20 mg [fluoxetine](#) capsules on day 1 to 8 and one dose [almotriptan](#) 12.5 mg on day 8, (2) one dose of [almotriptan](#) 12.5 mg on day 8 with no treatment on days 1 through 7. Peak [almotriptan](#) concentrations were 18% higher following concomitant administration of [fluoxetine](#) than after [almotriptan](#) administration alone. This difference was statistically significant (p equal 0.023). Mean [almotriptan](#) area under the concentration-time curve (AUC) and oral clearance were borderline statistically different between treatment groups. Mean half-life was not statistically different between the treatment groups. During [fluoxetine](#) coadministration, T_{max} was shorter, suggesting that the absorption rate of [almotriptan](#) may have been increased by [fluoxetine](#). The author concludes that based on the results of this study and the lack of effect of [fluoxetine](#) on [almotriptan](#) pharmacokinetics, [almotriptan](#) and [fluoxetine](#) can be safely used concomitantly in migraine management [353].

3.5.1.K] [Alprazolam](#)

- 1) Interaction Effect: an increased risk of [alprazolam](#) toxicity (somnolence, dizziness, ataxia, slurred speech, hypotension, [psychomotor impairment](#))
- 2) Summary: Coadministered [fluoxetine](#) increases [alprazolam](#) serum concentrations[569][570]. The mechanism of this interaction is thought to be inhibition by [fluoxetine](#) of the cytochrome P450 3A4 isoenzyme (CYP3A4), which is principally responsible for [alprazolam](#) metabolism. Some benzodiazepines ([lorazepam](#), [oxazepam](#)) are metabolized by glucuronidation rather than by the P450 system and may be the better choice for [fluoxetine](#) and benzodiazepine [cotherapy](#).
- 3) Severity: moderate
- 4) Onset: rapid
- 5) Substantiation: probable
- 6) Clinical Management: Monitor patients for signs and symptoms of [alprazolam](#) intoxication (somnolence, dizziness, ataxia, slurred speech, hypotension, [psychomotor impairment](#)). [Alprazolam](#) doses may need to be reduced. Alternatively, consider substituting a benzodiazepine (such as [lorazepam](#) or [oxazepam](#)) that has less potential for interacting with [fluoxetine](#).
- 7) Probable Mechanism: inhibition of cytochrome P450 3A-mediated [alprazolam](#) metabolism
- 8) Literature Reports

a) [Alprazolam](#) serum concentrations were analyzed in a double-blind, placebo-controlled study involving 80 healthy male volunteers [566]. Concurrent administration of [alprazolam](#) 1 mg four times a day and [fluoxetine](#) 60 mg each morning for four days resulted in a 30% increase in plasma [alprazolam](#) levels and a 21% decrease in the [alprazolam](#) elimination rate. The elevated [alprazolam](#) concentrations caused increased [psychomotor impairment](#), but did not affect mood status or sedation.

b) The effect of [fluoxetine](#) on the pharmacokinetics of [alprazolam](#) was analyzed in a 31-day, double-blind, crossover, placebo-controlled study, which included a 10-day washout period [567]. Twelve healthy male volunteers were given [fluoxetine](#) 20 mg twice a day or placebo and a single dose of [alprazolam](#) 1 mg on days 3 and 24. [Fluoxetine](#) significantly increased the half-life of [alprazolam](#) from 17 hours to 20 hours and significantly decreased its clearance from 61 mL/min to 48 mL/min.

c) Inhibition of [alprazolam](#) metabolism by [fluoxetine](#) occurs via cytochrome P450 3A4. A randomized, double-blind, placebo-controlled with-in subject design was used to assess this potential interaction. Twenty healthy volunteers attended four study sessions: [alprazolam](#)/placebo was given in the absence of an SSRI in the first two study sessions; [alprazolam](#)/placebo while at steady-state with either [citalopram](#) 20 mg/day or [fluoxetine](#) 20 mg/day was given in the last two study sessions. At each session they received [alprazolam](#) 1 mg orally or placebo. [Fluoxetine](#) significantly prolonged the half-life of [alprazolam](#) by 16% and increased the area under the concentration-time curve by 32%. [Citalopram](#) did not affect these parameters. The effects of [alprazolam](#) were not altered by either SSRI. These findings suggest that [citalopram](#) and [fluoxetine](#) differentially alter [alprazolam](#) concentrations [568].

3.5.1.L] Amifampridine

- 1) Interaction Effect: increased risk of QT-interval prolongation
- 2) Summary: The concomitant use of amifampridine with drugs that cause QT-interval prolongation is contraindicated, as coadministration may increase the risk of [ventricular arrhythmias](#)[82].
- 3) Severity: contraindicated
- 4) Onset: unspecified
- 5) Substantiation: theoretical

- 6) Clinical Management: The concomitant use of amifampridine with drugs that cause QT-interval prolongation is contraindicated, as coadministration may increase the risk of [ventricular arrhythmias](#)[82].
- 7) Probable Mechanism: additive QT-interval prolongation

3.5.1.M] Amineptine

- 1) Interaction Effect: increased risk of tricyclic antidepressant toxicity, QT prolongation and [serotonin syndrome](#)
- 2) Summary: [Fluoxetine](#), a potent CYP2D6 inhibitor, is associated with an increased risk of [serotonin syndrome](#), QT prolongation, and [ventricular arrhythmias](#) (including [torsade de pointes](#)). Concomitant therapy with CYP2D6-metabolized tricyclic antidepressants (TCAs) may potentiate these risks and introduce TCA toxicity[173]; concurrent use of [fluoxetine](#) and [desipramine](#), [nortriptyline](#), and [imipramine](#) has resulted in significant increases in TCA concentrations [517][523][524][525][526][527]. Use caution with concurrent administration of [fluoxetine](#) and TCAs. If [fluoxetine](#) is added to an existing TCA regimen, consider TCA dose reduction. If [fluoxetine](#) and a TCA are coadministered or [fluoxetine](#) has been recently discontinued, consider plasma TCA monitoring. If [serotonin syndrome](#) occurs, immediately discontinue [fluoxetine](#) and TCA. If [ventricular arrhythmias](#) develop, consider [fluoxetine](#) discontinuation and cardiac evaluation [173].
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Use caution with concurrent administration of [fluoxetine](#) and TCAs, as elevated TCA plasma concentrations may occur. If [fluoxetine](#) is added to an existing TCA regimen, consider TCA dose reduction. If [fluoxetine](#) and a TCA are coadministered or [fluoxetine](#) has been recently discontinued, consider plasma TCA monitoring. If [serotonin syndrome](#) occurs, immediately discontinue [fluoxetine](#) and TCA. If [ventricular arrhythmias](#) develop, consider [fluoxetine](#) discontinuation and cardiac evaluation[173]
- 7) Probable Mechanism: decreased CYP2D6-mediated metabolism of tricyclic antidepressants by [fluoxetine](#); additive effects on QT prolongation; additive serotonergic effects
- 8) Literature Reports

a) Previously stable plasma levels of [imipramine](#) and [desipramine](#) rose more than 2- to 10-fold with [fluoxetine](#) coadministration in 2 clinical studies. This effect may persist for 3 weeks or more after [fluoxetine](#) discontinuation. Dose reduction and temporary monitoring of tricyclic antidepressant plasma concentrations may be indicated with concurrent [fluoxetine](#) treatment or recent [fluoxetine](#) discontinuation [173].

b) [Fluoxetine](#) statistically and clinically significantly increased [desipramine](#) concentrations in 18 healthy subjects. When [fluoxetine](#) (20 mg daily) was added to [desipramine](#) (50 mg daily), the mean maximum concentration of [desipramine](#) increased by 278% and the AUC increased by 342%. [Desipramine](#) trough concentrations continued to be 198% above baseline 3 weeks after [fluoxetine](#) was discontinued. The same study compared pharmacokinetics of [desipramine](#) when combined with [sertraline](#). The impact of [sertraline](#) was modest, resulting in small and short-term increases in [desipramine](#) plasma concentrations [517].

c) Concomitant administration of [fluoxetine](#) and [desipramine](#) was reported to result in an increased [desipramine](#) level and new onset of [delirium](#) in a 69-year-old male within 10 days of the addition of [fluoxetine](#) to the patient's regimen [518].

d) [Fluoxetine](#) increased the level of tricyclic antidepressants ([nortriptyline](#), [imipramine](#), [desipramine](#)) in 4 patients. After the addition of [fluoxetine](#), the ratio of antidepressant level to dose increased by 109% to 486% in the patients. Three patients developed clinical symptoms

(anticholinergic effects, constipation, urinary hesitancy, sedation, unstable gait) as a result of the increased levels [519].

e) A 39-year-old female experienced symptomatic increases in her [desipramine](#) levels with concomitant [fluoxetine](#) therapy. Prior to [fluoxetine](#) therapy, the patient's measured levels of [desipramine](#) had ranged from 148 to 160 nanograms/milliliter (ng/mL; 556 to 601 nanomol/L) on a regimen of 300 mg daily. Five weeks after the addition of [fluoxetine](#) 20 mg daily, she reported anticholinergic symptoms, sedation, and confusion with a [desipramine](#) level of 527 ng/mL (1978 nanomol/L). The [desipramine](#) dose was lowered to 200 mg/day; 11 days later, the level was 244 ng/mL (916 nanomol/L); the patient reported decreased energy, impaired short-term memory, and some "garbled" speech, as well as an episode of nausea, dizziness, and syncope. The [desipramine](#) dose was reduced to 50 mg/day, and the adverse effects resolved in 6 days. Eight days later, the [desipramine](#) level was 122 ng/mL (458 nanomol/L) [520].

f) A 33-year-old depressed male developed adverse effects of dry mouth, tinnitus, and difficulties with alertness and memory while receiving [fluoxetine](#) 40 mg daily and [desipramine](#) 150 mg daily for 5 weeks; [fluoxetine](#) was discontinued and the blood levels of [desipramine](#) decreased from 938 to 48 nanograms/mL (3521 to 180 nanomol/L) with resolution of clinical symptoms [521].

g) A 75-year-old female experienced symptomatic increases in her [desipramine](#) serum concentrations when [fluoxetine](#) was added. [Desipramine](#) serum levels ranged from 109 to 150 ng/mL (409 to 563 nanomol/L) with oral doses of 300 mg at bedtime prior to [fluoxetine](#) therapy. Following the addition of oral [fluoxetine](#) 20 mg daily to the regimen, the [desipramine](#) serum level increased to 212 ng/mL (796 nanomol/L) within five days. The [fluoxetine](#) dose was increased to 40 mg/day three days later, and the [desipramine](#) serum level was 419 ng/mL (1573 nanomol/L) after four days. A worsening of depression and severe fatigue coincided with the increases in [desipramine](#) serum levels. Withdrawal of [fluoxetine](#) and reduction in the [desipramine](#) dose to 200 mg daily reduced the [desipramine](#) serum level to 231 ng/mL (867 nanomol/L) within two weeks [522].

3.5.1.N] [Amiodarone](#)

- 1) Interaction Effect: increased risk of QT prolongation and [torsades de pointes](#)
- 2) Summary: Avoid the concomitant administration of [amiodarone](#) and a QT prolonging agent since it may result in additive effects on the QT interval and increase the risk of [torsades de pointes](#). Due to the long half-life of [amiodarone](#), this interaction is possible even after the discontinuation of [amiodarone](#)[134].
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Avoid the concomitant administration of [amiodarone](#) and a QT prolonging agent since it may result in additive effects on the QT interval and increase the risk of [torsades de pointes](#). Due to the long half-life of [amiodarone](#), this interaction is possible even after the discontinuation of [amiodarone](#)[134].
- 7) Probable Mechanism: additive effects on QT interval

3.5.1.O] [Amiodarone](#)

- 1) Interaction Effect: an increased risk of [cardiotoxicity](#) (QT prolongation, [torsades de pointes](#), [cardiac arrest](#))
- 2) Summary: Even though no formal drug interaction studies have been done, the coadministration of Class III antiarrhythmics and other drugs known to prolong the QTc interval is not recommended[300]

[301][302]. [Fluoxetine](#) has been shown to prolong the QTc interval at the recommended therapeutic dose [303].

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

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

7) Probable Mechanism: additive effects on QT prolongation

3.5.1.P] Amisulpride

1) Interaction Effect: increased risk of [torsades de pointes](#)

2) Summary: The concomitant use of amisulpride with other agents that may induce [torsade de pointes](#) is contraindicated. Because amisulpride by itself prolongs the QT interval in a dose-dependent manner, coadministration with another medication that prolongs the QT interval increases the risk of [torsade de pointes](#)[129].

3) Severity: contraindicated

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: The concomitant use of amisulpride with other agents that may induce [torsade de pointes](#) is contraindicated. Because amisulpride by itself prolongs the QT interval in a dose-dependent manner, coadministration with another medication that prolongs the QT interval increases the risk of [torsade de pointes](#)[129].

7) Probable Mechanism: additive QT prolongation

3.5.1.Q] Amisulpride

1) Interaction Effect: increased risk of serious [ventricular arrhythmias](#) such as [torsades de pointes](#)

2) Summary: Use caution with the concomitant use of amisulpride with other agents that prolong the QT interval and monitor the patient's heart rhythm prior to coadministration. Because amisulpride by itself prolongs the QT interval in a dose-dependent manner, coadministration with another medication that prolongs the QT interval increases the risk of serious [ventricular arrhythmias](#) such as [torsade de pointes](#)[129].

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Use caution with the concomitant use of amisulpride with other agents that prolong the QT interval and monitor the patient's heart rhythm prior to coadministration. Because amisulpride by itself prolongs the QT interval in a dose-dependent manner, coadministration with another medication that prolongs the QT interval increases the risk of serious [ventricular arrhythmias](#) such as [torsade de pointes](#)[129].

7) Probable Mechanism: additive QT prolongation

3.5.1.R] Amitriptyline

1) Interaction Effect: increased risk of tricyclic antidepressant toxicity, QT prolongation and [serotonin syndrome](#)

2) Summary: [Fluoxetine](#), a potent CYP2D6 inhibitor, is associated with an increased risk of [serotonin syndrome](#), QT prolongation, and [ventricular arrhythmias](#) (including [torsade de pointes](#)). Concomitant therapy with CYP2D6-metabolized tricyclic antidepressants (TCAs) may potentiate these risks and introduce TCA toxicity[173]; concurrent use of [fluoxetine](#) and [desipramine](#), [nortriptyline](#), and [imipramine](#)

has resulted in significant increases in TCA concentrations [517][523][524][525][526][527]. Use caution with concurrent administration of [fluoxetine](#) and TCAs. If [fluoxetine](#) is added to an existing TCA regimen, consider TCA dose reduction. If [fluoxetine](#) and a TCA are coadministered or [fluoxetine](#) has been recently discontinued, consider plasma TCA monitoring. If [serotonin syndrome](#) occurs, immediately discontinue [fluoxetine](#) and TCA. If [ventricular arrhythmias](#) develop, consider [fluoxetine](#) discontinuation and cardiac evaluation [173].

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Use caution with concurrent administration of [fluoxetine](#) and TCAs, as elevated TCA plasma concentrations may occur. If [fluoxetine](#) is added to an existing TCA regimen, consider TCA dose reduction. If [fluoxetine](#) and a TCA are coadministered or [fluoxetine](#) has been recently discontinued, consider plasma TCA monitoring. If [serotonin syndrome](#) occurs, immediately discontinue [fluoxetine](#) and TCA. If [ventricular arrhythmias](#) develop, consider [fluoxetine](#) discontinuation and cardiac evaluation[173]

7) Probable Mechanism: decreased CYP2D6-mediated metabolism of tricyclic antidepressants by [fluoxetine](#); additive effects on QT prolongation; additive serotonergic effects

8) Literature Reports

a) Previously stable plasma levels of [imipramine](#) and [desipramine](#) rose more than 2- to 10-fold with [fluoxetine](#) coadministration in 2 clinical studies. This effect may persist for 3 weeks or more after [fluoxetine](#) discontinuation. Dose reduction and temporary monitoring of tricyclic antidepressant plasma concentrations may be indicated with concurrent [fluoxetine](#) treatment or recent [fluoxetine](#) discontinuation [173].

b) [Fluoxetine](#) statistically and clinically significantly increased [desipramine](#) concentrations in 18 healthy subjects. When [fluoxetine](#) (20 mg daily) was added to [desipramine](#) (50 mg daily), the mean maximum concentration of [desipramine](#) increased by 278% and the AUC increased by 342%. [Desipramine](#) trough concentrations continued to be 198% above baseline 3 weeks after [fluoxetine](#) was discontinued. The same study compared pharmacokinetics of [desipramine](#) when combined with [sertraline](#). The impact of [sertraline](#) was modest, resulting in small and short-term increases in [desipramine](#) plasma concentrations [517].

c) Concomitant administration of [fluoxetine](#) and [desipramine](#) was reported to result in an increased [desipramine](#) level and new onset of [delirium](#) in a 69-year-old male within 10 days of the addition of [fluoxetine](#) to the patient's regimen [518].

d) [Fluoxetine](#) increased the level of tricyclic antidepressants ([nortriptyline](#), [imipramine](#), [desipramine](#)) in 4 patients. After the addition of [fluoxetine](#), the ratio of antidepressant level to dose increased by 109% to 486% in the patients. Three patients developed clinical symptoms (anticholinergic effects, constipation, urinary hesitancy, sedation, unstable gait) as a result of the increased levels [519].

e) A 39-year-old female experienced symptomatic increases in her [desipramine](#) levels with concomitant [fluoxetine](#) therapy. Prior to [fluoxetine](#) therapy, the patient's measured levels of [desipramine](#) had ranged from 148 to 160 nanograms/milliliter (ng/mL; 556 to 601 nanomol/L) on a regimen of 300 mg daily. Five weeks after the addition of [fluoxetine](#) 20 mg daily, she reported anticholinergic symptoms, sedation, and confusion with a [desipramine](#) level of 527 ng/mL (1978 nanomol/L). The [desipramine](#) dose was lowered to 200 mg/day; 11 days later, the level was 244 ng/mL (916 nanomol/L); the patient reported decreased energy, impaired short-term memory, and some "garbled" speech, as well as an episode of nausea, dizziness, and syncope. The [desipramine](#)

dose was reduced to 50 mg/day, and the adverse effects resolved in 6 days. Eight days later, the [desipramine](#) level was 122 ng/mL (458 nanomol/L) [520].

f) A 33-year-old depressed male developed adverse effects of dry mouth, tinnitus, and difficulties with alertness and memory while receiving [fluoxetine](#) 40 mg daily and [desipramine](#) 150 mg daily for 5 weeks; [fluoxetine](#) was discontinued and the blood levels of [desipramine](#) decreased from 938 to 48 nanograms/mL (3521 to 180 nanomol/L) with resolution of clinical symptoms [521].

g) A 75-year-old female experienced symptomatic increases in her [desipramine](#) serum concentrations when [fluoxetine](#) was added. [Desipramine](#) serum levels ranged from 109 to 150 ng/mL (409 to 563 nanomol/L) with oral doses of 300 mg at bedtime prior to [fluoxetine](#) therapy. Following the addition of oral [fluoxetine](#) 20 mg daily to the regimen, the [desipramine](#) serum level increased to 212 ng/mL (796 nanomol/L) within five days. The [fluoxetine](#) dose was increased to 40 mg/day three days later, and the [desipramine](#) serum level was 419 ng/mL (1573 nanomol/L) after four days. A worsening of depression and severe fatigue coincided with the increases in [desipramine](#) serum levels. Withdrawal of [fluoxetine](#) and reduction in the [desipramine](#) dose to 200 mg daily reduced the [desipramine](#) serum level to 231 ng/mL (867 nanomol/L) within two weeks [522].

3.5.1.S] Amitriptylinoxide

1) Interaction Effect: increased risk of tricyclic antidepressant toxicity, QT prolongation and [serotonin syndrome](#)

2) Summary: [Fluoxetine](#), a potent CYP2D6 inhibitor, is associated with an increased risk of [serotonin syndrome](#), QT prolongation, and [ventricular arrhythmias](#) (including [torsade de pointes](#)). Concomitant therapy with CYP2D6-metabolized tricyclic antidepressants (TCAs) may potentiate these risks and introduce TCA toxicity[173]; concurrent use of [fluoxetine](#) and [desipramine](#), [nortriptyline](#), and [imipramine](#) has resulted in significant increases in TCA concentrations [517][523][524][525][526][527]. Use caution with concurrent administration of [fluoxetine](#) and TCAs. If [fluoxetine](#) is added to an existing TCA regimen, consider TCA dose reduction. If [fluoxetine](#) and a TCA are coadministered or [fluoxetine](#) has been recently discontinued, consider plasma TCA monitoring. If [serotonin syndrome](#) occurs, immediately discontinue [fluoxetine](#) and TCA. If [ventricular arrhythmias](#) develop, consider [fluoxetine](#) discontinuation and cardiac evaluation [173].

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Use caution with concurrent administration of [fluoxetine](#) and TCAs, as elevated TCA plasma concentrations may occur. If [fluoxetine](#) is added to an existing TCA regimen, consider TCA dose reduction. If [fluoxetine](#) and a TCA are coadministered or [fluoxetine](#) has been recently discontinued, consider plasma TCA monitoring. If [serotonin syndrome](#) occurs, immediately discontinue [fluoxetine](#) and TCA. If [ventricular arrhythmias](#) develop, consider [fluoxetine](#) discontinuation and cardiac evaluation[173]

7) Probable Mechanism: decreased CYP2D6-mediated metabolism of tricyclic antidepressants by [fluoxetine](#); additive effects on QT prolongation; additive serotonergic effects

8) Literature Reports

a) Previously stable plasma levels of [imipramine](#) and [desipramine](#) rose more than 2- to 10-fold with [fluoxetine](#) coadministration in 2 clinical studies. This effect may persist for 3 weeks or more after [fluoxetine](#) discontinuation. Dose reduction and temporary monitoring of tricyclic antidepressant plasma concentrations may be indicated with concurrent [fluoxetine](#) treatment or recent [fluoxetine](#) discontinuation [173].

b) **Fluoxetine** statistically and clinically significantly increased **desipramine** concentrations in 18 healthy subjects. When **fluoxetine** (20 mg daily) was added to **desipramine** (50 mg daily), the mean maximum concentration of **desipramine** increased by 278% and the AUC increased by 342%. **Desipramine** trough concentrations continued to be 198% above baseline 3 weeks after **fluoxetine** was discontinued. The same study compared pharmacokinetics of **desipramine** when combined with **sertraline**. The impact of **sertraline** was modest, resulting in small and short-term increases in **desipramine** plasma concentrations [517].

c) Concomitant administration of **fluoxetine** and **desipramine** was reported to result in an increased **desipramine** level and new onset of **delirium** in a 69-year-old male within 10 days of the addition of **fluoxetine** to the patient's regimen [518].

d) **Fluoxetine** increased the level of tricyclic antidepressants (**nortriptyline**, **imipramine**, **desipramine**) in 4 patients. After the addition of **fluoxetine**, the ratio of antidepressant level to dose increased by 109% to 486% in the patients. Three patients developed clinical symptoms (anticholinergic effects, constipation, urinary hesitancy, sedation, unstable gait) as a result of the increased levels [519].

e) A 39-year-old female experienced symptomatic increases in her **desipramine** levels with concomitant **fluoxetine** therapy. Prior to **fluoxetine** therapy, the patient's measured levels of **desipramine** had ranged from 148 to 160 nanograms/milliliter (ng/mL; 556 to 601 nanomol/L) on a regimen of 300 mg daily. Five weeks after the addition of **fluoxetine** 20 mg daily, she reported anticholinergic symptoms, sedation, and confusion with a **desipramine** level of 527 ng/mL (1978 nanomol/L). The **desipramine** dose was lowered to 200 mg/day; 11 days later, the level was 244 ng/mL (916 nanomol/L); the patient reported decreased energy, impaired short-term memory, and some "garbled" speech, as well as an episode of nausea, dizziness, and syncope. The **desipramine** dose was reduced to 50 mg/day, and the adverse effects resolved in 6 days. Eight days later, the **desipramine** level was 122 ng/mL (458 nanomol/L) [520].

f) A 33-year-old depressed male developed adverse effects of dry mouth, tinnitus, and difficulties with alertness and memory while receiving **fluoxetine** 40 mg daily and **desipramine** 150 mg daily for 5 weeks; **fluoxetine** was discontinued and the blood levels of **desipramine** decreased from 938 to 48 nanograms/mL (3521 to 180 nanomol/L) with resolution of clinical symptoms [521].

g) A 75-year-old female experienced symptomatic increases in her **desipramine** serum concentrations when **fluoxetine** was added. **Desipramine** serum levels ranged from 109 to 150 ng/mL (409 to 563 nanomol/L) with oral doses of 300 mg at bedtime prior to **fluoxetine** therapy. Following the addition of oral **fluoxetine** 20 mg daily to the regimen, the **desipramine** serum level increased to 212 ng/mL (796 nanomol/L) within five days. The **fluoxetine** dose was increased to 40 mg/day three days later, and the **desipramine** serum level was 419 ng/mL (1573 nanomol/L) after four days. A worsening of depression and severe fatigue coincided with the increases in **desipramine** serum levels. Withdrawal of **fluoxetine** and reduction in the **desipramine** dose to 200 mg daily reduced the **desipramine** serum level to 231 ng/mL (867 nanomol/L) within two weeks [522].

3.5.1.T] Amoxapine

1) Interaction Effect: increased risk of tricyclic antidepressant toxicity, QT prolongation and **serotonin syndrome**

2) Summary: **Fluoxetine**, a potent CYP2D6 inhibitor, is associated with an increased risk of **serotonin syndrome**, QT prolongation, and **ventricular arrhythmias** (including **torsade de pointes**). Concomitant therapy with CYP2D6-metabolized tricyclic antidepressants (TCAs) may potentiate these risks and introduce TCA toxicity[173]; concurrent use of **fluoxetine** and **desipramine**, **nortriptyline**, and **imipramine** has resulted in significant increases in TCA concentrations [517][523][524][525][526][527]. Use caution with concurrent administration of **fluoxetine** and TCAs. If **fluoxetine** is added to an existing TCA regimen, consider TCA dose reduction. If **fluoxetine** and a TCA are coadministered or **fluoxetine** has been recently discontinued, consider plasma TCA monitoring. If **serotonin syndrome** occurs, immediately discontinue **fluoxetine** and TCA. If **ventricular arrhythmias** develop, consider **fluoxetine** discontinuation and cardiac evaluation [173].

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Use caution with concurrent administration of **fluoxetine** and TCAs, as elevated TCA plasma concentrations may occur. If **fluoxetine** is added to an existing TCA regimen, consider TCA dose reduction. If **fluoxetine** and a TCA are coadministered or **fluoxetine** has been recently discontinued, consider plasma TCA monitoring. If **serotonin syndrome** occurs, immediately discontinue **fluoxetine** and TCA. If **ventricular arrhythmias** develop, consider **fluoxetine** discontinuation and cardiac evaluation[173]

7) Probable Mechanism: decreased CYP2D6-mediated metabolism of tricyclic antidepressants by **fluoxetine**; additive effects on QT prolongation; additive serotonergic effects

8) Literature Reports

a) Previously stable plasma levels of **imipramine** and **desipramine** rose more than 2- to 10-fold with **fluoxetine** coadministration in 2 clinical studies. This effect may persist for 3 weeks or more after **fluoxetine** discontinuation. Dose reduction and temporary monitoring of tricyclic antidepressant plasma concentrations may be indicated with concurrent **fluoxetine** treatment or recent **fluoxetine** discontinuation [173].

b) **Fluoxetine** statistically and clinically significantly increased **desipramine** concentrations in 18 healthy subjects. When **fluoxetine** (20 mg daily) was added to **desipramine** (50 mg daily), the mean maximum concentration of **desipramine** increased by 278% and the AUC increased by 342%. **Desipramine** trough concentrations continued to be 198% above baseline 3 weeks after **fluoxetine** was discontinued. The same study compared pharmacokinetics of **desipramine** when combined with **sertraline**. The impact of **sertraline** was modest, resulting in small and short-term increases in **desipramine** plasma concentrations [517].

c) Concomitant administration of **fluoxetine** and **desipramine** was reported to result in an increased **desipramine** level and new onset of **delirium** in a 69-year-old male within 10 days of the addition of **fluoxetine** to the patient's regimen [518].

d) **Fluoxetine** increased the level of tricyclic antidepressants (**nortriptyline**, **imipramine**, **desipramine**) in 4 patients. After the addition of **fluoxetine**, the ratio of antidepressant level to dose increased by 109% to 486% in the patients. Three patients developed clinical symptoms (anticholinergic effects, constipation, urinary hesitancy, sedation, unstable gait) as a result of the increased levels [519].

e) A 39-year-old female experienced symptomatic increases in her **desipramine** levels with concomitant **fluoxetine** therapy. Prior to **fluoxetine** therapy, the patient's measured levels of **desipramine** had ranged from 148 to 160 nanograms/milliliter (ng/mL; 556 to 601 nanomol/L) on a regimen of 300 mg daily. Five weeks after the addition of **fluoxetine** 20 mg daily, she reported anticholinergic symptoms, sedation, and confusion with a **desipramine** level of 527 ng/mL (1978

nanomol/L). The [desipramine](#) dose was lowered to 200 mg/day; 11 days later, the level was 244 ng/mL (916 nanomol/L); the patient reported decreased energy, impaired short-term memory, and some "garbled" speech, as well as an episode of nausea, dizziness, and syncope. The [desipramine](#) dose was reduced to 50 mg/day, and the adverse effects resolved in 6 days. Eight days later, the [desipramine](#) level was 122 ng/mL (458 nanomol/L) [520].

f) A 33-year-old depressed male developed adverse effects of dry mouth, tinnitus, and difficulties with alertness and memory while receiving [fluoxetine](#) 40 mg daily and [desipramine](#) 150 mg daily for 5 weeks; [fluoxetine](#) was discontinued and the blood levels of [desipramine](#) decreased from 938 to 48 nanograms/mL (3521 to 180 nanomol/L) with resolution of clinical symptoms [521].

g) A 75-year-old female experienced symptomatic increases in her [desipramine](#) serum concentrations when [fluoxetine](#) was added. [Desipramine](#) serum levels ranged from 109 to 150 ng/mL (409 to 563 nanomol/L) with oral doses of 300 mg at bedtime prior to [fluoxetine](#) therapy. Following the addition of oral [fluoxetine](#) 20 mg daily to the regimen, the [desipramine](#) serum level increased to 212 ng/mL (796 nanomol/L) within five days. The [fluoxetine](#) dose was increased to 40 mg/day three days later, and the [desipramine](#) serum level was 419 ng/mL (1573 nanomol/L) after four days. A worsening of depression and severe fatigue coincided with the increases in [desipramine](#) serum levels. Withdrawal of [fluoxetine](#) and reduction in the [desipramine](#) dose to 200 mg daily reduced the [desipramine](#) serum level to 231 ng/mL (867 nanomol/L) within two weeks [522].

3.5.1.U] [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[528].

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[528].

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

3.5.1.V] [Amprenavir](#)

1) Interaction Effect: reduced [olanzapine](#) exposure

2) Summary: Coadministration of [olanzapine](#) (CYP1A2 and UGT substrate) and [fosamprenavir](#) boosted with [ritonavir](#) (CYP1A2 and UGT inducer) may result in decreased [olanzapine](#) exposure[54] [55]. Increasing the [olanzapine](#) dose by 50% (from 10 to 15 mg/day) when coadministered with [fosamprenavir/ritonavir](#) compensated for the induction of CYP1A2- and UGT-mediated [olanzapine](#)

metabolism and resulted in [olanzapine](#) exposure that was comparable to when [olanzapine](#) was administered alone in a randomized trial in 20 healthy volunteers [54].

3) Severity: moderate

4) Onset: unspecified

5) Substantiation: established

6) Clinical Management: Coadministration of [olanzapine](#) (CYP1A2 and UGT substrate) and [fosamprenavir](#) boosted with [ritonavir](#) (CYP1A2 and UGT inducer) may result in decreased [olanzapine](#) exposure[54][55]. Increasing the [olanzapine](#) dose by 50% (from 10 to 15 mg/day) when coadministered with [fosamprenavir/ritonavir](#) compensated for the induction of CYP1A2- and UGT-mediated [olanzapine](#) metabolism and resulted in [olanzapine](#) exposure that was comparable to when [olanzapine](#) was administered alone in a randomized trial in 20 healthy volunteers [54].

7) Probable Mechanism: induction of CYP1A2- and glucuronosyl transferase-mediated metabolism of [olanzapine](#) by [fosamprenavir](#) boosted with [ritonavir](#)

8) Literature Reports

a) Increasing the [olanzapine](#) dose by 50% when coadministered with [fosamprenavir/ritonavir](#) compensated for the induction of CYP1A2- and UGT-mediated [olanzapine](#) metabolism and resulted in [olanzapine](#) exposure that was comparable to when [olanzapine](#) was administered alone in a randomized, crossover trial in 20 healthy volunteers. [Fosamprenavir](#) 700 mg/[ritonavir](#) 100 mg twice daily (for 16 days) was given with a single [olanzapine](#) 15 mg (on day 13), and when compared with [olanzapine](#) 10 mg alone resulted in similar AUC (438.3 vs 436.9 mcg x hr/L), increased C_{max} by 32% (17.4 vs 13.2 mcg/L), and decreased the t(1/2) by 32% (22.7 vs 33.4 hours). A higher C_{max} is due to induction by [fosamprenavir/ritonavir](#) having no effect on the absorption phase and was not associated with a higher incidence of olanzapine-associated adverse events in the combination group [54].

b) An open-label study involving 14 healthy volunteers revealed a significant alteration in pharmacokinetic parameters and a reduction in systemic exposure of [olanzapine](#) when administered in the presence of [ritonavir](#). Each volunteer received a single dose of [olanzapine](#) 10 mg. After a 14-day washout period, subjects received [ritonavir](#) 300 mg BID for 3 days, then 400 mg BID for 4 days, then 500 mg BID for 4 days. Significant reductions were seen in the mean [olanzapine](#) AUC by 53% (501 to 235 nanograms x hr/mL), t(1/2) by 50% (from 32 to 16 hours), and C_{max} by 40% (from 15 to 9 nanograms/mL). The oral clearance of [olanzapine](#) increased by 115% (from 20 to 43 L/hr) [55].

3.5.1.W) Amtolmetin Guacil

1) Interaction Effect: an increased risk of bleeding

2) Summary: Caution is recommended with the concomitant use of NSAIDs and antidepressants, including SSRIs due to an increased risk of [intracranial hemorrhage](#)[529] and [gastrointestinal bleeding](#) [533][534][530][531]. Bleeding events have included [epistaxis](#), ecchymosis, [hematoma](#), [petechiae](#), and life-threatening hemorrhages [536][535][537][538]. When an SSRI and an NSAID are given concurrently, monitor the patient for signs of increased bleeding.

3) Severity: major

4) Onset: unspecified

5) Substantiation: established

6) Clinical Management: Use caution if NSAIDs and SSRIs are coadministered. Concomitant use of NSAIDs and SSRIs may cause an increased risk of [intracranial hemorrhage](#)[529] and [gastrointestinal bleeding](#) [530][531]. When an SSRI and an NSAID are given concurrently, monitor the patient for signs of increased bleeding.

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

8J) Literature Reports

aJ) Concomitant use of NSAIDs and antidepressants, including tricyclic antidepressants, SSRIs, serotonin-norepinephrine reuptake inhibitors, and MAOIs, resulted in a 60% increased risk of [intracranial hemorrhage](#) within 30 days of concomitant use compared with antidepressant use alone. There was no significant difference between the antidepressant drug classes and the increased risk; however, there was an increased risk associated with male patients compared with female patients [529].

bJ) SSRIs increase the risk of upper gastrointestinal (GI) bleeding, and this effect is potentiated by concurrent use of NSAIDs or low-dose [aspirin](#). Hospitalizations for [upper GI bleeding](#) were searched among 26,005 users of antidepressant medications and compared with the number of hospitalizations in those patients who did not receive prescriptions for antidepressants. The amount of [upper GI bleeding](#) episodes was 3.6 times more than expected. Combined use of an SSRI and NSAIDs or low-dose [aspirin](#) increased the risk to 12.2 and 5.2 times, respectively. The findings of this study demonstrate an increased risk of [upper GI bleeding](#) during the use of SSRIs. Combined use of SSRIs and NSAIDs or low-dose [aspirin](#) increased the risk even further [532].

cJ) Two metaanalyses of incidents of upper GI bleed due to SSRIs, NSAIDs, and their combination found that SSRIs increased the risk by 1.73 [533] to 2.36 times [534], NSAIDs by 2.55 times [533], and the combination of SSRIs and NSAIDs by 4.02 [533] to 6.33 times [534].

dJ) The release of serotonin by [platelets](#) is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs and NSAIDs have been associated with an increased risk of bleeding [535].

3.5.1.X] [Anagrelide](#)

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

2J) Summary: [Anagrelide](#) has been associated with QT interval prolongation. Coadministration with another drug known to prolong the QT interval should be avoided because of risk for additive effects on the QT interval that can lead to serious cardiac adverse effects, including [torsade de pointes](#)[151].

3J) Severity: major

4J) Onset: unspecified

5J) Substantiation: theoretical

6J) Clinical Management: [Anagrelide](#) has been associated with QT interval prolongation. Coadministration with another drug known to prolong the QT interval should be avoided because of risk for additive effects on the QT interval that can lead to serious cardiac adverse effects, including [torsade de pointes](#)[151].

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

3.5.1.Y] [Anagrelide](#)

1J) Interaction Effect: increased risk of bleeding; increased risk of QT prolongation

2J) Summary: Avoid coadministering [anagrelide](#) with [fluoxetine](#). [Anagrelide](#) is associated with reports of [ventricular arrhythmia](#)[213] and [fluoxetine](#) is known to prolong QT interval; concomitant use of [fluoxetine](#) and QT-prolonging drugs may result in additive prolongation of the QT interval [173]. Additionally, [anagrelide](#) reduces [platelet](#) count [213] and [fluoxetine](#) is an SSRI. The release of serotonin by [platelets](#) is important for maintaining hemostasis. SSRIs may increase bleeding risk. Epidemiologic case-control and cohort studies have shown an association between drugs like [fluoxetine](#) that interfere with serotonin

reuptake and [gastrointestinal bleeding](#). Concomitant use with anticoagulants may increase this risk [173]. If coadministration of [anagrelide](#) with [fluoxetine](#) is necessary, consider a baseline ECG and on-treatment monitoring of QT interval and bleeding.

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Coadministration of [fluoxetine](#) with a drug known to prolong the QT interval, such as [anagrelide](#), should be avoided. Concurrent use may lead to an increased risk of serious cardiac adverse events, including [torsade de pointes](#)[173]. Additionally, concomitant use of [fluoxetine](#) with anticoagulants, such as [anagrelide](#), may increase bleeding risk [173]. If concurrent use of [anagrelide](#) with [fluoxetine](#) is necessary, consider a baseline ECG and on-treatment monitoring for QT prolongation and bleeding.

7) Probable Mechanism: altered anticoagulant effects; additive QT interval effects

3.5.1.Z] Ancrod

1) Interaction Effect: an increased risk of bleeding

2) Summary: The release of serotonin by [platelets](#) is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs and anticoagulants has been associated with an increased risk of bleeding[458][457]. Bleeding events reported have included [epistaxis](#), ecchymosis, [hematoma](#), [petechiae](#), and life-threatening hemorrhages. Altered anticoagulant effects (including increased bleeding) have been reported with the coadministration of SSRIs with anticoagulants [457].

3) Severity: major

4) Onset: delayed

5) Substantiation: probable

6) Clinical Management: When [fluoxetine](#) and an anticoagulant are given concurrently, monitor patient for signs of increased bleeding. Patients who are taking an anticoagulant should be monitored closely for altered anticoagulant effects, including increased bleeding, when [fluoxetine](#) therapy is initiated or discontinued[457].

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 a significant 1.7-fold increased risk for hospitalization for nongastrointestinal bleeding; however, the rate of [gastrointestinal bleeding](#) was not significantly different [458].

3.5.1.AA] Anisindione

1) Interaction Effect: an increased risk of bleeding

2) Summary: The release of serotonin by [platelets](#) is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs and anticoagulants has been associated with an increased risk of bleeding[458][457]. Bleeding events reported have included [epistaxis](#), ecchymosis, [hematoma](#), [petechiae](#), and life-threatening hemorrhages. Altered anticoagulant effects (including increased bleeding) have been reported with the coadministration of SSRIs with anticoagulants [457].

3) Severity: major

4) Onset: delayed

5) Substantiation: probable

6) Clinical Management: When [fluoxetine](#) and an anticoagulant are given concurrently, monitor patient for signs of increased bleeding. Patients who are taking an anticoagulant should be monitored closely for altered anticoagulant effects, including increased bleeding, when [fluoxetine](#) therapy is initiated or discontinued[457].

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 a significant 1.7-fold increased risk for hospitalization for nongastrointestinal bleeding; however, the rate of [gastrointestinal bleeding](#) was not significantly different [458].

3.5.1.AB] Antithrombin III Human

1) Interaction Effect: an increased risk of bleeding

2) Summary: The release of serotonin by [platelets](#) is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs and anticoagulants has been associated with an increased risk of bleeding[458][457]. Bleeding events reported have included [epistaxis](#), ecchymosis, [hematoma](#), [petechiae](#), and life-threatening hemorrhages. Altered anticoagulant effects (including increased bleeding) have been reported with the coadministration of SSRIs with anticoagulants [457].

3) Severity: major

4) Onset: delayed

5) Substantiation: probable

6) Clinical Management: When [fluoxetine](#) and an anticoagulant are given concurrently, monitor patient for signs of increased bleeding. Patients who are taking an anticoagulant should be monitored closely for altered anticoagulant effects, including increased bleeding, when [fluoxetine](#) therapy is initiated or discontinued[457].

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 a significant 1.7-fold increased risk for hospitalization for nongastrointestinal bleeding; however, the rate of [gastrointestinal bleeding](#) was not significantly different [458].

3.5.1.AC] Apixaban

1) Interaction Effect: an increased risk of bleeding

2) Summary: Coadministration of apixaban, a factor Xa inhibitor, and drugs that affect hemostasis, such as SSRI therapy, increases the risk of bleeding. There is no established reversal therapy or antidote for apixaban-induced bleeding, and its [anticoagulation](#) effects usually persist for 24 hours after the last

dose. Discontinue apixaban if active pathological bleeding occurs[429]. If concomitant apixaban and SSRI therapy is necessary, use caution and monitor the patient closely.

3J) Severity: major

4J) Onset: unspecified

5J) Substantiation: theoretical

6J) Clinical Management: Concomitant apixaban therapy with drugs that also affect hemostasis, such as an SSRI, increases the risk of bleeding. Discontinue apixaban if active pathological bleeding occurs. There is no established reversal therapy or antidote for apixaban-induced bleeding, and its [anticoagulation](#) effects usually persist for 24 hours after the last dose[429]. If concomitant apixaban and SSRI therapy is necessary, use caution and monitor the patient closely.

7J) Probable Mechanism: additive effects on hemostasis

3.5.1.AD] Aprindine

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

2J) Summary: Coadministration of a class I antiarrhythmic, such as aprindine, and [fluoxetine](#) should be avoided because of additive effects on QT interval prolongation and increased risk of [cardiotoxicity](#). If concomitant use is required and [fluoxetine](#) is initiated in patients at risk for QT prolongation and [ventricular arrhythmia](#), consider obtaining a baseline ECG and periodically monitor ECG during therapy. If signs or symptoms of [ventricular arrhythmia](#) occur, consider discontinuation of [fluoxetine](#) and obtain a cardiac evaluation[173].

3J) Severity: major

4J) Onset: unspecified

5J) Substantiation: theoretical

6J) Clinical Management: The concurrent administration of class I antiarrhythmic agents, such as aprindine, and agents that prolong the QT interval, such as [fluoxetine](#), should be avoided. If concomitant use is required and [fluoxetine](#) is initiated in patients at risk for QT prolongation and [ventricular arrhythmia](#), consider obtaining a baseline ECG and periodically monitor ECG during therapy. If signs or symptoms of [ventricular arrhythmia](#) occur, consider discontinuation of [fluoxetine](#) and obtain a cardiac evaluation[173].

7J) Probable Mechanism: additive QT interval prolongation

3.5.1.AE] [Ardeparin](#)

1J) Interaction Effect: an increased risk of bleeding

2J) Summary: The release of serotonin by [platelets](#) is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs and anticoagulants has been associated with an increased risk of bleeding[458][457]. Bleeding events reported have included [epistaxis](#), ecchymosis, [hematoma](#), [petechiae](#), and life-threatening hemorrhages. Altered anticoagulant effects (including increased bleeding) have been reported with the coadministration of SSRIs with anticoagulants [457].

3J) Severity: major

4J) Onset: delayed

5J) Substantiation: probable

6J) Clinical Management: When [fluoxetine](#) and an anticoagulant are given concurrently, monitor patient for signs of increased bleeding. Patients who are taking an anticoagulant should be monitored closely for altered anticoagulant effects, including increased bleeding, when [fluoxetine](#) therapy is initiated or discontinued[457].

7J) Probable Mechanism: unknown

8J) 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 a significant 1.7-fold increased risk for hospitalization for nongastrointestinal bleeding; however, the rate of [gastrointestinal bleeding](#) was not significantly different [458].

3.5.1.AF] Argatroban

- 1) Interaction Effect: increased risk of bleeding
- 2) Summary: Exercise caution when coadministering a SSRI and an antiplatelet agent or anticoagulant as this may increase the risk of bleeding events[272][173][385].
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Use caution with concomitant use of [fluoxetine](#) with anticoagulants or antiplatelet agents, as coadministration may increase bleeding risk[272][173][385].
- 7) Probable Mechanism: altered anticoagulant effects
- 8) Literature Reports

a) In a retrospective study of patients over 50 years of age with the diagnosis of acute [myocardial infarction](#) (N=27,058), SSRI use with any antiplatelet therapy significantly increased the risk of bleeding by 1.42-fold compared with [aspirin](#) use alone. Therapy with [aspirin](#), [clopidogrel](#), and an SSRI significantly increased risk by 2.35-fold compared with [aspirin](#) use alone and by 1.57-fold compared with [clopidogrel](#) and [aspirin](#) combination therapy [385].

b) In a systematic review and meta-analysis of 22 observational studies, SSRI use was associated with a significant 1.55 fold increase in risk of [upper gastrointestinal bleeding](#) (UGIB). Concomitant use of SSRIs and antiplatelet drugs was associated with a 2.48-fold increase in risk of UGIB (3 studies) [272].

3.5.1.AG] Aripiprazole

- 1) Interaction Effect: increased risk of QT interval prolongation
- 2) Summary: [Aripiprazole](#) has been associated with QTc interval prolongation[149], and coadministration with another drug known to prolong the QT interval should be undertaken with caution because of risk for additive effects on the QT interval that can lead to serious cardiac adverse effects, including [torsade de pointes](#).
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: [Aripiprazole](#) has been associated with QTc interval prolongation[149], and coadministration with another drug known to prolong the QT interval should be undertaken with caution because of risk for additive effects on the QT interval that can lead to serious cardiac adverse effects, including [torsade de pointes](#).
- 7) Probable Mechanism: additive effects on the QT interval

3.5.1.AH] Aripiprazole

- 1) Interaction Effect: increased [aripiprazole](#) exposure and increased risk for QT-interval prolongation
- 2) Summary: [Aripiprazole](#) is metabolized by CYP2D6 and CYP3A4 enzymes. Coadministration with CYP2D6 inhibitors, such as [fluoxetine](#), may inhibit [aripiprazole](#) elimination causing increased blood concentrations. If [aripiprazole](#) is coadministered with [fluoxetine](#), dose reduction of oral [fluoxetine](#) is required immediately, and dose reduction of [aripiprazole](#) long-acting injection is required when concurrent use exceeds 14 days. If [aripiprazole](#) and [fluoxetine](#) are concurrently used with a strong CYP3A4 inhibitor, further dose reduction of [aripiprazole](#) is required. If concurrent [fluoxetine](#) is discontinued, [aripiprazole](#) dose should then be increased[416][149]. Dosage adjustments with concomitant use are not recommended if low-dose [aripiprazole](#) is being used adjunctively for the treatment of [major depressive disorder](#) [149]. Additionally, coadministration may result in additive effects on the QT interval. Baseline ECG and on-treatment monitoring may be warranted [417]
- 3) Severity: major
- 4) Onset: delayed
- 5) Substantiation: theoretical
- 6) Clinical Management: Coadministration of [aripiprazole](#) with [fluoxetine](#) may result in increased [aripiprazole](#) plasma levels. Dose reduction of oral [aripiprazole](#) is required immediately during concurrent use of [fluoxetine](#), and dose reduction of [aripiprazole](#) long-acting injection is required when concurrent use exceeds 14 days. If [aripiprazole](#) and [fluoxetine](#) are concurrently used with a strong CYP3A4 inhibitor, further dose reduction of [aripiprazole](#) is required. If concurrent [fluoxetine](#) is discontinued, the dose of [aripiprazole](#) should then be increased[416][149]. Specific dosage adjustments are not recommended if low-dose oral [aripiprazole](#) is being used adjunctively for the treatment of [major depressive disorder](#) [149]. Additionally, coadministration may result in additive effects on the QT interval. Baseline ECG and on-treatment monitoring may be warranted [417].
- 7) Probable Mechanism: inhibition of CYP2D6- and CYP3A4-mediated [aripiprazole](#) metabolism by [fluoxetine](#); additive effects on QT interval
- 8) Literature Reports

a) During drug interaction studies, coadministration of [quinidine](#) 166 mg/day for 13 days (a strong CYP2D6 inhibitor) with a single dose of [aripiprazole](#) 10 mg resulted in a 112% increase in [aripiprazole](#) AUC. The AUC of dehydro-aripiprazole, the active metabolite of [aripiprazole](#), was decreased by 35% [149]

b) During drug interaction studies, coadministration of [ketoconazole](#) 200 mg/day for 14 days (a strong CYP3A4 inhibitor) with single dose [aripiprazole](#) 15 mg resulted in a 63% and 77% increase in the AUC of [aripiprazole](#) and its active metabolite, respectively [149].

3.5.1.A1] [Arsenic Trioxide](#)

- 1) Interaction Effect: increased risk of QT-interval prolongation and [torsade de pointes](#)
- 2) Summary: Avoid concurrent use of [arsenic trioxide](#), a drug known to prolong the QT interval, with other QT-prolonging drugs, as additive effects on the QT interval can progress to life-threatening [torsade de pointes](#). Whenever possible, discontinue or replace with an alternate drug that does not prolong the QT interval during [arsenic trioxide](#) treatment. Monitor ECGs more frequently if concomitant use is clinically required[108].
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Avoid concurrent use of [arsenic trioxide](#), a drug known to prolong the QT interval, with other QT-prolonging drugs, as additive effects on the QT interval can progress to life-threatening [torsade de pointes](#). Whenever possible, discontinue or replace with an alternate drug that

does not prolong the QT interval during [arsenic trioxide](#) treatment. Monitor ECGs more frequently if concomitant use is clinically required[108].

7) Probable Mechanism: additive effects on the QT interval

3.5.1.AJ] [Arsenic Trioxide](#)

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

2) Summary: [Arsenic trioxide](#) and [fluoxetine](#) have been shown to prolong the QTc interval at the recommended therapeutic dose[515][516]. Even though no formal drug interaction studies have been done, [arsenic trioxide](#) should not be administered with other drugs which are also known or have the potential to prolong the QTc interval, including [fluoxetine](#) [515].

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

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

7) Probable Mechanism: additive effects on QT prolongation

8) Literature Reports

a) QT/QTc prolongation should be expected during treatment with [arsenic trioxide](#) and [torsade de pointes](#) as well as [complete heart block](#) has been reported. Over 460 ECG tracings from 40 patients with refractory or relapsed APL treated with [arsenic trioxide](#) were evaluated for QTc prolongation. Sixteen of 40 patients (40%) had at least one ECG tracing with a QTc interval greater than 500 msec. Prolongation of the QTc was observed between 1 and 5 weeks after [arsenic trioxide](#) infusion, and then returned towards baseline by the end of 8 weeks after [arsenic trioxide](#) infusion. In these ECG evaluations, women did not experience more pronounced QT prolongation than men, and there was no correlation with age [513].

b) QT Prolongation was observed on the [electrocardiogram](#) (ECG) of a 52- year-old man who had been taking [fluoxetine](#) (20 milligrams/day for 2 weeks, followed by 40 milligrams/day thereafter) for depression for 3 months. An ECG just before the start of [fluoxetine](#) treatment showed a normal QT interval. The QT interval returned to normal within 10 days of discontinuing [fluoxetine](#) treatment [514].

3.5.1.AK] [Aspirin](#)

1) Interaction Effect: an increased risk of bleeding

2) Summary: Caution is recommended with the concomitant use of NSAIDs and antidepressants, including SSRIs due to an increased risk of [intracranial hemorrhage](#)[529] and [gastrointestinal bleeding](#) [533][534][530][531]. Bleeding events have included [epistaxis](#), ecchymosis, [hematoma](#), [petechiae](#), and life-threatening hemorrhages [536][535][537][538]. When an SSRI and an NSAID are given concurrently, monitor the patient for signs of increased bleeding.

3) Severity: major

4) Onset: unspecified

5) Substantiation: established

6) Clinical Management: Use caution if NSAIDs and SSRIs are coadministered. Concomitant use of NSAIDs and SSRIs may cause an increased risk of [intracranial hemorrhage](#)[529] and [gastrointestinal bleeding](#) [530][531]. When an SSRI and an NSAID are given concurrently, monitor the patient for signs of increased bleeding.

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

8) Literature Reports

a)) Concomitant use of NSAIDs and antidepressants, including tricyclic antidepressants, SSRIs, serotonin-norepinephrine reuptake inhibitors, and MAOIs, resulted in a 60% increased risk of [intracranial hemorrhage](#) within 30 days of concomitant use compared with antidepressant use alone. There was no significant difference between the antidepressant drug classes and the increased risk; however, there was an increased risk associated with male patients compared with female patients [529].

b)) SSRIs increase the risk of upper gastrointestinal (GI) bleeding, and this effect is potentiated by concurrent use of NSAIDs or low-dose [aspirin](#). Hospitalizations for [upper GI bleeding](#) were searched among 26,005 users of antidepressant medications and compared with the number of hospitalizations in those patients who did not receive prescriptions for antidepressants. The amount of [upper GI bleeding](#) episodes was 3.6 times more than expected. Combined use of an SSRI and NSAIDs or low-dose [aspirin](#) increased the risk to 12.2 and 5.2 times, respectively. The findings of this study demonstrate an increased risk of [upper GI bleeding](#) during the use of SSRIs. Combined use of SSRIs and NSAIDs or low-dose [aspirin](#) increased the risk even further [532].

c)) Two metaanalyses of incidents of upper GI bleed due to SSRIs, NSAIDs, and their combination found that SSRIs increased the risk by 1.73 [533] to 2.36 times [534], NSAIDs by 2.55 times [533], and the combination of SSRIs and NSAIDs by 4.02 [533] to 6.33 times [534].

d)) The release of serotonin by [platelets](#) is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs and NSAIDs have been associated with an increased risk of bleeding [535].

3.5.1.AL] [Astemizole](#)

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

2)) Summary: It is theoretically possible that an interaction might occur between [astemizole](#) and [fluoxetine](#) because both drugs are metabolized by the cytochrome P450 system. Astemizole is metabolized by CYP3A4. [Fluoxetine](#) is known to be a potent inhibitor of CYP2D6 and is suspected of inhibiting other P450 enzymes, including CYP3A4[191]. Coadministered [fluoxetine](#) may inhibit [astemizole](#) clearance, thereby leading to increased [astemizole](#) serum concentrations and potential [astemizole](#) toxicity. The manufacturer of [astemizole](#) recommends avoiding coadministration with [fluoxetine](#) [192]. In addition, [fluoxetine](#) has been shown to prolong the QTc interval at the recommended therapeutic dose [193].

3)) Severity: major

4)) Onset: rapid

5)) Substantiation: theoretical

6)) Clinical Management: Concomitant use of [astemizole](#) and [fluoxetine](#) is not recommended.

7)) Probable Mechanism: possible inhibition of [astemizole](#) P450 metabolism by [fluoxetine](#) and/or additive effects on QT prolongation

8)) Literature Reports

a)) [Astemizole](#) has been shown to prolong the QTc interval at the recommended therapeutic dose [190]. Even though no formal drug interaction studies have been done, the coadministration of [astemizole](#) and other drugs known to prolong the QTc interval, including [fluoxetine](#), is not recommended.

3.5.1.AM] [Atomoxetine](#)

1)) Interaction Effect: an increase in [atomoxetine](#) steady-state plasma concentrations

2) Summary: [Atomoxetine](#) is primarily metabolized by the cytochrome P450 2D6 (CYP 2D6) pathway to 4-hydroxyatomoxetine. In extensive metabolizers, [atomoxetine](#) steady-state plasma concentrations are increased with selective inhibitors of CYP2D6, such as [fluoxetine](#). The exposure is similar to that observed in poor metabolizers. In extensive metabolizers treated with [fluoxetine](#), the area under the concentration-time curve of [atomoxetine](#) is approximately 6- to 8-fold greater, and maximum plasma concentration at steady-state is about 3- to 4-fold greater than [atomoxetine](#) alone[281].

3) Severity: moderate

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Dosage adjustment of [atomoxetine](#) may be necessary when coadministered with [fluoxetine](#).

7) Probable Mechanism: inhibition of cytochrome P450 2D6-mediated metabolism of [atomoxetine](#) by [fluoxetine](#)

3.5.1.AN] Azimilide

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

2) Summary: Even though no formal drug interaction studies have been done, the coadministration of Class III antiarrhythmics and other drugs known to prolong the QTc interval is not recommended[300][301][302]. [Fluoxetine](#) has been shown to prolong the QTc interval at the recommended therapeutic dose [303].

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

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

7) Probable Mechanism: additive effects on QT prolongation

3.5.1.AO] Belladonna

1) Interaction Effect: excessive anticholinergic activity (severe dry mouth, constipation, decreased urination, excessive sedation, blurred vision)

2) Summary: The anticholinergic activity of the active alkaloids present in belladonna may predispose the patient to excessive anticholinergic activity if taken with [olanzapine](#). Belladonna contains L-hyoscyamine, [atropine](#), and [scopolamine](#) with a total alkaloid content of at least 0.3% in the leaves and 0.5% in the roots[170]. Because belladonna is typically available as a homeopathic preparation, the clinical severity of the interaction with [olanzapine](#) is unknown. Caution is advised.

3) Severity: minor

4) Onset: rapid

5) Substantiation: theoretical

6) Clinical Management: Excessive anticholinergic activity may be manifested by dry mouth, constipation, urinary retention, [tachycardia](#), decreased sweating, mydriasis, blurred vision, elevated temperature, muscular weakness, and sedation. If such effects are noted, belladonna should be discontinued immediately. In severe cases, [paralytic ileus](#), confusion, [psychoses](#), agitation, delusions, [delirium](#), and paranoia may be encountered as well as [tachycardia](#), [dysrhythmia](#), and [hypertension](#). In severe cases, immediate medical attention should be obtained.

7) Probable Mechanism: additive anticholinergic effect

3.5.1.AP] Belladonna Alkaloids

- 1) Interaction Effect: excessive anticholinergic activity (severe dry mouth, constipation, decreased urination, excessive sedation, blurred vision)
- 2) Summary: The anticholinergic activity of the active alkaloids present in belladonna may predispose the patient to excessive anticholinergic activity if taken with [olanzapine](#). Belladonna contains L-hyoscyamine, [atropine](#), and [scopolamine](#) with a total alkaloid content of at least 0.3% in the leaves and 0.5% in the roots[170]. Because belladonna is typically available as a homeopathic preparation, the clinical severity of the interaction with [olanzapine](#) is unknown. Caution is advised.
- 3) Severity: minor
- 4) Onset: rapid
- 5) Substantiation: theoretical
- 6) Clinical Management: Excessive anticholinergic activity may be manifested by dry mouth, constipation, urinary retention, [tachycardia](#), decreased sweating, mydriasis, blurred vision, elevated temperature, muscular weakness, and sedation. If such effects are noted, belladonna should be discontinued immediately. In severe cases, [paralytic ileus](#), confusion, [psychoses](#), agitation, delusions, [delirium](#), and paranoia may be encountered as well as [tachycardia](#), [dysrhythmia](#), and [hypertension](#). In severe cases, immediate medical attention should be obtained.
- 7) Probable Mechanism: additive anticholinergic effect

3.5.1.AQ] Bemiparin

- 1) Interaction Effect: an increased risk of bleeding
- 2) Summary: The release of serotonin by [platelets](#) is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs and anticoagulants has been associated with an increased risk of bleeding[458][457]. Bleeding events reported have included [epistaxis](#), ecchymosis, [hematoma](#), [petechiae](#), and life-threatening hemorrhages. Altered anticoagulant effects (including increased bleeding) have been reported with the coadministration of SSRIs with anticoagulants [457].
- 3) Severity: major
- 4) Onset: delayed
- 5) Substantiation: probable
- 6) Clinical Management: When [fluoxetine](#) and an anticoagulant are given concurrently, monitor patient for signs of increased bleeding. Patients who are taking an anticoagulant should be monitored closely for altered anticoagulant effects, including increased bleeding, when [fluoxetine](#) therapy is initiated or discontinued[457].
- 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 a significant 1.7-fold increased risk for hospitalization for nongastrointestinal bleeding; however, the rate of [gastrointestinal bleeding](#) was not significantly different [458].

3.5.1.AR] 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[528].

3J) Severity: major

4J) Onset: unspecified

5J) Substantiation: theoretical

6J) Clinical Management: Coadministration of an [amphetamine](#) and another serotonergic agent may result in [serotonin syndrome](#), because both drugs affect the serotonergic neurotransmitter system. Additionally, coadministration of an [amphetamine](#) with a CYP2D6 inhibitor may increase [amphetamine](#) exposure, because [amphetamines](#) and their derivatives are metabolized to some degree by CYP2D6. An increase in [amphetamine](#) exposure may further increase risk of [serotonin syndrome](#). If concomitant use of an [amphetamine](#) and a serotonergic agent that inhibits CYP2D6 is clinically required, initiate with lower doses and monitor patients carefully, especially during treatment initiation and dosage adjustment. Discontinue both drugs if [serotonin syndrome](#) is suspected[528].

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

3.5.1.AS] [Bepridil](#)

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

2J) Summary: The concomitant use of [bepridil](#) with drugs that cause QT-interval prolongation is contraindicated[172], as coadministration may increase the risk of [ventricular arrhythmias](#).

3J) Severity: contraindicated

4J) Onset: unspecified

5J) Substantiation: theoretical

6J) Clinical Management: The concomitant use of [bepridil](#) with drugs that cause QT-interval prolongation is contraindicated[172], as coadministration may increase the risk of [ventricular arrhythmias](#).

7J) Probable Mechanism: additive QT-interval prolongation

3.5.1.AT] [Betel Nut](#)

1J) Interaction Effect: increased extrapyramidal side effects of [olanzapine](#) (difficulty with movement or abnormal movement of muscles)

2J) Summary: Case reports have described increased extrapyramidal side effects when betel nut was chewed by patients taking [fluphenazine](#) and flupenthixol for [schizophrenia](#)[40]. The extrapyramidal effects were not improved with anticholinergic therapy with [procyclidine](#), and resolved with betel nut discontinuation [40]. A similar effect may occur if betel nut is chewed with concomitant [olanzapine](#) therapy. The cholinergic activity of betel nut has been attributed to the arecoline content. When given with peripheral anticholinergics, arecoline increased the heart rate due to central muscarinic agonist activity [41]. Case reports suggest the onset of betel nut activity to be within 3 weeks with resolution within 4 to 7 days after discontinuation [40].

3J) Severity: moderate

4J) Onset: delayed

5J) Substantiation: probable

6J) Clinical Management: It is unclear to what extent the cholinergic effect of betel nut may increase the incidence of extrapyramidal side effects of [olanzapine](#), especially if patients are treated with anticholinergic agents to control these side effects. Deterioration in symptoms of patients with [Parkinson's disease](#) or other extrapyramidal movement disorders may be expected. Persons who have been chewing betel nut have a characteristic red stain on the teeth which may help the clinician discover betel nut use.

7J) Probable Mechanism: cholinergic effect of betel nut

8J) Literature Reports

a) Within 3 weeks of initiating betel nut chewing, a 51-year-old Indian man experienced marked rigidity, bradykinesia, and jaw tremor. This patient had been stabilized for the previous 2 years on fluphenazine decanoate depot 50 milligrams (mg) every 3 weeks for schizophrenia and procyclidine 5 mg twice daily for a mild Parkinsonian tremor. Within one week of discontinuation of betel nut chewing, the patient's condition returned to baseline. This report appears to demonstrate decreased anticholinergic effects of procyclidine when coadministered with betel nut [36].

b) Following betel nut ingestion, a 45-year-old Indian man developed akathisia, tremor and stiffness which was not affected by dosage escalations of up to 20 mg daily of procyclidine. This patient had been previously stabilized on flupenthixol 60 mg depot every two weeks for the previous year for schizoaffective disorder without extrapyramidal side effects. His symptoms resolved over 4 days after discontinuing betel nut. It appears that the anticholinergic effects of procyclidine were diminished when betel nut was chewed concomitantly [36].

c) High doses (5 mg, 10 mg, and 20 mg) of subcutaneous (SC) arecoline given one hour after SC administration of 0.5 mg of the peripheral anticholinergic agent methscopolamine increased the heart rate and blood pressure of six patients with Huntington's disease. Significant increases in blood pressure occurred at doses of 5 mg, 10 mg (p less than 0.01) and 20 mg (p less than 0.05). Heart rate increased at doses of 5 mg and 20 mg (p less than 0.01), and 10 mg (p less than 0.05). Subjective effects in some patients included tremor, flushing or pallor at the time of peak drug effect and nausea, weakness, and mental changes at the higher doses. No peripheral cholinergic effects were noted. The results indicated a central muscarinic effect for arecoline [37].

d) A low dose (0.5 mg) of arecoline given intravenously 3 minutes after the peripheral anticholinergic agent glycopyrrolate 0.15 mg to 8 patients with major depressive disorder increased their heart rates. The peak heart rate increase in a non-REM portion of the sleep cycle during the 10 minute post-infusion period was 6.75 +/- 12.9 beats per minute for placebo and 25 +/- 10.3 beats per minute for arecoline. The peak heart rates all began 1 to 8 minutes after the arecoline infusion, and the mean heart rate was significantly elevated over placebo from 2 to 10 minutes after arecoline infusion (p less than 0.05) [38].

e) Though chewing betel nut alone does not significantly increase catecholamine levels, a popular betel nut preparation does. Six to eight minutes after chewing betel nut, 4 subjects had only a moderate increase in plasma noradrenaline from 266.2 +/- 105.7 picograms/milliliter (pg/mL) to 313.7 +/- 92.9 pg/mL (p equal to 0.0607). Combining betel nut with lime, catechu and Piper betel flower as is commonly done caused significant elevation of norepinephrine in nine subjects from 292.2 +/- 59.5 pg/mL to 375.1 +/- 130.0 pg/mL (p equal to 0.0244) and epinephrine from 62.5 +/- 23.9 pg/mL to 102.2 +/- 45.0 pg/mL (p equal to 0.0226). In this group dopamine was also elevated in 8 of 9 subjects, but the mean was not significant [39].

3.5.1.AU] Bivalirudin

1) Interaction Effect: an increased risk of bleeding

2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs and anticoagulants has been associated with an increased risk of bleeding[458][457]. Bleeding events reported have included epistaxis, ecchymosis, hematoma, petechiae, and life-threatening hemorrhages. Altered anticoagulant effects (including increased bleeding) have been reported with the coadministration of SSRIs with anticoagulants [457].

3) Severity: major

4) Onset: delayed

5) Substantiation: probable

6) Clinical Management: When [fluoxetine](#) and an anticoagulant are given concurrently, monitor patient for signs of increased bleeding. Patients who are taking an anticoagulant should be monitored closely for altered anticoagulant effects, including increased bleeding, when [fluoxetine](#) therapy is initiated or discontinued[457].

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 a significant 1.7-fold increased risk for hospitalization for nongastrointestinal bleeding; however, the rate of [gastrointestinal bleeding](#) was not significantly different [458].

3.5.1.AV] [Bretylum](#)

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

2) Summary: Even though no formal drug interaction studies have been done, the coadministration of Class III antiarrhythmics and other drugs known to prolong the QTc interval is not recommended[300] [301][302]. [Fluoxetine](#) has been shown to prolong the QTc interval at the recommended therapeutic dose [303].

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

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

7) Probable Mechanism: additive effects on QT prolongation

3.5.1.AW] [Brexipiprazole](#)

1) Interaction Effect: increased brexipiprazole exposure

2) Summary: Use caution with concomitant use of brexipiprazole (a CYP2D6 and CYP3A4 substrate) and a strong CYP2D6 inhibitor as this may increase brexipiprazole exposure and increase the risk of adverse effects. If concurrent use of brexipiprazole and a strong CYP2D6 inhibitor is required, administer half the usual brexipiprazole dose for the treatment of conditions other than [major depressive disorder](#) (MDD) because CYP considerations are already factored into the general MDD dosing recommendations. Drug interaction studies revealed a 5.1-fold increase in brexipiprazole AUC in patients who are extensive metabolizers of CYP2D6 taking both strong CYP2D6 and CYP3A4 inhibitors. Therefore, if brexipiprazole is coadministered with a strong CYP2D6 inhibitor AND a strong or moderate CYP3A4 inhibitor, administer a quarter of the usual brexipiprazole dose. If concurrent inhibitors are discontinued, adjust brexipiprazole to original dosage[179].

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Concomitant use of brexipiprazole (a CYP2D6 and CYP3A4 substrate) and a strong CYP2D6 inhibitor should be undertaken with caution as this may increase brexipiprazole exposure and increase the risk of adverse effects. If concurrent use of brexipiprazole and a strong CYP2D6 inhibitor

is required, administer half the usual brexpiprazole dose for the treatment of conditions other than [major depressive disorder](#) (MDD) because CYP considerations are already factored into the general MDD dosing recommendations. If brexpiprazole is coadministered with a strong CYP2D6 inhibitor AND a strong or moderate CYP3A4 inhibitor, administer a quarter of the usual brexpiprazole dose. If concurrent inhibitors are discontinued, adjust brexpiprazole to original dosage[179].

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

3.5.1.AX] [Bromazepam](#)

1J) Interaction Effect: increased risk of respiratory or cardiovascular depression

2J) Summary: Concomitant use of bromazepam with another CNS depressant should be avoided due to increased risk for respiratory or cardiovascular depression and profound sedation[59].

3J) Severity: major

4J) Onset: unspecified

5J) Substantiation: theoretical

6J) Clinical Management: Concomitant use of bromazepam, which is a CNS depressant, with another CNS depressant may result in respiratory or cardiovascular depression and profound sedation. Due to the added CNS depressant effects, avoid use of bromazepam and other CNS depressants[59].

7J) Probable Mechanism: additive CNS depression

3.5.1.AY] [Bromfenac](#)

1J) Interaction Effect: an increased risk of bleeding

2J) Summary: Caution is recommended with the concomitant use of NSAIDs and antidepressants, including SSRIs due to an increased risk of [intracranial hemorrhage](#)[529] and [gastrointestinal bleeding](#) [533][534][530][531]. Bleeding events have included [epistaxis](#), ecchymosis, [hematoma](#), [petechiae](#), and life-threatening hemorrhages [536][535][537][538]. When an SSRI and an NSAID are given concurrently, monitor the patient for signs of increased bleeding.

3J) Severity: major

4J) Onset: unspecified

5J) Substantiation: established

6J) Clinical Management: Use caution if NSAIDs and SSRIs are coadministered. Concomitant use of NSAIDs and SSRIs may cause an increased risk of [intracranial hemorrhage](#)[529] and [gastrointestinal bleeding](#) [530][531]. When an SSRI and an NSAID are given concurrently, monitor the patient for signs of increased bleeding.

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

8J) Literature Reports

aJ) Concomitant use of NSAIDs and antidepressants, including tricyclic antidepressants, SSRIs, serotonin-norepinephrine reuptake inhibitors, and MAOIs, resulted in a 60% increased risk of [intracranial hemorrhage](#) within 30 days of concomitant use compared with antidepressant use alone. There was no significant difference between the antidepressant drug classes and the increased risk; however, there was an increased risk associated with male patients compared with female patients [529].

bJ) SSRIs increase the risk of upper gastrointestinal (GI) bleeding, and this effect is potentiated by concurrent use of NSAIDs or low-dose [aspirin](#). Hospitalizations for [upper GI bleeding](#) were searched among 26,005 users of antidepressant medications and compared with the number of hospitalizations in those patients who did not receive prescriptions for antidepressants. The amount of [upper GI bleeding](#) episodes was 3.6 times more than expected. Combined use of an SSRI and NSAIDs or low-dose [aspirin](#) increased the risk to 12.2 and 5.2 times, respectively. The

findings of this study demonstrate an increased risk of [upper GI bleeding](#) during the use of SSRIs. Combined use of SSRIs and NSAIDs or low-dose [aspirin](#) increased the risk even further [532].

c) Two metaanalyses of incidents of upper GI bleed due to SSRIs, NSAIDs, and their combination found that SSRIs increased the risk by 1.73 [533] to 2.36 times [534], NSAIDs by 2.55 times [533], and the combination of SSRIs and NSAIDs by 4.02 [533] to 6.33 times [534].

d) The release of serotonin by [platelets](#) is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs and NSAIDs have been associated with an increased risk of bleeding [535].

3.5.1.AZ] 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[42].

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[42].

7) Probable Mechanism: additive extrapyramidal side effects

3.5.1.BA] Brompheniramine

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

2) Summary: [Serotonin syndrome](#) may the result from concomitant use of [fluoxetine](#) and serotonergic agents, such as a triptans or other antidepressants. Monitor patients for symptoms of [serotonin syndrome](#), including neuromuscular abnormalities, autonomic instability, and mental status changes, especially during treatment initiation and dose increases. [Serotonin syndrome](#) can be life-threatening. If [serotonin syndrome](#) develops, discontinue [fluoxetine](#) and any concomitant serotonergic agent and initiate supportive care[173].

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Exercise caution with coadministration of [fluoxetine](#) and serotonergic agents, such as a triptans or other antidepressants, because it may result in a life-threatening condition called [serotonin syndrome](#). If these agents are used together, discuss the risks of [serotonin syndrome](#) with the patient and monitor closely for symptoms of [serotonin syndrome](#) (mental status changes, autonomic instability, neuromuscular symptoms, seizures, and gastrointestinal symptoms), especially during treatment initiation and dose increases. If [serotonin syndrome](#) develops, discontinue [fluoxetine](#) and any concomitant serotonergic agent and initiate supportive care[173]

7) Probable Mechanism: additive serotonergic effect

3.5.1.BB] Bupropion

1) Interaction Effect: an increased risk of bleeding

2) Summary: Caution is recommended with the concomitant use of NSAIDs and antidepressants, including SSRIs due to an increased risk of [intracranial hemorrhage](#)[529] and [gastrointestinal bleeding](#) [533][534][530][531]. Bleeding events have included [epistaxis](#), ecchymosis, [hematoma](#), [petechiae](#), and life-

threatening hemorrhages [536][535][537][538]. When an SSRI and an NSAID are given concurrently, monitor the patient for signs of increased bleeding.

3) Severity: major

4) Onset: unspecified

5) Substantiation: established

6) Clinical Management: Use caution if NSAIDs and SSRIs are coadministered. Concomitant use of NSAIDs and SSRIs may cause an increased risk of [intracranial hemorrhage](#)[529] and [gastrointestinal bleeding](#) [530][531]. When an SSRI and an NSAID are given concurrently, monitor the patient for signs of increased bleeding.

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

8) Literature Reports

a) Concomitant use of NSAIDs and antidepressants, including tricyclic antidepressants, SSRIs, serotonin-norepinephrine reuptake inhibitors, and MAOIs, resulted in a 60% increased risk of [intracranial hemorrhage](#) within 30 days of concomitant use compared with antidepressant use alone. There was no significant difference between the antidepressant drug classes and the increased risk; however, there was an increased risk associated with male patients compared with female patients [529].

b) SSRIs increase the risk of upper gastrointestinal (GI) bleeding, and this effect is potentiated by concurrent use of NSAIDs or low-dose [aspirin](#). Hospitalizations for [upper GI bleeding](#) were searched among 26,005 users of antidepressant medications and compared with the number of hospitalizations in those patients who did not receive prescriptions for antidepressants. The amount of [upper GI bleeding](#) episodes was 3.6 times more than expected. Combined use of an SSRI and NSAIDs or low-dose [aspirin](#) increased the risk to 12.2 and 5.2 times, respectively. The findings of this study demonstrate an increased risk of [upper GI bleeding](#) during the use of SSRIs. Combined use of SSRIs and NSAIDs or low-dose [aspirin](#) increased the risk even further [532].

c) Two metaanalyses of incidents of upper GI bleed due to SSRIs, NSAIDs, and their combination found that SSRIs increased the risk by 1.73 [533] to 2.36 times [534], NSAIDs by 2.55 times [533], and the combination of SSRIs and NSAIDs by 4.02 [533] to 6.33 times [534].

d) The release of serotonin by [platelets](#) is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs and NSAIDs have been associated with an increased risk of bleeding [535].

3.5.1.BC] [Buprenorphine](#)

1) Interaction Effect: increased risk of [respiratory depression](#)

2) Summary: Coadministration of [buprenorphine](#) and a CNS depressant may result in additive CNS depression and an increased risk of [respiratory depression](#). If concomitant use is required, consider reducing the dose of one or both agents[119][120] and monitor for signs of [respiratory depression](#), sedation, and hypotension [119].

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Coadministration of [buprenorphine](#) and a CNS depressant may result in additive CNS depression and an increased risk of [respiratory depression](#). If concomitant use is required, consider reducing the dose of one or both agents[119][120] and monitor for signs of [respiratory depression](#), sedation, and hypotension [119].

7) Probable Mechanism: additive [respiratory depression](#)

3.5.1.BD] 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[320]
- 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[320]
- 7) Probable Mechanism: additive serotonergic effects

3.5.1.BE] 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[276].
- 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[276].
- 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 [277].

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](#) Cmax and AUC respectively. The effect persisted for 7 days following the last dose of [buPROPion](#) [278].

3.5.1.BF] Buserelin

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

2)) Summary: Use caution with coadministration of gonadotropin-releasing hormone (GnRH) agonists with QT-interval prolonging drugs. Androgen deprivation caused by GnRH agonists may prolong the QT interval and cause additive effects when administered with QT-interval prolonging drugs[141][142][143]. If concurrent therapy is necessary, monitor patients closely for signs and symptoms of [cardiac toxicity](#), including changes in the ECG.

3)) Severity: major

4)) Onset: unspecified

5)) Substantiation: theoretical

6)) Clinical Management: Use caution with coadministration of gonadotropin-releasing hormone (GnRH) agonists with QT-interval prolonging drugs, as additive effects on the QT interval may occur[141][142][143].

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

3.5.1.BG] Buspirone

1)) Interaction Effect: worsening of psychiatric symptoms

2)) Summary: In a number of case reports, the concomitant use of [busPIRone](#) and [fluoxetine](#) has been reported to result in a worsening of the patient's underlying anxiety/or [obsessive-compulsive disorder](#)[368][369][370]. One case report describes a patient maintained on [fluoxetine](#) who presented with symptoms of [serotonin syndrome](#), including confusion, diaphoresis, incoordination, diarrhea, and myoclonus after [busPIRone](#) was added to his drug regimen [371].

3)) Severity: moderate

4)) Onset: delayed

5)) Substantiation: probable

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

7)) Probable Mechanism: possible inhibition of [busPIRone](#) serotonergic effects

8)) Literature Reports

a)) One of 10 patients with [obsessive-compulsive disorder](#) experienced [anorgasmia](#) after [busPIRone](#) (mean maximum dose, 54 mg daily) was added to [fluoxetine](#) therapy (mean maximum dose, 78 mg daily). The [anorgasmia](#) could not be definitely attributed to the [busPIRone](#) or to an interaction between the two agents. Both [fluoxetine](#) and [busPIRone](#) have reported a low incidence of sexual dysfunction when taken as monotherapy [363][364][365].

b)) Three cases of potentiation of the antidepressant effects of [fluoxetine](#) by [busPIRone](#) have been reported [366]. All three patients had treatment-resistant symptoms of depression, obsessional traits, anxiety, and a history of eating disorder prior to adding [busPIRone](#) to the treatment regimen.

c) A case report describes a 37-year-old male patient maintained on fluoxetine 20mg per day who began combination treatment with busPIRone to augment the actions of fluoxetine. The starting dose of busPIRone was gradually increased from 5mg twice a day to 30mg twice a day over approximately five weeks. After five days at this dose, the patient complained of confusion, diaphoresis, incoordination, diarrhea, and myoclonus, which was thought to be serotonin syndrome. The patients symptoms resolved shortly after discontinuation of busPIRone [367].

3.5.1.BH] Butorphanol

- 1) Interaction Effect: increased risk of CNS depression (ie, respiratory depression, profound sedation, coma)
- 2) Summary: The concomitant use of butorphanol with other CNS depressants may result in profound sedation, respiratory depression, coma, and/or death. Reserve concomitant use to clinical settings where alternative treatment options are inadequate. If combination therapy is required, reduce the initial dose of the newly prescribed medication and titrate to clinical response while monitoring for respiratory depression and sedation[78].
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Reserve concomitant use of butorphanol with other CNS depressants to clinical settings where alternative treatment options are inadequate. If combination therapy is required, reduce the initial dose of the newly prescribed medication and titrate to clinical response while monitoring for respiratory depression and sedation[78].
- 7) Probable Mechanism: additive CNS depression

3.5.1.BI] Cangrelor

- 1) Interaction Effect: increased risk of bleeding
- 2) Summary: Exercise caution when coadministering a SSRI and an antiplatelet agent or anticoagulant as this may increase the risk of bleeding events[272][173][385].
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Use caution with concomitant use of fluoxetine with anticoagulants or antiplatelet agents, as coadministration may increase bleeding risk[272][173][385].
- 7) Probable Mechanism: altered anticoagulant effects
- 8) Literature Reports

a) In a retrospective study of patients over 50 years of age with the diagnosis of acute myocardial infarction (N=27,058), SSRI use with any antiplatelet therapy significantly increased the risk of bleeding by 1.42-fold compared with aspirin use alone. Therapy with aspirin, clopidogrel, and an SSRI significantly increased risk by 2.35-fold compared with aspirin use alone and by 1.57-fold compared with clopidogrel and aspirin combination therapy [385].

b) In a systematic review and meta-analysis of 22 observational studies, SSRI use was associated with a significant 1.55 fold increase in risk of upper gastrointestinal bleeding (UGIB). Concomitant use of SSRIs and antiplatelet drugs was associated with a 2.48-fold increase in risk of UGIB (3 studies) [272].

3.5.1.BJ] Cannabis

1) Interaction Effect: manic symptoms

2) Summary: One case of mania following use of marijuana with fluoxetine therapy has been reported[241]. Although an interaction is proposed, the authors also state the manic symptoms could have resulted from the fluoxetine or marijuana alone. Caution is advised for patients using marijuana and taking fluoxetine or other serotonin reuptake inhibitors.

3) Severity: moderate

4) Onset: rapid

5) Substantiation: theoretical

6) Clinical Management: Caution patients taking selective serotonin reuptake inhibitors to avoid concomitant use of marijuana.

7) Probable Mechanism: additive serotonergic stimulation

8) Literature Reports

a) A 21-year-old female presented with mania, agitation, and grandiose delusions following use of marijuana with fluoxetine therapy. She had been taking fluoxetine 20 mg daily for 4 weeks and reported smoking 2 "joints" during a 36-hour period. Over the next 24 hours, she developed increased energy, hypersexuality, pressured speech, and grandiose delusions. Lorazepam and perphenazine were given for agitation and excitement which gradually resolved over 4 days. She remained hospitalized for 36 days. Fluoxetine 20 mg every other day was reintroduced one week prior to discharge. One week after discharge, she discontinued fluoxetine due to insomnia and feeling "hyper". These symptoms resolved rapidly upon discontinuation of fluoxetine. Due to the rapid switch to mania after smoking marijuana with fluoxetine, the manic symptoms were associated with the concomitant use of fluoxetine and marijuana, though mania could have developed from either fluoxetine or marijuana alone [240].

3.5.1.BK] Carbamazepine

1) Interaction Effect: reduced olanzapine efficacy and increased carbamazepine exposure and risk for toxicity

2) Summary: Concomitant use of carbamazepine (CYP3A4 substrate, CYP1A2 inducer) and olanzapine (CYP3A4 inhibitor, CYP1A2 substrate) may cause elevated carbamazepine levels[110] and decreased olanzapine levels. Concomitant administration of olanzapine and carbamazepine 200 mg twice daily increased the clearance of olanzapine by 50% [111]. In a case report, after carbamazepine discontinuation there was a 114% increase in olanzapine serum concentrations [113]. Carbamazepine levels should be closely monitored and the dosage adjusted, if required [110]. Patients may also need to be monitored for olanzapine efficacy.

3) Severity: major

4) Onset: rapid

5) Substantiation: probable

6) Clinical Management: Concomitant use of carbamazepine (CYP3A4 substrate) and olanzapine (CYP3A4 inhibitor) may cause elevated carbamazepine levels. Closely monitor carbamazepine levels and adjust the dosage, if required[110]. Coadministration of carbamazepine (CYP1A2 inducer) and olanzapine (CYP1A2 substrate) may also result in decreased olanzapine exposure [111]. Monitor patients for olanzapine efficacy.

7) Probable Mechanism: induction of CYP1A2-mediated olanzapine metabolism by carbamazepine; inhibition of CYP3A4-mediated carbamazepine metabolism by olanzapine

8) Literature Reports

a) A 23-year-old paranoid schizophrenic female was treated with carbamazepine 600 mg daily for aggressive outbursts along with perphenazine, her only medication on admission. Olanzapine 15 mg daily was started and her psychiatric symptoms improved over the next 3 weeks. Because her aggressive outbursts were still present, carbamazepine was discontinued due to lack of efficacy. The day prior to carbamazepine discontinuation, the olanzapine serum concentration was 21 ng/mL. Over the next few weeks following carbamazepine discontinuation, the olanzapine concentration increased by 114% to 45 ng/mL. The dose of olanzapine was decreased to 10 mg daily and a corresponding fall in the olanzapine level occurred [112].

3.5.1.BL] Carbamazepine

- 1) Interaction Effect: increased carbamazepine exposure and increased risk of toxicity
- 2) Summary: The concomitant use of carbamazepine, a CYP3A4 substrate, and fluoxetine, a CYP3A4 inhibitor, may increase the exposure of carbamazepine[201] and increase the risk of toxicity [207][208] [209]. Conversely, in 1 study of 8 patients no changes in steady state carbamazepine levels have been reported with the addition of fluoxetine [210]. In a case report, symptoms of serotonin syndrome were reported with this combination [211]. If carbamazepine is used concomitantly with fluoxetine, closely monitor carbamazepine levels and adjust the carbamazepine dosage as needed [200].
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: probable
- 6) Clinical Management: Coadministration of carbamazepine, a CYP3A4 substrate, and fluoxetine, a CYP3A4 inhibitor, may result in increased carbamazepine exposure. If coadministering, closely monitor carbamazepine levels and adjust the carbamazepine dosage as needed[200][201].
- 7) Probable Mechanism: inhibition of CYP3A4-mediated metabolism of carbamazepine by fluoxetine
- 8) Literature Reports

a) An interaction between carbamazepine and fluoxetine was reported in 6 normal volunteers. Carbamazepine was given for 28 days, and fluoxetine was added to the regimen on day 7. The addition of fluoxetine 20 mg daily to carbamazepine 400 mg daily resulted in an increase in the AUC for both carbamazepine and carbamazepine-epoxide and a decrease in clearance of carbamazepine. No significant changes were observed in absorption, volume of distribution, or elimination rate constant, indicating that fluoxetine inhibits the metabolism of carbamazepine [202].

b) The effect of fluoxetine 20 mg daily was studied for 3 weeks in 8 epileptic patients who were stabilized on carbamazepine therapy. Steady-state plasma levels of carbamazepine and its epoxide metabolite were not significantly changed with concurrent use of fluoxetine. These results differ from previous reports. The authors speculate that chronic carbamazepine administration may have resulted in enzyme induction that caused decreased levels of fluoxetine, thereby lowering the chances of a metabolic interaction. Unfortunately, fluoxetine levels were not measured [203].

c) An interaction between carbamazepine and fluoxetine was reported in 2 patients receiving chronic carbamazepine dosages of 600 mg and 1000 mg daily respectively. Within 7 to 10 days of initiation of fluoxetine 20 mg daily, both patients developed symptoms of carbamazepine toxicity. Symptoms disappeared within 2 weeks in one patient following carbamazepine dosage reduction by 200 mg daily; in the other patient, fluoxetine was discontinued with symptom resolution within 2 weeks [204].

d) Two cases of [parkinsonism](#) were reported after [fluoxetine](#) was added to an existing [carbamazepine](#) regimen. One patient, a 74-year old man, developed symptoms 3 days after [fluoxetine](#) 20 mg per day was added to an existing 12-month regimen of [carbamazepine](#) 200 mg twice daily. The patient developed cogwheel rigidity, a mask-like face, and a parkinsonian gait. After discontinuation of [fluoxetine](#) and treatment with dextimide, the patient showed only a slight hypertonia of the arms 17 days later. The other patient, a 53-year old woman, developed parkinsonian symptoms after [fluoxetine](#) 20 mg per day was added to an existing regimen of [carbamazepine](#) 200 mg twice daily. The patient had also been taking [thioridazine](#) 275 mg per day which was stopped when [fluoxetine](#) was added. The patient developed cogwheel rigidity and a mask-like face 9 days after initiation of [fluoxetine](#) therapy [205].

e) A female patient experienced a drug interaction 14 days after she had [fluoxetine](#) 20 mg added to a regimen of [carbamazepine](#) 200 mg daily. The patient presented with symptoms of [serotonin syndrome](#), such as uncontrollable shivering, agitation, incoordination, myoclonus, hyperreflexia, and diaphoresis. The patient also had [leukopenia](#) and [thrombocytopenia](#). After discontinuation of [fluoxetine](#), all symptoms of [serotonin syndrome](#) and hematological abnormalities resolved over the next 72 hours [206].

3.5.1.BM] [Celecoxib](#)

1) Interaction Effect: an increased risk of bleeding

2) Summary: Caution is recommended with the concomitant use of NSAIDs and antidepressants, including SSRIs due to an increased risk of [intracranial hemorrhage](#)[529] and [gastrointestinal bleeding](#) [533][534][530][531]. Bleeding events have included [epistaxis](#), ecchymosis, [hematoma](#), [petechiae](#), and life-threatening hemorrhages [536][535][537][538]. When an SSRI and an NSAID are given concurrently, monitor the patient for signs of increased bleeding.

3) Severity: major

4) Onset: unspecified

5) Substantiation: established

6) Clinical Management: Use caution if NSAIDs and SSRIs are coadministered. Concomitant use of NSAIDs and SSRIs may cause an increased risk of [intracranial hemorrhage](#)[529] and [gastrointestinal bleeding](#) [530][531]. When an SSRI and an NSAID are given concurrently, monitor the patient for signs of increased bleeding.

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

8) Literature Reports

a) Concomitant use of NSAIDs and antidepressants, including tricyclic antidepressants, SSRIs, serotonin-norepinephrine reuptake inhibitors, and MAOIs, resulted in a 60% increased risk of [intracranial hemorrhage](#) within 30 days of concomitant use compared with antidepressant use alone. There was no significant difference between the antidepressant drug classes and the increased risk; however, there was an increased risk associated with male patients compared with female patients [529].

b) SSRIs increase the risk of upper gastrointestinal (GI) bleeding, and this effect is potentiated by concurrent use of NSAIDs or low-dose [aspirin](#). Hospitalizations for [upper GI bleeding](#) were searched among 26,005 users of antidepressant medications and compared with the number of hospitalizations in those patients who did not receive prescriptions for antidepressants. The amount of [upper GI bleeding](#) episodes was 3.6 times more than expected. Combined use of an SSRI and NSAIDs or low-dose [aspirin](#) increased the risk to 12.2 and 5.2 times, respectively. The

findings of this study demonstrate an increased risk of [upper GI bleeding](#) during the use of SSRIs. Combined use of SSRIs and NSAIDs or low-dose [aspirin](#) increased the risk even further [532].

c) Two metaanalyses of incidents of upper GI bleed due to SSRIs, NSAIDs, and their combination found that SSRIs increased the risk by 1.73 [533] to 2.36 times [534], NSAIDs by 2.55 times [533], and the combination of SSRIs and NSAIDs by 4.02 [533] to 6.33 times [534].

d) The release of serotonin by [platelets](#) is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs and NSAIDs have been associated with an increased risk of bleeding [535].

3.5.1.BN] Certoparin

1) Interaction Effect: an increased risk of bleeding

2) Summary: The release of serotonin by [platelets](#) is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs and anticoagulants has been associated with an increased risk of bleeding[458][457]. Bleeding events reported have included [epistaxis](#), ecchymosis, [hematoma](#), [petechiae](#), and life-threatening hemorrhages. Altered anticoagulant effects (including increased bleeding) have been reported with the coadministration of SSRIs with anticoagulants [457].

3) Severity: major

4) Onset: delayed

5) Substantiation: probable

6) Clinical Management: When [fluoxetine](#) and an anticoagulant are given concurrently, monitor patient for signs of increased bleeding. Patients who are taking an anticoagulant should be monitored closely for altered anticoagulant effects, including increased bleeding, when [fluoxetine](#) therapy is initiated or discontinued[457].

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 a significant 1.7-fold increased risk for hospitalization for nongastrointestinal bleeding; however, the rate of [gastrointestinal bleeding](#) was not significantly different [458].

3.5.1.BO] Chloral Hydrate

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

2) Summary: [Chloral](#) hydrate and [fluoxetine](#) have been shown to prolong the QTc interval at the recommended therapeutic dose[414][415]. Even though no formal drug interaction studies have been done, the coadministration of drugs known to prolong the QTc interval is not recommended.

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Concomitant use of [chloral](#) hydrate and [fluoxetine](#) is not recommended.

7) Probable Mechanism: additive effects on QT prolongation

8) Literature Reports

a) QT Prolongation was observed on the [electrocardiogram](#) (ECG) of a 52- year-old man who had been taking [fluoxetine](#) (20 milligrams/day for 2 weeks, followed by 40 milligrams/day thereafter) for depression for 3 months. An ECG just before the start of [fluoxetine](#) treatment showed a normal QT interval. The QT interval returned to normal within 10 days of discontinuing [fluoxetine](#) treatment [413].

3.5.1.BP| [Chloroquine](#)

- 1) Interaction Effect: an increased risk of [cardiotoxicity](#) (QT prolongation, [torsades de pointes](#), [cardiac arrest](#))
- 2) Summary: [Chloroquine](#) and [fluoxetine](#) have been shown to prolong the QTc interval at the recommended therapeutic dose[218][219]. Even though no formal drug interaction studies have been done, the coadministration of drugs known to prolong the QTc interval is not recommended.
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: The concurrent administration of [chloroquine](#) and [fluoxetine](#) is not recommended.
- 7) Probable Mechanism: additive effects on QT prolongation

3.5.1.BQ| [Chlorpheniramine](#)

- 1) Interaction Effect: increased risk of [serotonin syndrome](#)
- 2) Summary: [Serotonin syndrome](#) may the result from concomitant use of [fluoxetine](#) and serotonergic agents, such as a triptans or other antidepressants. Monitor patients for symptoms of [serotonin syndrome](#), including neuromuscular abnormalities, autonomic instability, and mental status changes, especially during treatment initiation and dose increases. [Serotonin syndrome](#) can be life-threatening. If [serotonin syndrome](#) develops, discontinue [fluoxetine](#) and any concomitant serotonergic agent and initiate supportive care[173].
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Exercise caution with coadministration of [fluoxetine](#) and serotonergic agents, such as a triptans or other antidepressants, because it may result in a life-threatening condition called [serotonin syndrome](#). If these agents are used together, discuss the risks of [serotonin syndrome](#) with the patient and monitor closely for symptoms of [serotonin syndrome](#) (mental status changes, autonomic instability, neuromuscular symptoms, seizures, and gastrointestinal symptoms), especially during treatment initiation and dose increases. If [serotonin syndrome](#) develops, discontinue [fluoxetine](#) and any concomitant serotonergic agent and initiate supportive care[173]
- 7) Probable Mechanism: additive serotonergic effect

3.5.1.BR| [Chlorpromazine](#)

- 1) Interaction Effect: increased [fluoxetine](#) exposure and increased risk of QT interval prolongation
- 2) Summary: Use caution with coadministration of [chlorpromazine](#) and [fluoxetine](#), as concomitant use may cause additive effects on QT interval prolongation. Additionally concomitant use of [chlorpromazine](#) (CYP2D6 inhibitor) and [fluoxetine](#) (CYP2D6 substrate) may increase [fluoxetine](#) exposure and increase the risk for [fluoxetine](#) toxicity. If concomitant use is required, consider [monitoring ECG](#) at baseline and periodically during therapy if initiating [fluoxetine](#) in patients with risk factors for QT interval prolongation and [ventricular arrhythmia](#). If signs or symptoms of [ventricular arrhythmia](#) occur

consider discontinuation of [fluoxetine](#) and follow-up with a cardiac evaluation [173]. Consider monitoring for signs and symptoms of [fluoxetine](#) toxicity.

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Use caution with coadministration of [chlorproMAZINE](#) and [fluoxetine](#), as concurrent use may increase the risk of QT interval prolongation and increase the risk of [fluoxetine](#) toxicity. If concomitant use is required, consider [monitoring ECG](#) at baseline and periodically during therapy if initiating [fluoxetine](#) in patients with risk factors for QT interval prolongation and [ventricular arrhythmia](#). If signs or symptoms of [ventricular arrhythmia](#) occur consider discontinuation of [fluoxetine](#) and follow-up with a cardiac evaluation[173]. Consider monitoring for [fluoxetine](#) toxicity.

7) Probable Mechanism: additive QT interval prolongation; inhibition of CYP2D6-mediated metabolism of [fluoxetine](#) by [chlorproMAZINE](#)

3.5.1.BS| [Choline Salicylate](#)

1) Interaction Effect: an increased risk of bleeding

2) Summary: Caution is recommended with the concomitant use of NSAIDs and antidepressants, including SSRIs due to an increased risk of [intracranial hemorrhage](#)[529] and [gastrointestinal bleeding](#) [533][534][530][531]. Bleeding events have included [epistaxis](#), ecchymosis, [hematoma](#), [petechiae](#), and life-threatening hemorrhages [536][535][537][538]. When an SSRI and an NSAID are given concurrently, monitor the patient for signs of increased bleeding.

3) Severity: major

4) Onset: unspecified

5) Substantiation: established

6) Clinical Management: Use caution if NSAIDs and SSRIs are coadministered. Concomitant use of NSAIDs and SSRIs may cause an increased risk of [intracranial hemorrhage](#)[529] and [gastrointestinal bleeding](#) [530][531]. When an SSRI and an NSAID are given concurrently, monitor the patient for signs of increased bleeding.

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

8) Literature Reports

a) Concomitant use of NSAIDs and antidepressants, including tricyclic antidepressants, SSRIs, serotonin-norepinephrine reuptake inhibitors, and MAOIs, resulted in a 60% increased risk of [intracranial hemorrhage](#) within 30 days of concomitant use compared with antidepressant use alone. There was no significant difference between the antidepressant drug classes and the increased risk; however, there was an increased risk associated with male patients compared with female patients [529].

b) SSRIs increase the risk of upper gastrointestinal (GI) bleeding, and this effect is potentiated by concurrent use of NSAIDs or low-dose [aspirin](#). Hospitalizations for [upper GI bleeding](#) were searched among 26,005 users of antidepressant medications and compared with the number of hospitalizations in those patients who did not receive prescriptions for antidepressants. The amount of [upper GI bleeding](#) episodes was 3.6 times more than expected. Combined use of an SSRI and NSAIDs or low-dose [aspirin](#) increased the risk to 12.2 and 5.2 times, respectively. The findings of this study demonstrate an increased risk of [upper GI bleeding](#) during the use of SSRIs. Combined use of SSRIs and NSAIDs or low-dose [aspirin](#) increased the risk even further [532].

c) Two metaanalyses of incidents of upper GI bleed due to SSRIs, NSAIDs, and their combination found that SSRIs increased the risk by 1.73 [533] to 2.36 times [534], NSAIDs by 2.55 times [533], and the combination of SSRIs and NSAIDs by 4.02 [533] to 6.33 times [534].

d)] The release of serotonin by [platelets](#) is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs and NSAIDs have been associated with an increased risk of bleeding [535].

3.5.1.BT] [Cilostazol](#)

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

2)] Summary: [Cilostazol](#) (a CYP2C19 substrate) exposure is increased with concomitant administration of [fluoxetine](#) (a CYP2C19 inhibitor)[292]. Concomitant use of [cilostazol](#) (a CYP2C19 substrate) and [omeprazole](#) (a CYP2C19 inhibitor) resulted in increased plasma concentrations of [cilostazol](#) and one of its active metabolites [294]. Additionally, case-control and cohort studies have shown that coadministration of SSRIs and antiplatelet agents has been associated with an increased risk of bleeding due to the additive effects on [platelets](#). Bleeding events reported have included [epistaxis](#), ecchymosis, [hematoma](#), [petechiae](#), and life-threatening hemorrhages [293]. If coadministration is required, consider reducing the [cilostazol](#) dose to 50 mg twice daily [292] and monitor patient for signs of increased bleeding [293].

3)] Severity: major

4)] Onset: unspecified

5)] Substantiation: probable

6)] Clinical Management: [Cilostazol](#) (a CYP2C19 substrate) exposure is increased with concomitant administration of [fluoxetine](#) (a CYP2C19 inhibitor)[292]. Additionally, concomitant use of SSRIs and antiplatelet agents may increase the risk of bleeding due to the additive effects on [platelets](#) [293]. If coadministration is required, consider reducing the [cilostazol](#) dose to 50 mg twice daily [292] and monitor patient for signs of increased bleeding [293].

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

8)] Literature Reports

a)] Concomitant use of [cilostazol](#), a CYP2C19 substrate, and [omeprazole](#), a CYP2C19 inhibitor, resulted in increased plasma concentrations of [cilostazol](#) and one of its active metabolites. Twenty healthy nonsmoking volunteers participated in a single-center, open-label study to evaluate the effect of [omeprazole](#) on the pharmacokinetics of a single dose of [cilostazol](#) 100 mg. Each study subject received [cilostazol](#) 100 mg on day 0 under fasting conditions. On days 7 through 18, [omeprazole](#) 40 mg was given each morning. Another single dose of [cilostazol](#) 100 mg was administered with [omeprazole](#) on day 14. After [omeprazole](#) administration, the C_{max} of [cilostazol](#) increased by 18% (from 782 mcg/L to 921 mcg/L) and the AUC increased by 26% (from 10,287 mcg/L/h to 13,033 mcg/L/hr). The mean C_{max} of OPC-13015, a pharmacologically active metabolite of [cilostazol](#), increased by 29% and the AUC increased by 69% in the presence of [omeprazole](#). Conversely, the C_{max} and AUC of OPC-13213, another pharmacologically active metabolite of [cilostazol](#), decreased by 22% and 31%, respectively. Although the changes in systemic exposure to [cilostazol](#) were well tolerated, the dose of [cilostazol](#) should be reduced to 50 mg twice daily when given concurrently with [omeprazole](#) [294].

3.5.1.BU] [Cinacalcet](#)

1)] Interaction Effect: elevated [fluoxetine](#) plasma concentrations and increased risk of QT-interval prolongation

2)] Summary: Concomitant treatment of [fluoxetine](#) with other CYP2D6 inhibitors can increase [fluoxetine](#) plasma concentrations and increase the risk of adverse effects, including episodes of QT-interval prolongation, [ventricular arrhythmia](#), and [torsade de pointes](#). Use caution in coadministration of these

drugs[173]. If concomitant use is required, initiate [fluoxetine](#) at the lowest dose possible and titrate dose carefully based on patient response [540].

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Use caution with coadministration of [fluoxetine](#) and CYP2D6 inhibitors, as increased [fluoxetine](#) plasma concentrations may increase the risk of adverse effects, including episodes of QT-interval prolongation, [ventricular arrhythmia](#), and [torsade de pointes](#)[173]. If concomitant use is required, initiate [fluoxetine](#) at the lowest dose possible and titrate dose carefully based on patient response [540].

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

3.5.1.BV] [Ciprofloxacin](#)

1) Interaction Effect: an increased risk of [olanzapine](#) toxicity (increased sedation, orthostatic hypotension)

2) Summary: [Ciprofloxacin](#) was suspected of inhibiting the metabolism of [olanzapine](#) in a 54-year-old female receiving concurrent therapy. Cytochrome P450 1A2 (CYP1A2) has been shown in vitro to be responsible for the formation of some of the metabolites of [olanzapine](#), and [ciprofloxacin](#) is a known potent inhibitor of CYP1A2. Although [olanzapine](#) has a wide therapeutic range and a correlation between plasma concentrations and adverse effects has not been established, this interaction may be clinically significant[137].

3) Severity: moderate

4) Onset: delayed

5) Substantiation: probable

6) Clinical Management: Patients receiving [olanzapine](#) and [ciprofloxacin](#) concurrently should be monitored for increased [olanzapine](#) adverse effects, such as increased sedation and orthostatic hypotension.

7) Probable Mechanism: inhibition by [ciprofloxacin](#) of cytochrome P450 1A2-mediated [olanzapine](#) metabolism

8) Literature Reports

a) A 54-year-old female was admitted to the hospital with [suicidal ideation](#) and [lacerations to her wrists](#). Medication prior to admission included [olanzapine](#) 10 mg at bedtime, [nefazodone](#) 100 mg twice daily, [atenolol](#) 25 mg daily, [levothyroxine](#) 0.25 mg daily, and [phenytoin](#) 100 mg twice daily. [Nefazodone](#) was tapered off prior to [electroconvulsive therapy](#), and [ciprofloxacin](#) 250 mg twice daily for seven days was initiated for a suspected [urinary tract infection](#). Immediately before her last dose of [ciprofloxacin](#), the plasma [olanzapine](#) concentration was 32.6 ng/mL (104.3 nanomol/L). Three days after [ciprofloxacin](#) was discontinued, her [olanzapine](#) concentration had decreased by more than 50% to 14.6 ng/mL (46.7 nanomol/L). Although this patient did not experience any adverse effects from her increased [olanzapine](#) level, higher doses of [ciprofloxacin](#) could potentially cause more inhibition of [olanzapine](#) metabolism [136].

3.5.1.BW] [Cisapride](#)

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

2) Summary: The concomitant use of [cisapride](#) with drugs that cause QT-interval prolongation is contraindicated, as coadministration may increase the risk of QT prolongation and serious [ventricular arrhythmias](#)[71].

3) Severity: contraindicated

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: The concomitant use of [cisapride](#) with drugs that cause QT-interval prolongation is contraindicated, as coadministration may increase the risk of QT prolongation and serious [ventricular arrhythmias](#)[71].

7) Probable Mechanism: additive QT-interval prolongation

3.5.1.BX] [Citalopram](#)

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

2) Summary: [Fluoxetine](#) is an SSRI and a moderate CYP2C19 inhibitor associated with QT prolongation (and [ventricular arrhythmias](#) including [torsade de pointes](#))[173], and [citalopram](#) is an SSRI and a CYP2C19 substrate associated with dose-dependent QT prolongation. In a [pharmacokinetic study](#), patients who received [citalopram](#) 40 mg/day for 21 days coadministered with [cimetidine](#) (a potent CYP2C19 inhibitor) 400 mg/day for 8 days experienced an increase in [citalopram](#) AUC and Cmax of 43% and 39%, respectively [237]. Although the interaction between [citalopram](#) and [fluoxetine](#) has not been studied specifically, concomitant use may result in increased [citalopram](#) exposure, an increased risk of QT prolongation, and additive serotonergic effects. If coadministration of [citalopram](#) with [fluoxetine](#) is required, do not exceed [citalopram](#) 20 mg/day, and additionally monitor for symptoms of [serotonin syndrome](#), including neuromuscular abnormalities, autonomic instability, gastrointestinal symptoms, and mental status changes, especially during treatment initiation and dose increases. [Serotonin syndrome](#) can be life-threatening. If [serotonin syndrome](#) develops, discontinue [citalopram](#) and [fluoxetine](#) and initiate supportive care [237].

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: The concomitant use of [citalopram](#) with [fluoxetine](#) may result in increased [citalopram](#) exposure and risk of QT prolongation. If coadministration of [citalopram](#) with [fluoxetine](#) is required, do not exceed [citalopram](#) doses of 20 mg/day. Additionally, concurrent use of [citalopram](#) with [fluoxetine](#) is not recommended because it may result in a life-threatening condition called [serotonin syndrome](#). If concomitant use is necessary, discuss the risks of [serotonin syndrome](#) with the patient and monitor closely for symptoms of [serotonin syndrome](#) (mental status changes, autonomic instability, neuromuscular symptoms, seizures, and gastrointestinal symptoms), especially during treatment initiation and dose increases. If [serotonin syndrome](#) develops, discontinue [citalopram](#) and [fluoxetine](#) and initiate supportive care[237].

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

3.5.1.BY] [Clarithromycin](#)

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

2) Summary: Use caution with coadministration of [clarithromycin](#) with other selected QT-prolonging agents, as additive prolongation effects on the QT interval may occur[138].

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Use caution with coadministration of [clarithromycin](#) with other selected QT-prolonging agents, as additive prolongation effects on the QT interval may occur[138].

7) Probable Mechanism: additive prolongation effects on QT interval

3.5.1.BZ] [Clobazam](#)

- 1) Interaction Effect: increased [fluoxetine](#) plasma concentrations
- 2) Summary: The concomitant use of [fluoxetine](#), a CYP2D6 substrate[270], and clobazam, a CYP2D6 inhibitor, may increase [fluoxetine](#) plasma concentrations. Dose reduction of [fluoxetine](#) may be required when coadministered with clobazam [463].
- 3) Severity: moderate
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: The concomitant use of clobazam with [fluoxetine](#) may cause increased [fluoxetine](#) plasma concentrations. If administered concomitantly, a dose reduction of [fluoxetine](#) may be warranted[463].
- 7) Probable Mechanism: inhibition of CYP2D6-mediated [fluoxetine](#) metabolism by clobazam

3.5.1.CA] [Clomipramine](#)

- 1) Interaction Effect: an increased risk of seizures
- 2) Summary: Psychotropic drugs have been shown to reduce the seizure threshold. A case report describes a patient without an underlying seizure disorder who received treatment with [olanzapine](#) and [clomiPRAMINE](#) concomitantly. This combination resulted in seizures which were repeated upon rechallenge with [olanzapine](#) and [clomiPRAMINE](#). It is advised to use caution when administering [olanzapine](#) concomitantly with [clomiPRAMINE](#), or any agent known to reduce seizure threshold[95].
- 3) Severity: major
- 4) Onset: delayed
- 5) Substantiation: probable
- 6) Clinical Management: It is advised to use caution when administering [olanzapine](#) concomitantly with [clomiPRAMINE](#), or other agents known to lower the seizure threshold.
- 7) Probable Mechanism: unknown
- 8) Literature Reports

a) A 34-year-old male with [schizophrenia](#) and [obsessive-compulsive disorder](#) (OCD) without any underlying seizure disorder, presented for treatment following long-term noncompliance. Inpatient [olanzapine](#) treatment (20 mg/day) was initiated and positive psychotic symptoms subsequently resolved. Patient was discharged and readmitted because of inability to control symptoms. [ClomiPRAMINE](#) 250 mg per day was initiated. Within a week, dizziness and myoclonic jerks were reported which quickly progressed to general motor seizures and postictal somnolence (without incontinence). Spike waves and paroxysmal slowing on the EEG was consistent with seizure activity. [ClomiPRAMINE](#) and [olanzapine](#) were subsequently withheld, and the seizures were controlled with [diazepam](#) 30 mg per day for three days. This pattern repeated upon re-challenge with the combination of [olanzapine](#) and [clomiPRAMINE](#). Presumably from the temporal relationship between [clomiPRAMINE](#) and [olanzapine](#) administration and seizure manifestation, it can be suspected that this adverse event is due to an interaction between these two drugs. [ClomiPRAMINE](#) and [olanzapine](#) are both metabolized by the cytochrome P450 isoenzymes 1A2 and 2D6. One theory is that coadministration may result in elevated levels of both compounds. Although the mechanism by which this interaction occurs is not yet known, it is advised to use caution when administering [olanzapine](#) concomitantly with [clomiPRAMINE](#), or other agents known to lower the seizure threshold [94].

3.5.1.CB] [Clomipramine](#)

- 1) Interaction Effect: increased risk of tricyclic antidepressant toxicity, QT prolongation and [serotonin syndrome](#)

2) Summary: **Fluoxetine**, a potent CYP2D6 inhibitor, is associated with an increased risk of **serotonin syndrome**, QT prolongation, and **ventricular arrhythmias** (including **torsade de pointes**). Concomitant therapy with CYP2D6-metabolized tricyclic antidepressants (TCAs) may potentiate these risks and introduce TCA toxicity[173]; concurrent use of **fluoxetine** and **desipramine**, **nortriptyline**, and **imipramine** has resulted in significant increases in TCA concentrations [517][523][524][525][526][527]. Use caution with concurrent administration of **fluoxetine** and TCAs. If **fluoxetine** is added to an existing TCA regimen, consider TCA dose reduction. If **fluoxetine** and a TCA are coadministered or **fluoxetine** has been recently discontinued, consider plasma TCA monitoring. If **serotonin syndrome** occurs, immediately discontinue **fluoxetine** and TCA. If **ventricular arrhythmias** develop, consider **fluoxetine** discontinuation and cardiac evaluation [173].

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Use caution with concurrent administration of **fluoxetine** and TCAs, as elevated TCA plasma concentrations may occur. If **fluoxetine** is added to an existing TCA regimen, consider TCA dose reduction. If **fluoxetine** and a TCA are coadministered or **fluoxetine** has been recently discontinued, consider plasma TCA monitoring. If **serotonin syndrome** occurs, immediately discontinue **fluoxetine** and TCA. If **ventricular arrhythmias** develop, consider **fluoxetine** discontinuation and cardiac evaluation[173]

7) Probable Mechanism: decreased CYP2D6-mediated metabolism of tricyclic antidepressants by **fluoxetine**; additive effects on QT prolongation; additive serotonergic effects

8) Literature Reports

a) Previously stable plasma levels of **imipramine** and **desipramine** rose more than 2- to 10-fold with **fluoxetine** coadministration in 2 clinical studies. This effect may persist for 3 weeks or more after **fluoxetine** discontinuation. Dose reduction and temporary monitoring of tricyclic antidepressant plasma concentrations may be indicated with concurrent **fluoxetine** treatment or recent **fluoxetine** discontinuation [173].

b) **Fluoxetine** statistically and clinically significantly increased **desipramine** concentrations in 18 healthy subjects. When **fluoxetine** (20 mg daily) was added to **desipramine** (50 mg daily), the mean maximum concentration of **desipramine** increased by 278% and the AUC increased by 342%. **Desipramine** trough concentrations continued to be 198% above baseline 3 weeks after **fluoxetine** was discontinued. The same study compared pharmacokinetics of **desipramine** when combined with **sertraline**. The impact of **sertraline** was modest, resulting in small and short-term increases in **desipramine** plasma concentrations [517].

c) Concomitant administration of **fluoxetine** and **desipramine** was reported to result in an increased **desipramine** level and new onset of **delirium** in a 69-year-old male within 10 days of the addition of **fluoxetine** to the patient's regimen [518].

d) **Fluoxetine** increased the level of tricyclic antidepressants (**nortriptyline**, **imipramine**, **desipramine**) in 4 patients. After the addition of **fluoxetine**, the ratio of antidepressant level to dose increased by 109% to 486% in the patients. Three patients developed clinical symptoms (anticholinergic effects, constipation, urinary hesitancy, sedation, unstable gait) as a result of the increased levels [519].

e) A 39-year-old female experienced symptomatic increases in her **desipramine** levels with concomitant **fluoxetine** therapy. Prior to **fluoxetine** therapy, the patient's measured levels of **desipramine** had ranged from 148 to 160 nanograms/milliliter (ng/mL; 556 to 601 nanomol/L) on a regimen of 300 mg daily. Five weeks after the addition of **fluoxetine** 20 mg daily, she reported anticholinergic symptoms, sedation, and confusion with a **desipramine** level of 527 ng/mL (1978

nanomol/L). The [desipramine](#) dose was lowered to 200 mg/day; 11 days later, the level was 244 ng/mL (916 nanomol/L); the patient reported decreased energy, impaired short-term memory, and some "garbled" speech, as well as an episode of nausea, dizziness, and syncope. The [desipramine](#) dose was reduced to 50 mg/day, and the adverse effects resolved in 6 days. Eight days later, the [desipramine](#) level was 122 ng/mL (458 nanomol/L) [520].

f) A 33-year-old depressed male developed adverse effects of dry mouth, tinnitus, and difficulties with alertness and memory while receiving [fluoxetine](#) 40 mg daily and [desipramine](#) 150 mg daily for 5 weeks; [fluoxetine](#) was discontinued and the blood levels of [desipramine](#) decreased from 938 to 48 nanograms/mL (3521 to 180 nanomol/L) with resolution of clinical symptoms [521].

g) A 75-year-old female experienced symptomatic increases in her [desipramine](#) serum concentrations when [fluoxetine](#) was added. [Desipramine](#) serum levels ranged from 109 to 150 ng/mL (409 to 563 nanomol/L) with oral doses of 300 mg at bedtime prior to [fluoxetine](#) therapy. Following the addition of oral [fluoxetine](#) 20 mg daily to the regimen, the [desipramine](#) serum level increased to 212 ng/mL (796 nanomol/L) within five days. The [fluoxetine](#) dose was increased to 40 mg/day three days later, and the [desipramine](#) serum level was 419 ng/mL (1573 nanomol/L) after four days. A worsening of depression and severe fatigue coincided with the increases in [desipramine](#) serum levels. Withdrawal of [fluoxetine](#) and reduction in the [desipramine](#) dose to 200 mg daily reduced the [desipramine](#) serum level to 231 ng/mL (867 nanomol/L) within two weeks [522].

3.5.1.CC] [Clonidine](#)

- 1) Interaction Effect: induction or exacerbation of orthostatic regulation disturbances
- 2) Summary: [Olanzapine](#) is a neuroleptic agent which may enhance the effects of certain antihypertensive medications, which may induce hypotension[50]. As the concomitant use of [clonidine](#) with [olanzapine](#) may result in orthostatic regulation disturbance induction or exacerbation [51][52], coadministration should be approached with caution.
- 3) Severity: moderate
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: The concomitant use of [clonidine](#) and neuroleptics, such as [olanzapine](#)[50], may induce or exacerbate orthostatic regulation disturbances (eg, dizziness, fatigue, orthostatic hypotension) [51][52] and should be approached with caution.
- 7) Probable Mechanism: unknown

3.5.1.CD] [Clonixin](#)

- 1) Interaction Effect: an increased risk of bleeding
- 2) Summary: Caution is recommended with the concomitant use of NSAIDs and antidepressants, including SSRIs due to an increased risk of [intracranial hemorrhage](#)[529] and [gastrointestinal bleeding](#) [533][534][530][531]. Bleeding events have included [epistaxis](#), ecchymosis, [hematoma](#), [petechiae](#), and life-threatening hemorrhages [536][535][537][538]. When an SSRI and an NSAID are given concurrently, monitor the patient for signs of increased bleeding.
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: established
- 6) Clinical Management: Use caution if NSAIDs and SSRIs are coadministered. Concomitant use of NSAIDs and SSRIs may cause an increased risk of [intracranial hemorrhage](#)[529] and [gastrointestinal](#)

bleeding [530][531]. When an SSRI and an NSAID are given concurrently, monitor the patient for signs of increased bleeding.

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

8j) Literature Reports

aj) Concomitant use of NSAIDs and antidepressants, including tricyclic antidepressants, SSRIs, serotonin-norepinephrine reuptake inhibitors, and MAOIs, resulted in a 60% increased risk of **intracranial hemorrhage** within 30 days of concomitant use compared with antidepressant use alone. There was no significant difference between the antidepressant drug classes and the increased risk; however, there was an increased risk associated with male patients compared with female patients [529].

bj) SSRIs increase the risk of upper gastrointestinal (GI) bleeding, and this effect is potentiated by concurrent use of NSAIDs or low-dose **aspirin**. Hospitalizations for **upper GI bleeding** were searched among 26,005 users of antidepressant medications and compared with the number of hospitalizations in those patients who did not receive prescriptions for antidepressants. The amount of **upper GI bleeding** episodes was 3.6 times more than expected. Combined use of an SSRI and NSAIDs or low-dose **aspirin** increased the risk to 12.2 and 5.2 times, respectively. The findings of this study demonstrate an increased risk of **upper GI bleeding** during the use of SSRIs. Combined use of SSRIs and NSAIDs or low-dose **aspirin** increased the risk even further [532].

cj) Two metaanalyses of incidents of upper GI bleed due to SSRIs, NSAIDs, and their combination found that SSRIs increased the risk by 1.73 [533] to 2.36 times [534], NSAIDs by 2.55 times [533], and the combination of SSRIs and NSAIDs by 4.02 [533] to 6.33 times [534].

dj) The release of serotonin by **platelets** is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs and NSAIDs have been associated with an increased risk of bleeding [535].

3.5.1.CE] **Clopidogrel**

1j) Interaction Effect: paradoxical effects due to decreased plasma concentrations of the active metabolite of **clopidogrel** and additive bleeding risk

2j) Summary: The interaction between **clopidogrel** and **fluoxetine** may cause uncertain clinical outcomes due to paradoxical interaction effects. **Clopidogrel** is metabolized to its active metabolite in part by CYP2C19. Concomitant use of **clopidogrel** and **fluoxetine** (a moderate CYP2C19 inhibitor) has the potential for reduced **clopidogrel** active metabolite concentrations and reduced **platelet** inhibition[274]. Additionally, concomitant use may increase the risk of bleeding, as the release of serotonin by **platelets** is important for maintaining hemostasis. Case reports and epidemiological studies have shown that use of SSRIs, including **fluoxetine**, is associated with **gastrointestinal bleeding** [270]. If concomitant use is required, use caution [270].

3j) Severity: major

4j) Onset: unspecified

5j) Substantiation: theoretical

6j) Clinical Management: Use caution with the concomitant use of **clopidogrel** and **fluoxetine**, as an increased risk of bleeding has been demonstrated with the concomitant use of some SSRIs and antiplatelet drugs[270]. Concomitant use of **clopidogrel** and **fluoxetine** also has the potential for reduced **clopidogrel** active metabolite concentrations and reduced **platelet** inhibition [271].

7j) Probable Mechanism: inhibition of CYP2C19-mediated **clopidogrel** metabolism to its active metabolite by **fluoxetine**; additive antiplatelet effects on hemostasis

8j) Literature Reports

a) SSRI use was associated with a significant 55% increase in the risk of developing an upper GI bleed according to a meta-analysis of 22 studies (6 cohort and 16 case-control studies, involving more than 1,073,000 patients). Subgroup analyses reported concurrent antiplatelet drug use resulted in a 2.48-fold increase in upper GI bleed risk. [Paroxetine](#), [sertraline](#), [fluoxetine](#), [citalopram](#), and escitalopram significantly increased risk while [fluvoxamine](#) and [venlafaxine](#) did not. Using acid suppressing drugs may reduce this risk [272].

b) [Fluoxetine](#) reduced the pharmacological activity of [clopidogrel](#) in healthy volunteers in an open-label crossover study (N=8). The AUC and Cmax of the active metabolite of [clopidogrel](#) was 20.6% and 25.3% lower after coadministration of [fluoxetine](#) compared with administration of [clopidogrel](#) alone. The percentage maximum [platelet](#) aggregation values were 13.9% to 22.4% lower and the [platelet](#) reactivity index was 36.8% lower when [clopidogrel](#) was administered in conjunction with [fluoxetine](#). Overall, the antiplatelet effect of [clopidogrel](#) was decreased by approximately 25% [273].

3.5.1.CF] Clorgyline

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

2) Summary: Concurrent administration or overlapping therapy with [fluoxetine](#) and a monoamine oxidase (MAO) inhibitor may result in CNS toxicity or [serotonin syndrome](#), a hyperserotonergic state characterized by symptoms such as restlessness, myoclonus, changes in mental status, hyperreflexia, diaphoresis, shivering, and tremor. Serious, even fatal, reactions have been reported[560][561][562][563][564][565]. Concomitant use is contraindicated.

3) Severity: contraindicated

4) Onset: rapid

5) Substantiation: theoretical

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

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

8) Literature Reports

a) Concomitant use of serotonin specific reuptake inhibitors and monoamine oxidase inhibitors can produce a toxic reaction known as [serotonin syndrome](#) [555]. [Serotonin syndrome](#) is a condition of serotonergic hyperstimulation and manifests as restlessness, myoclonus, changes in mental status, hyperreflexia, diaphoresis, shivering, and tremor [555]. If the syndrome is not recognized and correctly treated, death can result.

b) It has been suggested that [fluoxetine](#) therapy be discontinued for five weeks before beginning therapy with a monoamine oxidase inhibitor. However, one case report describes a 28-year old woman who had discontinued a 2-year [fluoxetine](#) regimen for six weeks before starting therapy with [tranylcypromine](#). Over the next few days the patient developed fever, paresthesias, confusion, abdominal cramping, and various other CNS symptoms. Upon discontinuation of [tranylcypromine](#), the patient's symptoms began to resolve. Blood samples taken three days after discontinuation of [tranylcypromine](#) revealed no presence of [fluoxetine](#); however, the norfluoxetine level was 84 nanogram/mL (284 nanomol/L) [556].

c) Adverse reactions reported when [fluoxetine](#) was given concomitantly with [phenelzine](#) (n=9) or [tranylcypromine](#) (n=4) include tremor (50%), agitation or restlessness (42%), mental status

changes (42%), myoclonus (33%), diarrhea (33%), and blood pressure changes (25%) [557]. All but one of the patients were taking other medications (ie, benzodiazepines, neuroleptics, anticonvulsants, antidepressants) that may have contributed to the adverse reactions.

d) Ten hours after her last dose of [fluoxetine](#), a 45-year-old woman began [tranylcypromine](#) therapy [558]. Headache, muscle contractions, insomnia, and unsteady gait were reported on the second day. [Thioridazine](#) and tryptophan were added to her therapy. The patient experienced fever, rigidity of the arms and legs, and hyperreflexia. She died in the intensive care unit of a hospital 44 hours later.

e) Two cases suggestive of an interaction between [fluoxetine](#) and [selegiline](#) were reported [559]. One case involved a first episode of mania being observed approximately one month after adding [selegiline](#) to [fluoxetine](#) therapy. The patient improved two months after both drugs were discontinued, and no further details were provided. The second case involved diaphoresis, vasoconstriction, and cyanosis of the hands which occurred in close temporal relationship to adding [fluoxetine](#) and [selegiline](#). Both drugs were discontinued, with relatively quick resolution of symptoms. Rechallenge with [fluoxetine](#) alone occurred without incident.

3.5.1.CG| Clozapine

1) Interaction Effect: increased [clozapine](#) exposure and increased risk of adverse effects; increased risk of QT prolongation

2) Summary: Avoid coadministration of [clozapine](#) with [fluoxetine](#). [Clozapine](#) is a CYP2D6 substrate, [fluoxetine](#) is strong CYP2D6 inhibitor, and both agents are associated with QT prolongation[173][180]. Concurrent use may lead to increased [clozapine](#) exposure, increased risk of [clozapine](#) adverse events [180], and additive effects on QT interval, increasing risk for serious cardiac adverse events [173][180]. If coadministration is necessary, closely monitor patients for adverse reactions and consider a [clozapine](#) dose reduction if necessary. If coadministration is discontinued, monitor for reduced [clozapine](#) effectiveness and consider increasing the [clozapine](#) dose if indicated [180]. Baseline ECG and on-treatment monitoring for QT prolongation is also warranted during coadministration.

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Coadministration of [fluoxetine](#) with [clozapine](#) should be avoided[173] as concurrent use may lead to an increased risk of serious cardiac adverse events, including [torsade de pointes](#) [173][180]. Additionally, coadministration may increase [clozapine](#) exposure and the risk of [clozapine](#) adverse events. If coadministration is necessary, closely monitor patients for adverse reactions and consider a [clozapine](#) dose reduction if necessary. If coadministration is discontinued, monitor for reduced [clozapine](#) effectiveness and consider increasing the [clozapine](#) dose if indicated [180]. Baseline ECG and on-treatment monitoring for QT prolongation is also warranted during coadministration.

7) Probable Mechanism: inhibition of CYP2D6-mediated metabolism of [clozapine](#) by [fluoxetine](#); additive QT interval effects

8) Literature Reports

a) While minor changes in the levels of [clozapine](#) and its metabolites were reported in patients with [schizophrenia](#) when [paroxetine](#) was added to their steady-state [clozapine](#) treatment regimen (n=14), other clinical reports have described a less than 2-fold elevation in [clozapine](#) and metabolite concentrations with [fluoxetine](#), [paroxetine](#), and [sertraline](#) coadministration [180].

b) A 44-year-old man receiving [fluoxetine](#) and [clozapine](#) was found dead in his yard. The dates of the prescriptions and the number of tablets that remained indicated that he had been taking his

medications as prescribed. Autopsy results showed a high therapeutic fluoxetine concentration (0.7 mcg/mL) and also a high therapeutic norfluoxetine concentration (0.6 mcg/mL). Fluoxetine found in his gastric contents also indicated that the medication was being taken as directed. The clozapine blood concentration was in the lethal concentration range (4.9 mcg/mL), but the clozapine in the gastric contents suggested that the clozapine was being taken as prescribed and that the patient had not consumed a large overdose amount prior to his death. Other pathological findings included pulmonary edema, visceral vascular congestion, paralytic ileus, gastroenteritis, and eosinophilia, which are all consistent with clozapine toxicity. The combined central nervous system, respiratory, and cardiovascular depression caused by these 2 drugs was sufficient to result in the death of this patient, and his death was ruled to be a clozapine overdose due to a fatal drug interaction [181].

c) Ten institutionalized schizophrenic patients stabilized on clozapine therapy for at least 1 month participated in a prospective study to evaluate the effect of fluoxetine on clozapine pharmacokinetics. Fluoxetine 20 mg once daily was administered for 8 consecutive weeks. Mean plasma clozapine concentrations increased from 348 nanograms/milliliter (ng/mL) to 550 ng/mL (58%) at week 8. Plasma levels of norclozapine were also increased by 36% (from 280 ng/mL to 381 ng/mL). Clozapine N-oxide levels rose from 89 ng/mL at baseline to 128 ng/mL, representing a 38% increase. However, these increases in clozapine and metabolite plasma concentrations were not associated with significant changes in efficacy or safety [182].

d) A study evaluated the serum concentrations of clozapine and norclozapine, the major metabolite, 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 among the 3 SSRIs were minor, and the study groups were too limited for an accurate statistical comparison among the individual SSRIs [183].

e) Subjects receiving concurrent clozapine and fluoxetine had 76% higher serum clozapine concentrations and 61% higher metabolite concentrations on average compared with controls receiving only clozapine. The mean ratio of total drug level (clozapine plus metabolites) to dose was 60% higher and the mean ratio of concentrations to dose was 75% higher in patients receiving clozapine and fluoxetine compared with concentrations in patients receiving clozapine alone [184].

3.5.1.CH] Cobicistat

1) Interaction Effect: elevated fluoxetine plasma concentrations and increased risk of QT-interval prolongation

2) Summary: Concomitant treatment of fluoxetine with other CYP2D6 inhibitors can increase fluoxetine plasma concentrations and increase the risk of adverse effects, including episodes of QT-interval prolongation, ventricular arrhythmia, and torsade de pointes. Use caution in coadministration of these drugs[173]. If concomitant use is required, initiate fluoxetine at the lowest dose possible and titrate dose carefully based on patient response [540].

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Use caution with coadministration of [fluoxetine](#) and CYP2D6 inhibitors, as increased [fluoxetine](#) plasma concentrations may increase the risk of adverse effects, including episodes of QT-interval prolongation, [ventricular arrhythmia](#), and [torsade de pointes](#)[173]. If concomitant use is required, initiate [fluoxetine](#) at the lowest dose possible and titrate dose carefully based on patient response [540].

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

3.5.1.CI] Cocaine

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

2) Summary: [Serotonin syndrome](#) may the result from concomitant use of [fluoxetine](#) and serotonergic agents, such as a triptans or other antidepressants. Monitor patients for symptoms of [serotonin syndrome](#), including neuromuscular abnormalities, autonomic instability, and mental status changes, especially during treatment initiation and dose increases. [Serotonin syndrome](#) can be life-threatening. If [serotonin syndrome](#) develops, discontinue [fluoxetine](#) and any concomitant serotonergic agent and initiate supportive care[173].

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Exercise caution with coadministration of [fluoxetine](#) and serotonergic agents, such as a triptans or other antidepressants, because it may result in a life-threatening condition called [serotonin syndrome](#). If these agents are used together, discuss the risks of [serotonin syndrome](#) with the patient and monitor closely for symptoms of [serotonin syndrome](#) (mental status changes, autonomic instability, neuromuscular symptoms, seizures, and gastrointestinal symptoms), especially during treatment initiation and dose increases. If [serotonin syndrome](#) develops, discontinue [fluoxetine](#) and any concomitant serotonergic agent and initiate supportive care[173]

7) Probable Mechanism: additive serotonergic effect

3.5.1.CJ] Codeine

1) Interaction Effect: increased risk of CNS depression (ie, [respiratory depression](#), profound sedation, coma)

2) Summary: The concomitant use of [codeine](#) with other CNS depressants may result in profound sedation, [respiratory depression](#), coma, and/or death. Reserve concomitant use to clinical settings where alternative treatment options are inadequate. If combination therapy is required, reduce the initial dose of the newly prescribed medication and titrate to clinical response while monitoring for [respiratory depression](#) and sedation. Avoid concomitant use of [codeine cough](#) medications with CNS depressants[78].

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Reserve concomitant use of [codeine](#) with other CNS depressants to clinical settings where alternative treatment options are inadequate. If combination therapy is required, reduce the initial dose of the newly prescribed medication and titrate to clinical response while monitoring for [respiratory depression](#) and sedation. Avoid concomitant use of [codeine cough](#) medications with CNS depressants[78].

7) Probable Mechanism: additive CNS depression

3.5.1.CK] Crizotinib

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

2) Summary: QT-interval prolongation has occurred during crizotinib therapy. Risk of additive QT-interval prolongation increases during coadministration with other drugs associated with QT prolongation. If concomitant use is clinically indicated, use caution and consider periodic ECG and [electrolyte monitoring](#) during therapy[126]. Dose reduction of crizotinib may be warranted.

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Use caution in coadministering crizotinib with a drug known to prolong the QT interval, as concurrent use of such agents may lead to an increased risk of serious cardiac adverse events. If concomitant use is clinically indicated, consider periodic ECG and [electrolyte monitoring](#) during therapy[126]. Dose reduction of crizotinib may be warranted.

7) Probable Mechanism: additive effects on QT interval

3.5.1.CL| [Cyclobenzaprine](#)

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

2) Summary: [Serotonin syndrome](#), a life-threatening condition, has occurred with coadministration of [cyclobenzaprine](#) and other drugs, such as [fluoxetine](#). 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[381][382]. [Cyclobenzaprine](#) and [fluoxetine](#) are both known to prolong the QT interval. A 59-year-old woman receiving [fluoxetine](#) and [cyclobenzaprine](#) experienced [ventricular tachycardia](#) consistent with [torsade de pointes](#), which progressed into [ventricular fibrillation](#) and [cardiac arrest](#) [384]. If coadministration of [cyclobenzaprine](#) and [fluoxetine](#) is necessary, monitor patients for [cardiac arrhythmias](#) and QT prolongation.

3) Severity: major

4) Onset: unspecified

5) Substantiation: probable

6) Clinical Management: Coadministration of [cyclobenzaprine](#) and [fluoxetine](#) 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[381][382]. Additionally, [cyclobenzaprine](#) and [fluoxetine](#) are both known to prolong the QT interval. If coadministration is warranted, monitor patients for [cardiac arrhythmias](#) and QT prolongation.

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

8) Literature Reports

a) A 59-year-old woman was receiving [fluoxetine](#) 30 mg daily, [cyclobenzaprine](#) 10 mg daily, [amlodipine](#) 5 mg daily, [diclofenac](#) 100 mg daily, and [triamterene](#) 37.5 mg/[hydrochlorothiazide](#) 25 mg daily. Five days prior to elective Achilles [tendon surgery](#), her QTc was prolonged at 497 msec. Despite this finding, she was premedicated for surgery with IV [droperidol](#) 0.625 mg and [metoclopramide](#) 10 mg. Approximately 105 minutes into the surgery, the patient developed [ventricular tachycardia](#) consistent with [torsade de pointes](#), which progressed into [ventricular fibrillation](#) and [cardiac arrest](#). Immediately following [cardioversion](#), the patient's QTc was 500

msec. All preadmission medications were discontinued following surgery. On postoperative day 1, the QTc was 440 msec and an ECG showed normal sinus rhythm. The administration of [droperidol](#) preoperatively to this patient may have resulted in [torsade de pointes](#) and [cardiac arrest](#). The metabolism of [cyclobenzaprine](#), which is structurally similar to the tricyclic antidepressants, may have been inhibited by [fluoxetine](#). CYP2D6 hepatic enzymes are inhibited by [fluoxetine](#), and [cyclobenzaprine](#) may also be metabolized via this pathway [383].

3.5.1.CM] [Cyproheptadine](#)

- 1) Interaction Effect: decreased [fluoxetine](#) efficacy
- 2) Summary: Coadministration of [cyproheptadine](#) with [fluoxetine](#) may result in reduced [fluoxetine](#) effectiveness. [Cyproheptadine](#) acts to antagonize postsynaptic serotonin. Concomitant use of [cyproheptadine](#) with drugs that possess serotonergic activity (such as the selective serotonin reuptake inhibitors or SSRIs) might be expected to result in a pharmacodynamic interaction. Lack of antidepressant efficacy has been reported when [cyproheptadine](#) was given concomitantly with [fluoxetine](#) and [paroxetine](#)[509][510][511][512].
- 3) Severity: moderate
- 4) Onset: rapid
- 5) Substantiation: probable
- 6) Clinical Management: Monitor patients for a reduction in [fluoxetine](#) efficacy. When [cyproheptadine](#) is coadministered with [fluoxetine](#), [fluoxetine](#) doses might need to be adjusted upward. In some cases, it may be necessary to withdraw [cyproheptadine](#).
- 7) Probable Mechanism: unknown; because [cyproheptadine](#) is a serotonin antagonist, it may oppose effects of agents that inhibit serotonin reuptake
- 8) Literature Reports

a) Although not consistently reported, decreased antidepressant effects were found in some patients when [cyproheptadine](#) was added to [fluoxetine](#) therapy [505][506][507]. A 42-year-old woman using [fluoxetine](#) 40 mg once a day for episodes of depression, subsequently started [cyproheptadine](#) (4 mg per dose) for its antihistaminic properties [505]. Approximately 36 hours later and after four doses of [cyproheptadine](#), she experienced [dysphoria](#), irritability, and [suicidal ideation](#). She improved after withdrawal of [cyproheptadine](#). On rechallenge, her feelings of [dysphoria](#) returned.

b) A 54-year-old woman was using [paroxetine](#) 20 mg per day for the treatment of nonpsychotic [major depression](#) [508]. [Cyproheptadine](#) 2 mg twice a day was added to her therapy. Two days later, her depression worsened and she experienced confusion and [paranoid delusions](#). Her psychotic symptoms resolved two days after [cyproheptadine](#) was discontinued. She declined to be rechallenged.

3.5.1.CN] [Dabigatran Etexilate](#)

- 1) Interaction Effect: increased risk of bleeding
- 2) Summary: Exercise caution when coadministering a SSRI and an antiplatelet agent or anticoagulant as this may increase the risk of bleeding events[272][173][385].
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Use caution with concomitant use of [fluoxetine](#) with anticoagulants or antiplatelet agents, as coadministration may increase bleeding risk[272][173][385].
- 7) Probable Mechanism: altered anticoagulant effects

8) Literature Reports

a) In a retrospective study of patients over 50 years of age with the diagnosis of acute [myocardial infarction](#) (N=27,058), SSRI use with any antiplatelet therapy significantly increased the risk of bleeding by 1.42-fold compared with [aspirin](#) use alone. Therapy with [aspirin](#), [clopidogrel](#), and an SSRI significantly increased risk by 2.35-fold compared with [aspirin](#) use alone and by 1.57-fold compared with [clopidogrel](#) and [aspirin](#) combination therapy [385].

b) In a systematic review and meta-analysis of 22 observational studies, SSRI use was associated with a significant 1.55 fold increase in risk of [upper gastrointestinal bleeding](#) (UGIB). Concomitant use of SSRIs and antiplatelet drugs was associated with a 2.48-fold increase in risk of UGIB (3 studies) [272].

3.5.1.CO] Dabrafenib

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

2) Summary: Dabrafenib, as a single agent, has potential to prolong the QT interval; therefore, concomitant use with other drugs that can prolong the QT interval may cause additive effects on the QT interval[144]. Therefore, caution should be exercised with concomitant use and consider assessment and periodic monitoring for [ventricular arrhythmia](#).

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Coadministration of dabrafenib with other drugs that cause QT-interval prolongation may result in additive effects on the QT interval[144]. Exercise caution with concomitant use and consider assessment and periodic monitoring for [ventricular arrhythmia](#).

7) Probable Mechanism: additive QT prolongation

3.5.1.CP] Dalteparin

1) Interaction Effect: an increased risk of bleeding

2) Summary: The release of serotonin by [platelets](#) is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs and anticoagulants has been associated with an increased risk of bleeding[458][457]. Bleeding events reported have included [epistaxis](#), ecchymosis, [hematoma](#), [petechiae](#), and life-threatening hemorrhages. Altered anticoagulant effects (including increased bleeding) have been reported with the coadministration of SSRIs with anticoagulants [457].

3) Severity: major

4) Onset: delayed

5) Substantiation: probable

6) Clinical Management: When [fluoxetine](#) and an anticoagulant are given concurrently, monitor patient for signs of increased bleeding. Patients who are taking an anticoagulant should be monitored closely for altered anticoagulant effects, including increased bleeding, when [fluoxetine](#) therapy is initiated or discontinued[457].

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 a significant 1.7-fold increased risk for hospitalization for nongastrointestinal bleeding; however, the rate of [gastrointestinal bleeding](#) was not significantly different [458].

3.5.1.CQ] Danaparoid

1) Interaction Effect: an increased risk of bleeding

2) Summary: The release of serotonin by [platelets](#) is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs and anticoagulants has been associated with an increased risk of bleeding[458][457]. Bleeding events reported have included [epistaxis](#), ecchymosis, [hematoma](#), [petechiae](#), and life-threatening hemorrhages. Altered anticoagulant effects (including increased bleeding) have been reported with the coadministration of SSRIs with anticoagulants [457].

3) Severity: major

4) Onset: delayed

5) Substantiation: probable

6) Clinical Management: When [fluoxetine](#) and an anticoagulant are given concurrently, monitor patient for signs of increased bleeding. Patients who are taking an anticoagulant should be monitored closely for altered anticoagulant effects, including increased bleeding, when [fluoxetine](#) therapy is initiated or discontinued[457].

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 a significant 1.7-fold increased risk for hospitalization for nongastrointestinal bleeding; however, the rate of [gastrointestinal bleeding](#) was not significantly different [458].

3.5.1.CR] Defibrotide

1) Interaction Effect: an increased risk of bleeding

2) Summary: The release of serotonin by [platelets](#) is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs and anticoagulants has been associated with an increased risk of bleeding[458][457]. Bleeding events reported have included [epistaxis](#), ecchymosis, [hematoma](#), [petechiae](#), and life-threatening hemorrhages. Altered anticoagulant effects (including increased bleeding) have been reported with the coadministration of SSRIs with anticoagulants [457].

3) Severity: major

4) Onset: delayed

5) Substantiation: probable

6) Clinical Management: When [fluoxetine](#) and an anticoagulant are given concurrently, monitor patient for signs of increased bleeding. Patients who are taking an anticoagulant should be monitored closely for altered anticoagulant effects, including increased bleeding, when [fluoxetine](#) therapy is initiated or discontinued[457].

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 a significant 1.7-fold increased risk for hospitalization for nongastrointestinal bleeding; however, the rate of [gastrointestinal bleeding](#) was not significantly different [458].

3.5.1.CS] Degarelix

- 1) Interaction Effect: increased risk of QT-interval prolongation
- 2) Summary: Use caution with coadministration of gonadotropin-releasing hormone (GnRH) agonists with QT-interval prolonging drugs. Androgen deprivation caused by GnRH agonists may prolong the QT interval and cause additive effects when administered with QT-interval prolonging drugs[141][142][143]. If concurrent therapy is necessary, monitor patients closely for signs and symptoms of [cardiac toxicity](#), including changes in the ECG.
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Use caution with coadministration of gonadotropin-releasing hormone (GnRH) agonists with QT-interval prolonging drugs, as additive effects on the QT interval may occur[141][142][143].
- 7) Probable Mechanism: additive effects on the QT interval

3.5.1.CT] Dehydroepiandrosterone

- 1) Interaction Effect: reduced effectiveness of [olanzapine](#)
- 2) Summary: Dehydroepiandrosterone (DHEA) levels within the normal range of 100 to 400 microgram/deciliter (mcg/dL) are conducive for optimal treatment of patients with [psychosis](#)[47]. In case reports, patients have been resistant to antipsychotics when DHEA levels were elevated [47]. Patients being treated with [olanzapine](#) should avoid DHEA supplementation.
- 3) Severity: moderate
- 4) Onset: delayed
- 5) Substantiation: theoretical
- 6) Clinical Management: Avoid concomitant use of dehydroepiandrosterone (DHEA) and [olanzapine](#). If DHEA is elevated, treatment with [dexamethasone](#) 1 mg orally per day may be used to normalize DHEA levels.
- 7) Probable Mechanism: elevated dehydroepiandrosterone (DHEA) blood levels may reduce responsiveness to [olanzapine](#)
- 8) Literature Reports

a) A 24-year-old female diagnosed with [schizophrenia](#) was resistant to daily doses of [haloperidol](#) 20 milligrams (mg), [fluphenazine](#) 40 mg, [lithium](#) carbonate 1200 mg, and [lithium](#) carbonate 900 mg plus [thioridazine](#) 300 mg. The patient appeared Cushingoid with moon face, acne, facial hair, abdominal hair, and a 40 pound weight gain in the previous 8 months. Dehydroepiandrosterone (DHEA) measured as part of an endocrine panel was 725 micrograms/deciliter (mcg/dL) (normal: 100 to 400 mcg/dL). [Dexamethasone](#) 1 mg orally at bedtime resulted in substantial improvement within one week. The patient appeared calmer, more alert with improved psychotic symptoms and ability to concentrate. At two weeks, a repeated DHEA level was within normal range (328 mcg/dL). The author concluded that elevated DHEA levels were associated with severe [psychosis](#) resistant to conventional antipsychotic therapy [46].

b)) A 13-year-old male decompensated with a subsequent two-year period of emotional problems accompanied by heavy use of LSD, hashish, barbiturates, and alcohol. His mental status included bizarre, disorganized, delusional thinking, auditory and visual hallucinations, paranoia, lack of attention to personal hygiene, agitation, and combativeness. He was diagnosed with [chronic paranoid schizophrenia](#); [schizophrenia](#), chronic undifferentiated type, and [schizoaffective disorder](#), excited type. He was resistant to daily doses of [trifluoperazine](#) 40 mg, [chlorpromazine](#) 400 mg, and [imipramine](#) 100 mg. He was also resistant to combination therapy with [chlorpromazine](#) 400 mg with [thiothixene](#) 80 mg, [thioridazine](#) 1000 mg, [perphenazine](#) 48 mg with [lithium](#) carbonate 1200 mg, [clonazepam](#) 4 mg, and [carbamazepine](#) 1200 mg daily. Baseline DHEA level exceeded 900 mcg/dL. A seven-day suppression test with [dexamethasone](#) 1 mg orally at bedtime resulted in a normal DHEA level of 200 mcg/dL. By day 5, [psychosis](#) improved and the patient was well-oriented, conversational, and was making good eye contact. Once [dexamethasone](#) was discontinued, rapid decompensation and florid [psychosis](#) ensued despite "substantial amounts of psychotropic medications". DHEA increased to 536 mcg/dL. The author concluded that elevated DHEA levels were associated with florid [psychosis](#) resistant to conventional antipsychotic therapy [46].

3.5.1.CU] Dehydroepiandrosterone

1)) Interaction Effect: development of manic symptoms

2)) Summary: A case has been reported in which concomitant dehydroepiandrosterone (DHEA) and [sertraline](#) use was suggested to precipitate a [manic episode](#) in a patient with a history of [bipolar disorder](#) [404]. DHEA was also noted to cause mania in a patient with no previous personal or family history of [bipolar disorder](#) [405]. Elevated DHEA levels have been found in patients with mental disorders; DHEA suppression has lead to improvement in psychotic symptoms [406]. DHEA possesses proserotonergic activity which may predispose patients to [manic episodes](#) [407]. DHEA is a precursor to androgenic steroids, which in high doses may precipitate mania [405]. Patients taking medication for [bipolar disorder](#) or patients with a personal and/or family history of [bipolar disorder](#) should not take DHEA until further data is available to characterize this drug-herb interaction. Concomitant use of DHEA with selective serotonin reuptake inhibitors (SSRIs) should be avoided due to the potential additive precipitation of mania.

3)) Severity: moderate

4)) Onset: delayed

5)) Substantiation: theoretical

6)) Clinical Management: Avoid concomitant use of dehydroepiandrosterone (DHEA) and selective serotonin reuptake inhibitors. If patients present with manic symptoms (i.e. agitation, anger, irritability, aggressive behavior), determine if the patient is using DHEA and discontinue DHEA.

7)) Probable Mechanism: serotonergic activity of dehydroepiandrosterone, possibly increased androgen levels

8)) Literature Reports

a)) A 31-year-old male was admitted following threats to commit suicide and injure family members. He had self-initiated [sertraline](#) 100 milligrams (mg) daily for the previous 2 to 3 weeks for depression. [Sertraline](#) had been prescribed 3 years prior when he was diagnosed with [bipolar disorder](#), which he discontinued after 2 weeks. He had also taken dehydroepiandrosterone (DHEA) 300 mg to 500 mg daily for the previous 2 months apparently for weight training. Following use of DHEA for a short time, he became more irritable, was not sleeping well, and began threatening a female friend and family members. He also drank alcohol occasionally and reportedly had difficulty controlling his anger when intoxicated. [Sertraline](#) was stopped and the

patient was treated with [valproic acid](#) with the dose titrated to 500 mg twice daily. The combination of DHEA, [sertraline](#), and alcohol was suggested responsible for the developing of the [manic episode](#) [403].

3.5.1.CV] Delamanid

- 1) Interaction Effect: increased risk of QT-interval prolongation
- 2) Summary: Delamanid is a QT-interval-prolonging drug. Treatment initiation is not recommended in patients on other QT-interval-prolonging agents due to increased risk of the additive QT-interval prolongation effect. If the concurrent use cannot be avoided, an ECG should be obtained baseline and frequently (eg, more than once a month) during the full course of delamanid therapy[100].
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Delamanid is a QT-interval-prolonging drug. Treatment initiation is not recommended in patients on other QT-interval-prolonging agents due to increased risk of the additive QT-interval prolongation effect. If the concurrent use cannot be avoided, an ECG should be obtained baseline and frequently (eg, more than once a month) during the full course of delamanid therapy[100].
- 7) Probable Mechanism: additive QT- interval prolongation

3.5.1.CW] Delavirdine

- 1) Interaction Effect: increased trough delavirdine concentrations
- 2) Summary: Population pharmacokinetic data in 36 patients suggested that coadministration of delavirdine and [fluoxetine](#) resulted in an approximate 50% increase in trough delavirdine concentrations[468]. The clinical significance of this interaction is not known.
- 3) Severity: moderate
- 4) Onset: delayed
- 5) Substantiation: probable
- 6) Clinical Management: Concurrent use of delavirdine with [fluoxetine](#) should be coadministered with caution. Monitor patients for an increased incidence of delavirdine adverse effects.
- 7) Probable Mechanism: unknown

3.5.1.CX] Dermatan Sulfate

- 1) Interaction Effect: an increased risk of bleeding
- 2) Summary: The release of serotonin by [platelets](#) is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs and anticoagulants has been associated with an increased risk of bleeding[458][457]. Bleeding events reported have included [epistaxis](#), ecchymosis, [hematoma](#), [petechiae](#), and life-threatening hemorrhages. Altered anticoagulant effects (including increased bleeding) have been reported with the coadministration of SSRIs with anticoagulants [457].
- 3) Severity: major
- 4) Onset: delayed
- 5) Substantiation: probable
- 6) Clinical Management: When [fluoxetine](#) and an anticoagulant are given concurrently, monitor patient for signs of increased bleeding. Patients who are taking an anticoagulant should be monitored closely for altered anticoagulant effects, including increased bleeding, when [fluoxetine](#) therapy is initiated or discontinued[457].
- 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 a significant 1.7-fold increased risk for hospitalization for nongastrointestinal bleeding; however, the rate of [gastrointestinal bleeding](#) was not significantly different [458].

3.5.1.CY] [Desipramine](#)

1) Interaction Effect: increased risk of tricyclic antidepressant toxicity, QT prolongation and [serotonin syndrome](#)

2) Summary: [Fluoxetine](#), a potent CYP2D6 inhibitor, is associated with an increased risk of [serotonin syndrome](#), QT prolongation, and [ventricular arrhythmias](#) (including [torsade de pointes](#)). Concomitant therapy with CYP2D6-metabolized tricyclic antidepressants (TCAs) may potentiate these risks and introduce TCA toxicity[173]; concurrent use of [fluoxetine](#) and [desipramine](#), [nortriptyline](#), and [imipramine](#) has resulted in significant increases in TCA concentrations [517][523][524][525][526][527]. Use caution with concurrent administration of [fluoxetine](#) and TCAs. If [fluoxetine](#) is added to an existing TCA regimen, consider TCA dose reduction. If [fluoxetine](#) and a TCA are coadministered or [fluoxetine](#) has been recently discontinued, consider plasma TCA monitoring. If [serotonin syndrome](#) occurs, immediately discontinue [fluoxetine](#) and TCA. If [ventricular arrhythmias](#) develop, consider [fluoxetine](#) discontinuation and cardiac evaluation [173].

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Use caution with concurrent administration of [fluoxetine](#) and TCAs, as elevated TCA plasma concentrations may occur. If [fluoxetine](#) is added to an existing TCA regimen, consider TCA dose reduction. If [fluoxetine](#) and a TCA are coadministered or [fluoxetine](#) has been recently discontinued, consider plasma TCA monitoring. If [serotonin syndrome](#) occurs, immediately discontinue [fluoxetine](#) and TCA. If [ventricular arrhythmias](#) develop, consider [fluoxetine](#) discontinuation and cardiac evaluation[173]

7) Probable Mechanism: decreased CYP2D6-mediated metabolism of tricyclic antidepressants by [fluoxetine](#); additive effects on QT prolongation; additive serotonergic effects

8) Literature Reports

a) Previously stable plasma levels of [imipramine](#) and [desipramine](#) rose more than 2- to 10-fold with [fluoxetine](#) coadministration in 2 clinical studies. This effect may persist for 3 weeks or more after [fluoxetine](#) discontinuation. Dose reduction and temporary monitoring of tricyclic antidepressant plasma concentrations may be indicated with concurrent [fluoxetine](#) treatment or recent [fluoxetine](#) discontinuation [173].

b) [Fluoxetine](#) statistically and clinically significantly increased [desipramine](#) concentrations in 18 healthy subjects. When [fluoxetine](#) (20 mg daily) was added to [desipramine](#) (50 mg daily), the mean maximum concentration of [desipramine](#) increased by 278% and the AUC increased by 342%. [Desipramine](#) trough concentrations continued to be 198% above baseline 3 weeks after [fluoxetine](#) was discontinued. The same study compared pharmacokinetics of [desipramine](#) when combined with [sertraline](#). The impact of [sertraline](#) was modest, resulting in small and short-term increases in [desipramine](#) plasma concentrations [517].

c) Concomitant administration of fluoxetine and desipramine was reported to result in an increased desipramine level and new onset of delirium in a 69-year-old male within 10 days of the addition of fluoxetine to the patient's regimen [518].

d) Fluoxetine increased the level of tricyclic antidepressants (nortriptyline, imipramine, desipramine) in 4 patients. After the addition of fluoxetine, the ratio of antidepressant level to dose increased by 109% to 486% in the patients. Three patients developed clinical symptoms (anticholinergic effects, constipation, urinary hesitancy, sedation, unstable gait) as a result of the increased levels [519].

e) A 39-year-old female experienced symptomatic increases in her desipramine levels with concomitant fluoxetine therapy. Prior to fluoxetine therapy, the patient's measured levels of desipramine had ranged from 148 to 160 nanograms/milliliter (ng/mL; 556 to 601 nanomol/L) on a regimen of 300 mg daily. Five weeks after the addition of fluoxetine 20 mg daily, she reported anticholinergic symptoms, sedation, and confusion with a desipramine level of 527 ng/mL (1978 nanomol/L). The desipramine dose was lowered to 200 mg/day; 11 days later, the level was 244 ng/mL (916 nanomol/L); the patient reported decreased energy, impaired short-term memory, and some "garbled" speech, as well as an episode of nausea, dizziness, and syncope. The desipramine dose was reduced to 50 mg/day, and the adverse effects resolved in 6 days. Eight days later, the desipramine level was 122 ng/mL (458 nanomol/L) [520].

f) A 33-year-old depressed male developed adverse effects of dry mouth, tinnitus, and difficulties with alertness and memory while receiving fluoxetine 40 mg daily and desipramine 150 mg daily for 5 weeks; fluoxetine was discontinued and the blood levels of desipramine decreased from 938 to 48 nanograms/mL (3521 to 180 nanomol/L) with resolution of clinical symptoms [521].

g) A 75-year-old female experienced symptomatic increases in her desipramine serum concentrations when fluoxetine was added. Desipramine serum levels ranged from 109 to 150 ng/mL (409 to 563 nanomol/L) with oral doses of 300 mg at bedtime prior to fluoxetine therapy. Following the addition of oral fluoxetine 20 mg daily to the regimen, the desipramine serum level increased to 212 ng/mL (796 nanomol/L) within five days. The fluoxetine dose was increased to 40 mg/day three days later, and the desipramine serum level was 419 ng/mL (1573 nanomol/L) after four days. A worsening of depression and severe fatigue coincided with the increases in desipramine serum levels. Withdrawal of fluoxetine and reduction in the desipramine dose to 200 mg daily reduced the desipramine serum level to 231 ng/mL (867 nanomol/L) within two weeks [522].

3.5.1.CZ| Desirudin

1) Interaction Effect: an increased risk of bleeding

2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs and anticoagulants has been associated with an increased risk of bleeding[458][457]. Bleeding events reported have included epistaxis, ecchymosis, hematoma, petechiae, and life-threatening hemorrhages. Altered anticoagulant effects (including increased bleeding) have been reported with the coadministration of SSRIs with anticoagulants [457].

3) Severity: major

4) Onset: delayed

5) Substantiation: probable

6) Clinical Management: When fluoxetine and an anticoagulant are given concurrently, monitor patient for signs of increased bleeding. Patients who are taking an anticoagulant should be monitored closely

for altered anticoagulant effects, including increased bleeding, when [fluoxetine](#) therapy is initiated or discontinued[457].

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 a significant 1.7-fold increased risk for hospitalization for nongastrointestinal bleeding; however, the rate of [gastrointestinal bleeding](#) was not significantly different [458].

3.5.1.DA| Deslorelin

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

2) Summary: Use caution with coadministration of gonadotropin-releasing hormone (GnRH) agonists with QT-interval prolonging drugs. Androgen deprivation caused by GnRH agonists may prolong the QT interval and cause additive effects when administered with QT-interval prolonging drugs[141][142][143]. If concurrent therapy is necessary, monitor patients closely for signs and symptoms of [cardiac toxicity](#), including changes in the ECG.

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Use caution with coadministration of gonadotropin-releasing hormone (GnRH) agonists with QT-interval prolonging drugs, as additive effects on the QT interval may occur[141][142][143].

7) Probable Mechanism: additive effects on the QT interval

3.5.1.DB| Desvenlafaxine

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

2) 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[325].

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[325].

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

8J) Literature Reports

aJ) 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) [325].

3.5.1.DCJ Dexfenfluramine

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

2J) Summary: Dexfenfluramine is a nonspecific serotonin agonist that both enhances the release of serotonin and inhibits serotonin reuptake. Combination therapy with dexfenfluramine and another selective serotonin reuptake inhibitor, such as [fluoxetine](#), has the potential to cause [serotonin syndrome](#)[430]. [Serotonin syndrome](#) is a hyperserotonergic state characterized by symptoms such as restlessness, myoclonus, changes in mental status, hyperreflexia, diaphoresis, shivering, and tremor. Serious, even fatal, reactions have been reported [431]. Dexfenfluramine should not be used in combination with [fluoxetine](#) [432].

3J) Severity: major

4J) Onset: rapid

5J) Substantiation: theoretical

6J) Clinical Management: Concurrent use of dexfenfluramine and [fluoxetine](#) may result in an additive increase in serotonin levels in the central nervous system, and could result in [serotonin syndrome](#) ([hypertension](#), [hyperthermia](#), myoclonus, mental status changes). Dexfenfluramine should not be used in combination with [fluoxetine](#) or other serotonin specific reuptake inhibitors.

7J) Probable Mechanism: additive serotonergic effects

3.5.1.DDJ Dexibuprofen

1J) Interaction Effect: an increased risk of bleeding

2J) Summary: Caution is recommended with the concomitant use of NSAIDs and antidepressants, including SSRIs due to an increased risk of [intracranial hemorrhage](#)[529] and [gastrointestinal bleeding](#) [533][534][530][531]. Bleeding events have included [epistaxis](#), ecchymosis, [hematoma](#), [petechiae](#), and life-threatening hemorrhages [536][535][537][538]. When an SSRI and an NSAID are given concurrently, monitor the patient for signs of increased bleeding.

3J) Severity: major

4J) Onset: unspecified

5J) Substantiation: established

6J) Clinical Management: Use caution if NSAIDs and SSRIs are coadministered. Concomitant use of NSAIDs and SSRIs may cause an increased risk of [intracranial hemorrhage](#)[529] and [gastrointestinal](#)

bleeding [530][531]. When an SSRI and an NSAID are given concurrently, monitor the patient for signs of increased bleeding.

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

8) Literature Reports

a) Concomitant use of NSAIDs and antidepressants, including tricyclic antidepressants, SSRIs, serotonin-norepinephrine reuptake inhibitors, and MAOIs, resulted in a 60% increased risk of intracranial hemorrhage within 30 days of concomitant use compared with antidepressant use alone. There was no significant difference between the antidepressant drug classes and the increased risk; however, there was an increased risk associated with male patients compared with female patients [529].

b) SSRIs increase the risk of upper gastrointestinal (GI) bleeding, and this effect is potentiated by concurrent use of NSAIDs or low-dose aspirin. Hospitalizations for upper GI bleeding were searched among 26,005 users of antidepressant medications and compared with the number of hospitalizations in those patients who did not receive prescriptions for antidepressants. The amount of upper GI bleeding episodes was 3.6 times more than expected. Combined use of an SSRI and NSAIDs or low-dose aspirin increased the risk to 12.2 and 5.2 times, respectively. The findings of this study demonstrate an increased risk of upper GI bleeding during the use of SSRIs. Combined use of SSRIs and NSAIDs or low-dose aspirin increased the risk even further [532].

c) Two metaanalyses of incidents of upper GI bleed due to SSRIs, NSAIDs, and their combination found that SSRIs increased the risk by 1.73 [533] to 2.36 times [534], NSAIDs by 2.55 times [533], and the combination of SSRIs and NSAIDs by 4.02 [533] to 6.33 times [534].

d) The release of serotonin by platelets is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs and NSAIDs have been associated with an increased risk of bleeding [535].

3.5.1.DE] Dexketoprofen

1) Interaction Effect: an increased risk of bleeding

2) Summary: Caution is recommended with the concomitant use of NSAIDs and antidepressants, including SSRIs due to an increased risk of intracranial hemorrhage[529] and gastrointestinal bleeding [533][534][530][531]. Bleeding events have included epistaxis, ecchymosis, hematoma, petechiae, and life-threatening hemorrhages [536][535][537][538]. When an SSRI and an NSAID are given concurrently, monitor the patient for signs of increased bleeding.

3) Severity: major

4) Onset: unspecified

5) Substantiation: established

6) Clinical Management: Use caution if NSAIDs and SSRIs are coadministered. Concomitant use of NSAIDs and SSRIs may cause an increased risk of intracranial hemorrhage[529] and gastrointestinal bleeding [530][531]. When an SSRI and an NSAID are given concurrently, monitor the patient for signs of increased bleeding.

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

8) Literature Reports

a) Concomitant use of NSAIDs and antidepressants, including tricyclic antidepressants, SSRIs, serotonin-norepinephrine reuptake inhibitors, and MAOIs, resulted in a 60% increased risk of intracranial hemorrhage within 30 days of concomitant use compared with antidepressant use alone. There was no significant difference between the antidepressant drug classes and the

increased risk; however, there was an increased risk associated with male patients compared with female patients [529].

b)) SSRIs increase the risk of upper gastrointestinal (GI) bleeding, and this effect is potentiated by concurrent use of NSAIDs or low-dose [aspirin](#). Hospitalizations for [upper GI bleeding](#) were searched among 26,005 users of antidepressant medications and compared with the number of hospitalizations in those patients who did not receive prescriptions for antidepressants. The amount of [upper GI bleeding](#) episodes was 3.6 times more than expected. Combined use of an SSRI and NSAIDs or low-dose [aspirin](#) increased the risk to 12.2 and 5.2 times, respectively. The findings of this study demonstrate an increased risk of [upper GI bleeding](#) during the use of SSRIs. Combined use of SSRIs and NSAIDs or low-dose [aspirin](#) increased the risk even further [532].

c)) Two metaanalyses of incidents of upper GI bleed due to SSRIs, NSAIDs, and their combination found that SSRIs increased the risk by 1.73 [533] to 2.36 times [534], NSAIDs by 2.55 times [533], and the combination of SSRIs and NSAIDs by 4.02 [533] to 6.33 times [534].

d)) The release of serotonin by [platelets](#) is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs and NSAIDs have been associated with an increased risk of bleeding [535].

3.5.1.DF] [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[528].

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[528].

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

3.5.1.DG] [Dextromethorphan](#)

1)) Interaction Effect: possible [dextromethorphan](#) toxicity (nausea, vomiting, blurred vision, hallucinations) or [serotonin syndrome](#) (hypertension, hyperthermia, myoclonus, mental status changes)

2)) Summary: [Fluoxetine](#) strongly inhibits hepatic cytochrome P450IID6 (CYP2D6), the isoenzyme known to catalyze [dextromethorphan](#) metabolism[422]. [Fluoxetine](#) inhibits [dextromethorphan](#) metabolism [423]. With concomitant administration, it is possible that both agents may competitively inhibit each others metabolism, increasing serum levels of both drugs. [Serotonin syndrome](#), characterized by restlessness, myoclonus, and changes in mental status [424], is a possibility with the combined use of [dextromethorphan](#)

and serotonergic agents. There have been two case reports of [serotonin syndrome](#) associated with concurrent [paroxetine](#) and [dextromethorphan](#) therapy [425][426].

3) Severity: major

4) Onset: rapid

5) Substantiation: theoretical

6) Clinical Management: Caution patients taking [fluoxetine](#) that an interaction could occur with [dextromethorphan](#). A reduction in the [dextromethorphan](#) dose may be necessary.

7) Probable Mechanism: competitively inhibited metabolism of both agents

8) Literature Reports

a) Therapeutic doses of [fluoxetine](#) were found to potently inhibit the metabolism of [dextromethorphan](#), a marker of cytochrome P450 2D6 (CYP2D6) function [419]. A 30 mg dose of [dextromethorphan](#) hydrobromide was given to 19 patients taking [fluoxetine](#) for [clinical depression](#). In addition, [dextromethorphan](#) was given to 208 known extensive metabolizers and to 15 known poor metabolizers (those lacking CYP2D6 function). While [dextromethorphan](#) metabolism was reduced in the fluoxetine-treated patients, it was more significantly affected in the poor metabolizer controls. This indicates that patients who are slow metabolizers may be at greater risk for experiencing [dextromethorphan](#) toxicity when used in combination with [fluoxetine](#).

b) A 32-year-old woman experienced visual hallucinations after concomitant use of [fluoxetine](#) and [dextromethorphan](#) [420]. She had taken [fluoxetine](#) 20 mg daily for 18 days prior to taking two doses of [dextromethorphan](#). After each dose of [dextromethorphan](#) she experienced distorted vision and saw bright colors. These effects continued for six to eight hours. [Fluoxetine](#) was withdrawn and she had no more hallucinations.

c) A 51-year old male patient with [vascular disease](#) following concurrent use of [dextromethorphan](#) and [paroxetine](#) developed [serotonin syndrome](#). Two days after self-medication with a dextromethorphan-containing cold product, the patient experienced shortness of breath, nausea, headache, and confusion. Upon arrival to the hospital, the patient presented with diaphoresis, tremor, confusion, abdominal pain, and severe shortness of breath. After administration of benzodiazepines and discontinuation of [paroxetine](#), the patient's condition improved and no further complications were seen [421].

3.5.1.DH| [Diazepam](#)

1) Interaction Effect: potentiation of excessive sedation and cardiorespiratory depression

2) Summary: The concomitant use of intramuscularly administered [olanzapine](#) and parenteral benzodiazepines ([diazepam](#), [lorazepam](#), [midazolam](#)) is not recommended due to the potentiation of excessive sedation and cardiorespiratory depression[68].

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: The concomitant use of intramuscularly administered [olanzapine](#) and parenteral benzodiazepines ([diazepam](#), [lorazepam](#), [midazolam](#)) is not recommended due to additive CNS depression[68].

7) Probable Mechanism: additive CNS depression

3.5.1.DI| [Diazepam](#)

1) Interaction Effect: higher serum concentrations of [diazepam](#)

2j) Summary: During coadministration of fluoxetine with diazepam, the fluoxetine area under the concentration-time curve (AUC) was increased, but this was not associated with increased impairment[232]. Conversely, a controlled study observed significant decreases in psychomotor performance when diazepam was added to fluoxetine [233]. The metabolism of diazepam is mediated by several P450 enzymes which may be inhibited by fluoxetine [234][235][236]. Further case reports or controlled studies are necessary to appropriately define the pharmacokinetic effects as well as the degree of psychomotor impairment resulting from coadministration of these two agents.

3j) Severity: minor

4j) Onset: delayed

5j) Substantiation: probable

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

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

8j) Literature Reports

a) Coadministration of fluoxetine and diazepam resulted in prolonged half-life, reduced plasma clearance, and increased AUC for diazepam. Oral diazepam 10 mg was given alone, after a single dose of oral fluoxetine 60 mg, and after 8 daily doses of fluoxetine 60 mg. Psychometric data demonstrated no effect of fluoxetine on the psychomotor response to diazepam. Thus, although fluoxetine decreases the clearance of diazepam, this does not appear to be of clinical relevance and dosing adjustments are not required during combined therapy [225].

b) Combined therapy with diazepam and fluoxetine caused an increase in the half-life of the metabolite desmethyldiazepam, but this did not appear to be clinically significant. Diazepam had no effect on the disposition of fluoxetine or norfluoxetine [226].

c) To date, in-vitro studies have found that diazepam demethylation occurs via P450 1A2, 3A4, 2C9, and 2C19. Evidence with drugs known to be metabolized by these enzymes suggests that fluoxetine strongly inhibits 2C9, moderately inhibits 2C19 and 3A4, and has no effect on 1A2 [227] [228][229].

d) In a controlled study of performance of 90 healthy volunteers, the effects of fluoxetine, amitriptyline, or placebo with diazepam were studied. Volunteers received one of six treatment combinations, and were given performance tests including a critical tracking test, divided attention test, visual search task, memory test, and vigilance test. Fluoxetine alone did not affect performance, but when fluoxetine was added to diazepam, there was a significant increase in the divided attention tracking error and significant impairment on the vigilance test. For amitriptyline alone and during coadministration with diazepam, significant impairment was observed. On most tests, the combination of amitriptyline and diazepam resulted in additive effects. The authors concluded that the combination of diazepam and an antidepressant may increase an individual's risk during driving and while performing other complex tasks [230].

e) A case was reported in which an 83-year old man developed delirium after the addition of fluoxetine and diazepam to a regimen of warfarin, lisinopril, furosemide, potassium, digoxin, and acetaminophen. The patient was given fluoxetine 20 mg per day and diazepam 2.5 mg three to four times per day for symptoms of depression, anxiety, and insomnia. The patient then developed symptoms of drug delirium, including confusion, incoherence, and irrational speaking. The patient also developed an increased international normalized ratio (INR), after which fluoxetine was discontinued. The patient presented to the hospital with left-sided weakness and later died from

complications of a large interparenchymal hemorrhage. The authors proposed that the addition of [fluoxetine](#) to the patient's regimen resulted in increased serum levels of both [warfarin](#) and [diazepam](#), resulting in drug-induced [delirium](#) and loss of anticoagulant control [231].

3.5.1.DJ] Dibenzepin

1J) Interaction Effect: increased risk of tricyclic antidepressant toxicity, QT prolongation and [serotonin syndrome](#)

2J) Summary: [Fluoxetine](#), a potent CYP2D6 inhibitor, is associated with an increased risk of [serotonin syndrome](#), QT prolongation, and [ventricular arrhythmias](#) (including [torsade de pointes](#)). Concomitant therapy with CYP2D6-metabolized tricyclic antidepressants (TCAs) may potentiate these risks and introduce TCA toxicity[173]; concurrent use of [fluoxetine](#) and [desipramine](#), [nortriptyline](#), and [imipramine](#) has resulted in significant increases in TCA concentrations [517][523][524][525][526][527]. Use caution with concurrent administration of [fluoxetine](#) and TCAs. If [fluoxetine](#) is added to an existing TCA regimen, consider TCA dose reduction. If [fluoxetine](#) and a TCA are coadministered or [fluoxetine](#) has been recently discontinued, consider plasma TCA monitoring. If [serotonin syndrome](#) occurs, immediately discontinue [fluoxetine](#) and TCA. If [ventricular arrhythmias](#) develop, consider [fluoxetine](#) discontinuation and cardiac evaluation [173].

3J) Severity: major

4J) Onset: unspecified

5J) Substantiation: theoretical

6J) Clinical Management: Use caution with concurrent administration of [fluoxetine](#) and TCAs, as elevated TCA plasma concentrations may occur. If [fluoxetine](#) is added to an existing TCA regimen, consider TCA dose reduction. If [fluoxetine](#) and a TCA are coadministered or [fluoxetine](#) has been recently discontinued, consider plasma TCA monitoring. If [serotonin syndrome](#) occurs, immediately discontinue [fluoxetine](#) and TCA. If [ventricular arrhythmias](#) develop, consider [fluoxetine](#) discontinuation and cardiac evaluation[173]

7J) Probable Mechanism: decreased CYP2D6-mediated metabolism of tricyclic antidepressants by [fluoxetine](#); additive effects on QT prolongation; additive serotonergic effects

8J) Literature Reports

aJ) Previously stable plasma levels of [imipramine](#) and [desipramine](#) rose more than 2- to 10-fold with [fluoxetine](#) coadministration in 2 clinical studies. This effect may persist for 3 weeks or more after [fluoxetine](#) discontinuation. Dose reduction and temporary monitoring of tricyclic antidepressant plasma concentrations may be indicated with concurrent [fluoxetine](#) treatment or recent [fluoxetine](#) discontinuation [173].

bJ) [Fluoxetine](#) statistically and clinically significantly increased [desipramine](#) concentrations in 18 healthy subjects. When [fluoxetine](#) (20 mg daily) was added to [desipramine](#) (50 mg daily), the mean maximum concentration of [desipramine](#) increased by 278% and the AUC increased by 342%. [Desipramine](#) trough concentrations continued to be 198% above baseline 3 weeks after [fluoxetine](#) was discontinued. The same study compared pharmacokinetics of [desipramine](#) when combined with [sertraline](#). The impact of [sertraline](#) was modest, resulting in small and short-term increases in [desipramine](#) plasma concentrations [517].

cJ) Concomitant administration of [fluoxetine](#) and [desipramine](#) was reported to result in an increased [desipramine](#) level and new onset of [delirium](#) in a 69-year-old male within 10 days of the addition of [fluoxetine](#) to the patient's regimen [518].

dJ) [Fluoxetine](#) increased the level of tricyclic antidepressants ([nortriptyline](#), [imipramine](#), [desipramine](#)) in 4 patients. After the addition of [fluoxetine](#), the ratio of antidepressant level to dose increased by 109% to 486% in the patients. Three patients developed clinical symptoms

(anticholinergic effects, constipation, urinary hesitancy, sedation, unstable gait) as a result of the increased levels [519].

e) A 39-year-old female experienced symptomatic increases in her [desipramine](#) levels with concomitant [fluoxetine](#) therapy. Prior to [fluoxetine](#) therapy, the patient's measured levels of [desipramine](#) had ranged from 148 to 160 nanograms/milliliter (ng/mL; 556 to 601 nanomol/L) on a regimen of 300 mg daily. Five weeks after the addition of [fluoxetine](#) 20 mg daily, she reported anticholinergic symptoms, sedation, and confusion with a [desipramine](#) level of 527 ng/mL (1978 nanomol/L). The [desipramine](#) dose was lowered to 200 mg/day; 11 days later, the level was 244 ng/mL (916 nanomol/L); the patient reported decreased energy, impaired short-term memory, and some "garbled" speech, as well as an episode of nausea, dizziness, and syncope. The [desipramine](#) dose was reduced to 50 mg/day, and the adverse effects resolved in 6 days. Eight days later, the [desipramine](#) level was 122 ng/mL (458 nanomol/L) [520].

f) A 33-year-old depressed male developed adverse effects of dry mouth, tinnitus, and difficulties with alertness and memory while receiving [fluoxetine](#) 40 mg daily and [desipramine](#) 150 mg daily for 5 weeks; [fluoxetine](#) was discontinued and the blood levels of [desipramine](#) decreased from 938 to 48 nanograms/mL (3521 to 180 nanomol/L) with resolution of clinical symptoms [521].

g) A 75-year-old female experienced symptomatic increases in her [desipramine](#) serum concentrations when [fluoxetine](#) was added. [Desipramine](#) serum levels ranged from 109 to 150 ng/mL (409 to 563 nanomol/L) with oral doses of 300 mg at bedtime prior to [fluoxetine](#) therapy. Following the addition of oral [fluoxetine](#) 20 mg daily to the regimen, the [desipramine](#) serum level increased to 212 ng/mL (796 nanomol/L) within five days. The [fluoxetine](#) dose was increased to 40 mg/day three days later, and the [desipramine](#) serum level was 419 ng/mL (1573 nanomol/L) after four days. A worsening of depression and severe fatigue coincided with the increases in [desipramine](#) serum levels. Withdrawal of [fluoxetine](#) and reduction in the [desipramine](#) dose to 200 mg daily reduced the [desipramine](#) serum level to 231 ng/mL (867 nanomol/L) within two weeks [522].

3.5.1.DK] [Diclofenac](#)

1) Interaction Effect: an increased risk of bleeding

2) Summary: Caution is recommended with the concomitant use of NSAIDs and antidepressants, including SSRIs due to an increased risk of [intracranial hemorrhage](#)[529] and [gastrointestinal bleeding](#) [533][534][530][531]. Bleeding events have included [epistaxis](#), ecchymosis, [hematoma](#), [petechiae](#), and life-threatening hemorrhages [536][535][537][538]. When an SSRI and an NSAID are given concurrently, monitor the patient for signs of increased bleeding.

3) Severity: major

4) Onset: unspecified

5) Substantiation: established

6) Clinical Management: Use caution if NSAIDs and SSRIs are coadministered. Concomitant use of NSAIDs and SSRIs may cause an increased risk of [intracranial hemorrhage](#)[529] and [gastrointestinal bleeding](#) [530][531]. When an SSRI and an NSAID are given concurrently, monitor the patient for signs of increased bleeding.

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

8) Literature Reports

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

use alone. There was no significant difference between the antidepressant drug classes and the increased risk; however, there was an increased risk associated with male patients compared with female patients [529].

b)) SSRIs increase the risk of upper gastrointestinal (GI) bleeding, and this effect is potentiated by concurrent use of NSAIDs or low-dose [aspirin](#). Hospitalizations for [upper GI bleeding](#) were searched among 26,005 users of antidepressant medications and compared with the number of hospitalizations in those patients who did not receive prescriptions for antidepressants. The amount of [upper GI bleeding](#) episodes was 3.6 times more than expected. Combined use of an SSRI and NSAIDs or low-dose [aspirin](#) increased the risk to 12.2 and 5.2 times, respectively. The findings of this study demonstrate an increased risk of [upper GI bleeding](#) during the use of SSRIs. Combined use of SSRIs and NSAIDs or low-dose [aspirin](#) increased the risk even further [532].

c)) Two metaanalyses of incidents of upper GI bleed due to SSRIs, NSAIDs, and their combination found that SSRIs increased the risk by 1.73 [533] to 2.36 times [534], NSAIDs by 2.55 times [533], and the combination of SSRIs and NSAIDs by 4.02 [533] to 6.33 times [534].

d)) The release of serotonin by [platelets](#) is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs and NSAIDs have been associated with an increased risk of bleeding [535].

3.5.1.DL] Dicumarol

1)) Interaction Effect: an increased risk of bleeding

2)) Summary: The release of serotonin by [platelets](#) is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs and anticoagulants has been associated with an increased risk of bleeding[458][457]. Bleeding events reported have included [epistaxis](#), ecchymosis, [hematoma](#), [petechiae](#), and life-threatening hemorrhages. Altered anticoagulant effects (including increased bleeding) have been reported with the coadministration of SSRIs with anticoagulants [457].

3)) Severity: major

4)) Onset: delayed

5)) Substantiation: probable

6)) Clinical Management: When [fluoxetine](#) and an anticoagulant are given concurrently, monitor patient for signs of increased bleeding. Patients who are taking an anticoagulant should be monitored closely for altered anticoagulant effects, including increased bleeding, when [fluoxetine](#) therapy is initiated or discontinued[457].

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 a significant 1.7-fold increased risk for hospitalization for nongastrointestinal bleeding; however, the rate of [gastrointestinal bleeding](#) was not significantly different [458].

3.5.1.DM] Diflunisal

1)) Interaction Effect: an increased risk of bleeding

2j) Summary: Caution is recommended with the concomitant use of NSAIDs and antidepressants, including SSRIs due to an increased risk of [intracranial hemorrhage](#)[529] and [gastrointestinal bleeding](#) [533][534][530][531]. Bleeding events have included [epistaxis](#), ecchymosis, [hematoma](#), [petechiae](#), and life-threatening hemorrhages [536][535][537][538]. When an SSRI and an NSAID are given concurrently, monitor the patient for signs of increased bleeding.

3j) Severity: major

4j) Onset: unspecified

5j) Substantiation: established

6j) Clinical Management: Use caution if NSAIDs and SSRIs are coadministered. Concomitant use of NSAIDs and SSRIs may cause an increased risk of [intracranial hemorrhage](#)[529] and [gastrointestinal bleeding](#) [530][531]. When an SSRI and an NSAID are given concurrently, monitor the patient for signs of increased bleeding.

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

8j) Literature Reports

aj) Concomitant use of NSAIDs and antidepressants, including tricyclic antidepressants, SSRIs, serotonin-norepinephrine reuptake inhibitors, and MAOIs, resulted in a 60% increased risk of [intracranial hemorrhage](#) within 30 days of concomitant use compared with antidepressant use alone. There was no significant difference between the antidepressant drug classes and the increased risk; however, there was an increased risk associated with male patients compared with female patients [529].

bj) SSRIs increase the risk of upper gastrointestinal (GI) bleeding, and this effect is potentiated by concurrent use of NSAIDs or low-dose [aspirin](#). Hospitalizations for [upper GI bleeding](#) were searched among 26,005 users of antidepressant medications and compared with the number of hospitalizations in those patients who did not receive prescriptions for antidepressants. The amount of [upper GI bleeding](#) episodes was 3.6 times more than expected. Combined use of an SSRI and NSAIDs or low-dose [aspirin](#) increased the risk to 12.2 and 5.2 times, respectively. The findings of this study demonstrate an increased risk of [upper GI bleeding](#) during the use of SSRIs. Combined use of SSRIs and NSAIDs or low-dose [aspirin](#) increased the risk even further [532].

cj) Two metaanalyses of incidents of upper GI bleed due to SSRIs, NSAIDs, and their combination found that SSRIs increased the risk by 1.73 [533] to 2.36 times [534], NSAIDs by 2.55 times [533], and the combination of SSRIs and NSAIDs by 4.02 [533] to 6.33 times [534].

dj) The release of serotonin by [platelets](#) is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs and NSAIDs have been associated with an increased risk of bleeding [535].

3.5.1.DN] [Digitoxin](#)

1j) Interaction Effect: an increased risk of [digitoxin](#) toxicity (nausea, vomiting, [arrhythmias](#))

2j) Summary: The administration of [fluoxetine](#) to a patient taking [digitoxin](#), also tightly bound to plasma protein, may cause a shift in plasma concentrations of [digitoxin](#)[550].

3j) Severity: moderate

4j) Onset: delayed

5j) Substantiation: theoretical

6j) Clinical Management: Patients receiving [fluoxetine](#) and [digitoxin](#) therapy concomitantly should be monitored for increasing levels of [digitoxin](#), along with signs and symptoms of [digitoxin](#) toxicity.

7j) Probable Mechanism: unknown

3.5.1.DO| Digoxin

- 1) Interaction Effect: an increased risk of **digoxin toxicity** (nausea, vomiting, **arrhythmias**)
- 2) Summary: One case report describes a 93-year-old female stabilized on **digoxin** who experienced toxic levels of **digoxin** after **fluoxetine** had been added to her regimen for depression. Rechallenge with **fluoxetine** again caused her **digoxin** levels to increase dramatically. While the mechanism of this interaction is not clear, it could be related to displacement of **digoxin** from binding sites or reduced clearance of **digoxin**[401].
- 3) Severity: moderate
- 4) Onset: delayed
- 5) Substantiation: probable
- 6) Clinical Management: Patients receiving **fluoxetine** and **digoxin** therapy concomitantly should be monitored for increasing levels of **digoxin**, along with signs and symptoms of **digoxin toxicity**, including anorexia.
- 7) Probable Mechanism: unknown
- 8) Literature Reports

a) **Digoxin** 0.125 mg daily was being administered to a 93-year-old female for **congestive heart failure** and **paroxysmal atrial fibrillation**. **Digoxin** levels ranged from 1.0 to 1.4 nmol/L during the two months preceding the initiation of **fluoxetine** 10 mg daily. Within one week, the patient complained of anorexia. Her **digoxin** level measured 4.2 nmol/L, while renal function and potassium levels remained unchanged. Both **digoxin** and **fluoxetine** were discontinued, and her **digoxin** level returned to normal in five days with resolution of the anorexia. During the next three weeks her **digoxin** serum levels ranged from 0.9 nmol/L to 1.4 nmol/L. Because the symptoms of depression persisted, **fluoxetine** was again initiated at 10 mg daily and the **digoxin** serum level was closely monitored. After two days of **fluoxetine** therapy, the **digoxin** level increased to 2.0 nmol/L, and after four days it was 2.8 nmol/L. Renal function remained unchanged, as did serum electrolytes. The patient again experienced anorexia, and treatment with **fluoxetine** was discontinued [400].

3.5.1.DP| Dihydrocodeine

- 1) Interaction Effect: increased risk of CNS depression (ie, **respiratory depression**, profound sedation, coma)
- 2) Summary: The concomitant use of **dihydrocodeine** with other CNS depressants may result in profound sedation, **respiratory depression**, coma, and/or death. Reserve concomitant use to clinical settings where alternative treatment options are inadequate. If combination therapy is required, reduce the initial dose of the newly prescribed medication and titrate to clinical response while monitoring for **respiratory depression** and sedation. Avoid concomitant use of **dihydrocodeine cough** medications with CNS depressants[78].
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Reserve concomitant use of **dihydrocodeine** with other CNS depressants to clinical settings where alternative treatment options are inadequate. If combination therapy is required, reduce the initial dose of the newly prescribed medication and titrate to clinical response while monitoring for **respiratory depression** and sedation. Avoid concomitant use of **dihydrocodeine cough** medications with CNS depressants[78].
- 7) Probable Mechanism: additive CNS depression

3.5.1.DQ| Dihydroergotamine

- 1) Interaction Effect: increased plasma concentrations of ergot derivatives and increased risk of [ergotism](#) (nausea, vomiting, vasospastic ischemia)
- 2) Summary: Concomitant use of [fluoxetine](#), a weak CYP3A4 inhibitor, and an ergot derivative may result in increased plasma concentrations of the ergot derivative due to inhibition of CYP3A4-mediated ergot metabolism. Because of the potential for serious toxicity including [vasospasm](#) can occur, use caution with the concurrent use of [fluoxetine](#) and ergot derivatives[189][188].
- 3) Severity: moderate
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: [Fluoxetine](#) may increase the plasma concentrations of ergot derivatives. Use caution when [fluoxetine](#) is coadministered with an ergot derivative, such as [dihydroergotamine](#), [ergotamine](#), or [methylergonovine](#), due to the potential for serious toxicity including [vasospasm](#) that can occur[188][189].
- 7) Probable Mechanism: inhibition of CYP3A4-mediated ergot metabolism by [fluoxetine](#)

3.5.1.DR| Dipyridamole

- 1) Interaction Effect: increased risk of bleeding
- 2) Summary: Exercise caution when coadministering a SSRI and an antiplatelet agent or anticoagulant as this may increase the risk of bleeding events[272][173][385].
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Use caution with concomitant use of [fluoxetine](#) with anticoagulants or antiplatelet agents, as coadministration may increase bleeding risk[272][173][385].
- 7) Probable Mechanism: altered anticoagulant effects
- 8) Literature Reports

a) In a retrospective study of patients over 50 years of age with the diagnosis of acute [myocardial infarction](#) (N=27,058), SSRI use with any antiplatelet therapy significantly increased the risk of bleeding by 1.42-fold compared with [aspirin](#) use alone. Therapy with [aspirin](#), [clopidogrel](#), and an SSRI significantly increased risk by 2.35-fold compared with [aspirin](#) use alone and by 1.57-fold compared with [clopidogrel](#) and [aspirin](#) combination therapy [385].

b) In a systematic review and meta-analysis of 22 observational studies, SSRI use was associated with a significant 1.55 fold increase in risk of [upper gastrointestinal bleeding](#) (UGIB). Concomitant use of SSRIs and antiplatelet drugs was associated with a 2.48-fold increase in risk of UGIB (3 studies) [272].

3.5.1.DS| Dipyrene

- 1) Interaction Effect: an increased risk of bleeding
- 2) Summary: Caution is recommended with the concomitant use of NSAIDs and antidepressants, including SSRIs due to an increased risk of [intracranial hemorrhage](#)[529] and [gastrointestinal bleeding](#) [533][534][530][531]. Bleeding events have included [epistaxis](#), ecchymosis, [hematoma](#), [petechiae](#), and life-threatening hemorrhages [536][535][537][538]. When an SSRI and an NSAID are given concurrently, monitor the patient for signs of increased bleeding.
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: established

6j) Clinical Management: Use caution if NSAIDs and SSRIs are coadministered. Concomitant use of NSAIDs and SSRIs may cause an increased risk of [intracranial hemorrhage](#)[529] and [gastrointestinal bleeding](#) [530][531]. When an SSRI and an NSAID are given concurrently, monitor the patient for signs of increased bleeding.

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

8j) Literature Reports

a) Concomitant use of NSAIDs and antidepressants, including tricyclic antidepressants, SSRIs, serotonin-norepinephrine reuptake inhibitors, and MAOIs, resulted in a 60% increased risk of [intracranial hemorrhage](#) within 30 days of concomitant use compared with antidepressant use alone. There was no significant difference between the antidepressant drug classes and the increased risk; however, there was an increased risk associated with male patients compared with female patients [529].

b) SSRIs increase the risk of upper gastrointestinal (GI) bleeding, and this effect is potentiated by concurrent use of NSAIDs or low-dose [aspirin](#). Hospitalizations for [upper GI bleeding](#) were searched among 26,005 users of antidepressant medications and compared with the number of hospitalizations in those patients who did not receive prescriptions for antidepressants. The amount of [upper GI bleeding](#) episodes was 3.6 times more than expected. Combined use of an SSRI and NSAIDs or low-dose [aspirin](#) increased the risk to 12.2 and 5.2 times, respectively. The findings of this study demonstrate an increased risk of [upper GI bleeding](#) during the use of SSRIs. Combined use of SSRIs and NSAIDs or low-dose [aspirin](#) increased the risk even further [532].

c) Two metaanalyses of incidents of upper GI bleed due to SSRIs, NSAIDs, and their combination found that SSRIs increased the risk by 1.73 [533] to 2.36 times [534], NSAIDs by 2.55 times [533], and the combination of SSRIs and NSAIDs by 4.02 [533] to 6.33 times [534].

d) The release of serotonin by [platelets](#) is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs and NSAIDs have been associated with an increased risk of bleeding [535].

3.5.1.DT] [Disopyramide](#)

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

2j) Summary: Even though no formal drug interaction studies have been done, the coadministration of Class Ia antiarrhythmics and other drugs known to prolong the QTc interval is not recommended[343]. [Fluoxetine](#) has demonstrated QT prolongation at therapeutic doses [344].

3j) Severity: major

4j) Onset: unspecified

5j) Substantiation: theoretical

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

7j) Probable Mechanism: additive effects on QT prolongation

3.5.1.DU] [Dofetilide](#)

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

2j) Summary: Even though no formal drug interaction studies have been done, the coadministration of Class III antiarrhythmics and other drugs known to prolong the QTc interval is not recommended[300]

[301][302]. [Fluoxetine](#) has been shown to prolong the QTc interval at the recommended therapeutic dose [303].

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

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

7) Probable Mechanism: additive effects on QT prolongation

3.5.1.DV] [Dolasetron](#)

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

2) Summary: Concomitant use of [dolasetron](#) with a drug that is a serotonergic agent with QT-interval prolonging effects may increase the risks of [serotonin syndrome](#) or QT-interval prolongation. [Serotonin syndrome](#) has been reported with the concurrent use of 5-hydroxytryptamine-3 antagonists and serotonergic drugs, primarily in infusion centers or in post-anesthesia care units. Inform patients of this increased risk and monitor for the emergence of [serotonin syndrome](#). If symptoms of [serotonin syndrome](#) occur, discontinue [dolasetron](#) and institute supportive therapy. Because [dolasetron](#) is known to prolong the QT-interval, administration with other QT-interval prolonging agents may result in additive effects, and should be undertaken with caution[242][243].

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Concomitant use of [dolasetron](#) with a drug that is a serotonergic agent with QT-interval prolonging effects may increase the risks of [serotonin syndrome](#) or QT-interval prolongation. Inform patients of the increased risk of [serotonin syndrome](#) and monitor for the emergence of [serotonin syndrome](#). If symptoms of [serotonin syndrome](#) occur, discontinue [dolasetron](#) and institute supportive therapy. Because [dolasetron](#) is known to prolong the QT-interval, coadministration with other QT-interval prolonging agents may result in additive effects, and should be undertaken with caution[242][243].

7) Probable Mechanism: unknown; additive QT-interval prolongation

3.5.1.DW] [Domperidone](#)

1) Interaction Effect: increased domperidone exposure and an increased risk of QT prolongation

2) Summary: Coadministration of [fluoxetine](#), a potential CYP3A4 inhibitor[552], with domperidone may result in increased plasma concentrations of domperidone and may have an effect on QT interval prolongation. Concomitant use of domperidone and [fluoxetine](#) may increase the risk of serious cardiac events, including [ventricular arrhythmias](#) and sudden cardiac death, and therefore should be undertaken with caution. Case-control studies demonstrated an association of serious [ventricular arrhythmias](#) and sudden cardiac death, particularly with domperidone doses greater than 30 mg/day and in patients older than 60 years. Domperidone should be initiated at the lowest possible dose and titrated with caution. Discontinue domperidone if the patient experiences dizziness, palpitations, syncope, or seizure [551].

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Use caution with the concomitant administration of domperidone and [fluoxetine](#) as this may result in increased plasma concentrations of domperidone and may increase the risk of serious cardiac effects, including [ventricular arrhythmias](#) and sudden cardiac death, particularly at domperidone doses greater than 30 mg/day and in patients older than 60 years. Domperidone should be initiated at

the lowest possible dose and titrated with caution. Discontinue domperidone if the patient experiences dizziness, palpitations, syncope, or seizure[551].

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

3.5.1.DX] Donepezil

1) Interaction Effect: increased risk of QT-interval prolongation and [torsade de pointes](#)

2) Summary: [Donepezil](#) has been associated with QT-interval prolongation[114][115]. Use caution when administering [donepezil](#) concomitantly with other drugs that cause QT-interval prolongation.

3) Severity: major

4) Onset: delayed

5) Substantiation: probable

6) Clinical Management: [Donepezil](#) has been associated with QT-interval prolongation[114][115]. Use caution when administering [donepezil](#) concomitantly with other drugs that cause QT-interval prolongation

7) Probable Mechanism: additive QT-interval prolongation

3.5.1.DY] Doxepin

1) Interaction Effect: increased risk of tricyclic antidepressant toxicity, QT prolongation and [serotonin syndrome](#)

2) Summary: [Fluoxetine](#), a potent CYP2D6 inhibitor, is associated with an increased risk of [serotonin syndrome](#), QT prolongation, and [ventricular arrhythmias](#) (including [torsade de pointes](#)). Concomitant therapy with CYP2D6-metabolized tricyclic antidepressants (TCAs) may potentiate these risks and introduce TCA toxicity[173]; concurrent use of [fluoxetine](#) and [desipramine](#), [nortriptyline](#), and [imipramine](#) has resulted in significant increases in TCA concentrations [517][523][524][525][526][527]. Use caution with concurrent administration of [fluoxetine](#) and TCAs. If [fluoxetine](#) is added to an existing TCA regimen, consider TCA dose reduction. If [fluoxetine](#) and a TCA are coadministered or [fluoxetine](#) has been recently discontinued, consider plasma TCA monitoring. If [serotonin syndrome](#) occurs, immediately discontinue [fluoxetine](#) and TCA. If [ventricular arrhythmias](#) develop, consider [fluoxetine](#) discontinuation and cardiac evaluation [173].

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Use caution with concurrent administration of [fluoxetine](#) and TCAs, as elevated TCA plasma concentrations may occur. If [fluoxetine](#) is added to an existing TCA regimen, consider TCA dose reduction. If [fluoxetine](#) and a TCA are coadministered or [fluoxetine](#) has been recently discontinued, consider plasma TCA monitoring. If [serotonin syndrome](#) occurs, immediately discontinue [fluoxetine](#) and TCA. If [ventricular arrhythmias](#) develop, consider [fluoxetine](#) discontinuation and cardiac evaluation[173]

7) Probable Mechanism: decreased CYP2D6-mediated metabolism of tricyclic antidepressants by [fluoxetine](#); additive effects on QT prolongation; additive serotonergic effects

8) Literature Reports

a) Previously stable plasma levels of [imipramine](#) and [desipramine](#) rose more than 2- to 10-fold with [fluoxetine](#) coadministration in 2 clinical studies. This effect may persist for 3 weeks or more after [fluoxetine](#) discontinuation. Dose reduction and temporary monitoring of tricyclic antidepressant plasma concentrations may be indicated with concurrent [fluoxetine](#) treatment or recent [fluoxetine](#) discontinuation [173].

b) [Fluoxetine](#) statistically and clinically significantly increased [desipramine](#) concentrations in 18 healthy subjects. When [fluoxetine](#) (20 mg daily) was added to [desipramine](#) (50 mg daily), the mean

maximum concentration of [desipramine](#) increased by 278% and the AUC increased by 342%. [Desipramine](#) trough concentrations continued to be 198% above baseline 3 weeks after [fluoxetine](#) was discontinued. The same study compared pharmacokinetics of [desipramine](#) when combined with [sertraline](#). The impact of [sertraline](#) was modest, resulting in small and short-term increases in [desipramine](#) plasma concentrations [517].

c) Concomitant administration of [fluoxetine](#) and [desipramine](#) was reported to result in an increased [desipramine](#) level and new onset of [delirium](#) in a 69-year-old male within 10 days of the addition of [fluoxetine](#) to the patient's regimen [518].

d) [Fluoxetine](#) increased the level of tricyclic antidepressants ([nortriptyline](#), [imipramine](#), [desipramine](#)) in 4 patients. After the addition of [fluoxetine](#), the ratio of antidepressant level to dose increased by 109% to 486% in the patients. Three patients developed clinical symptoms (anticholinergic effects, constipation, urinary hesitancy, sedation, unstable gait) as a result of the increased levels [519].

e) A 39-year-old female experienced symptomatic increases in her [desipramine](#) levels with concomitant [fluoxetine](#) therapy. Prior to [fluoxetine](#) therapy, the patient's measured levels of [desipramine](#) had ranged from 148 to 160 nanograms/milliliter (ng/mL; 556 to 601 nanomol/L) on a regimen of 300 mg daily. Five weeks after the addition of [fluoxetine](#) 20 mg daily, she reported anticholinergic symptoms, sedation, and confusion with a [desipramine](#) level of 527 ng/mL (1978 nanomol/L). The [desipramine](#) dose was lowered to 200 mg/day; 11 days later, the level was 244 ng/mL (916 nanomol/L); the patient reported decreased energy, impaired short-term memory, and some "garbled" speech, as well as an episode of nausea, dizziness, and syncope. The [desipramine](#) dose was reduced to 50 mg/day, and the adverse effects resolved in 6 days. Eight days later, the [desipramine](#) level was 122 ng/mL (458 nanomol/L) [520].

f) A 33-year-old depressed male developed adverse effects of dry mouth, tinnitus, and difficulties with alertness and memory while receiving [fluoxetine](#) 40 mg daily and [desipramine](#) 150 mg daily for 5 weeks; [fluoxetine](#) was discontinued and the blood levels of [desipramine](#) decreased from 938 to 48 nanograms/mL (3521 to 180 nanomol/L) with resolution of clinical symptoms [521].

g) A 75-year-old female experienced symptomatic increases in her [desipramine](#) serum concentrations when [fluoxetine](#) was added. [Desipramine](#) serum levels ranged from 109 to 150 ng/mL (409 to 563 nanomol/L) with oral doses of 300 mg at bedtime prior to [fluoxetine](#) therapy. Following the addition of oral [fluoxetine](#) 20 mg daily to the regimen, the [desipramine](#) serum level increased to 212 ng/mL (796 nanomol/L) within five days. The [fluoxetine](#) dose was increased to 40 mg/day three days later, and the [desipramine](#) serum level was 419 ng/mL (1573 nanomol/L) after four days. A worsening of depression and severe fatigue coincided with the increases in [desipramine](#) serum levels. Withdrawal of [fluoxetine](#) and reduction in the [desipramine](#) dose to 200 mg daily reduced the [desipramine](#) serum level to 231 ng/mL (867 nanomol/L) within two weeks [522].

3.5.1.DZ] [Doxorubicin](#)

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

2) Summary: Avoid concurrent use of [DOXOrubicin](#), a CYP2D6 substrate, with CYP2D6 inhibitors, as increased [DOXOrubicin](#) plasma concentrations may occur[298]. 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](#) [299].

3) Severity: major

- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Avoid concurrent use of [DOXOrubicin](#) with CYP2D6 inhibitors, as increased [DOXOrubicin](#) plasma concentrations may result[298].
- 7) Probable Mechanism: inhibition of CYP2D6-mediated [DOXOrubicin](#) metabolism

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

- 1) Interaction Effect: increased [DOXOrubicin](#) exposure
- 2) Summary: Avoid concurrent use of [DOXOrubicin](#), a CYP2D6 substrate, with CYP2D6 inhibitors, as increased [DOXOrubicin](#) plasma concentrations may occur[298]. 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](#) [299].
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Avoid concurrent use of [DOXOrubicin](#) with CYP2D6 inhibitors, as increased [DOXOrubicin](#) plasma concentrations may result[298].
- 7) Probable Mechanism: inhibition of CYP2D6-mediated [DOXOrubicin](#) metabolism

3.5.1.EB] [Doxylamine](#)

- 1) Interaction Effect: increased risk of CNS depression
- 2) Summary: Coadministration of [doxylamine](#) and a CNS depressant is not recommended due to the potential for additive CNS depression[131][132]. If concomitant use is required, consider monitoring and dose reduction of one or both agents.
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Coadministration of [doxylamine](#) and a CNS depressant is not recommended due to the potential for additive CNS depression[131][132]. If concomitant use is required, consider monitoring and dose reduction of one or both agents.
- 7) Probable Mechanism: additive CNS depression

3.5.1.EC] [Dronedarone](#)

- 1) Interaction Effect: increased risk of QT-interval prolongation
- 2) Summary: The concomitant use of dronedarone with drugs that cause QT-interval prolongation is contraindicated, as coadministration may increase the risk of QT prolongation and serious [ventricular arrhythmias](#)[97].
- 3) Severity: contraindicated
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: The concomitant use of dronedarone with drugs that cause QT-interval prolongation is contraindicated, as coadministration may increase the risk of QT prolongation and serious [ventricular arrhythmias](#)[97].
- 7) Probable Mechanism: additive QT-interval prolongation

3.5.1.ED] [Droperidol](#)

- 1) Interaction Effect: an increased risk of [cardiotoxicity](#) (QT prolongation, [torsades de pointes](#), [cardiac arrest](#))
- 2) Summary: [Droperidol](#) has been shown to prolong the QTc interval at the recommended therapeutic dose. Even though no formal drug interaction studies have been done, the coadministration of [droperidol](#) and other drugs known to prolong the QTc interval, including [fluoxetine](#) is not recommended[433][434].
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: The concurrent administration of [droperidol](#) and [fluoxetine](#) is not recommended.
- 7) Probable Mechanism: additive cardiac effects

3.5.1.EE] [Drotrecogin Alfa](#)

- 1) Interaction Effect: increased risk of bleeding
- 2) Summary: Exercise caution when coadministering a SSRI and an antiplatelet agent or anticoagulant as this may increase the risk of bleeding events[272][173][385].
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Use caution with concomitant use of [fluoxetine](#) with anticoagulants or antiplatelet agents, as coadministration may increase bleeding risk[272][173][385].
- 7) Probable Mechanism: altered anticoagulant effects
- 8) Literature Reports

a) In a retrospective study of patients over 50 years of age with the diagnosis of acute [myocardial infarction](#) (N=27,058), SSRI use with any antiplatelet therapy significantly increased the risk of bleeding by 1.42-fold compared with [aspirin](#) use alone. Therapy with [aspirin](#), [clopidogrel](#), and an SSRI significantly increased risk by 2.35-fold compared with [aspirin](#) use alone and by 1.57-fold compared with [clopidogrel](#) and [aspirin](#) combination therapy [385].

b) In a systematic review and meta-analysis of 22 observational studies, SSRI use was associated with a significant 1.55 fold increase in risk of [upper gastrointestinal bleeding](#) (UGIB). Concomitant use of SSRIs and antiplatelet drugs was associated with a 2.48-fold increase in risk of UGIB (3 studies) [272].

3.5.1.EF] [Droxicam](#)

- 1) Interaction Effect: an increased risk of bleeding
- 2) Summary: Caution is recommended with the concomitant use of NSAIDs and antidepressants, including SSRIs due to an increased risk of [intracranial hemorrhage](#)[529] and [gastrointestinal bleeding](#) [533][534][530][531]. Bleeding events have included [epistaxis](#), ecchymosis, [hematoma](#), [petechiae](#), and life-threatening hemorrhages [536][535][537][538]. When an SSRI and an NSAID are given concurrently, monitor the patient for signs of increased bleeding.
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: established
- 6) Clinical Management: Use caution if NSAIDs and SSRIs are coadministered. Concomitant use of NSAIDs and SSRIs may cause an increased risk of [intracranial hemorrhage](#)[529] and [gastrointestinal bleeding](#) [530][531]. When an SSRI and an NSAID are given concurrently, monitor the patient for signs of increased bleeding.

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

8j) Literature Reports

a) Concomitant use of NSAIDs and antidepressants, including tricyclic antidepressants, SSRIs, serotonin-norepinephrine reuptake inhibitors, and MAOIs, resulted in a 60% increased risk of [intracranial hemorrhage](#) within 30 days of concomitant use compared with antidepressant use alone. There was no significant difference between the antidepressant drug classes and the increased risk; however, there was an increased risk associated with male patients compared with female patients [529].

b) SSRIs increase the risk of upper gastrointestinal (GI) bleeding, and this effect is potentiated by concurrent use of NSAIDs or low-dose [aspirin](#). Hospitalizations for [upper GI bleeding](#) were searched among 26,005 users of antidepressant medications and compared with the number of hospitalizations in those patients who did not receive prescriptions for antidepressants. The amount of [upper GI bleeding](#) episodes was 3.6 times more than expected. Combined use of an SSRI and NSAIDs or low-dose [aspirin](#) increased the risk to 12.2 and 5.2 times, respectively. The findings of this study demonstrate an increased risk of [upper GI bleeding](#) during the use of SSRIs. Combined use of SSRIs and NSAIDs or low-dose [aspirin](#) increased the risk even further [532].

c) Two metaanalyses of incidents of upper GI bleed due to SSRIs, NSAIDs, and their combination found that SSRIs increased the risk by 1.73 [533] to 2.36 times [534], NSAIDs by 2.55 times [533], and the combination of SSRIs and NSAIDs by 4.02 [533] to 6.33 times [534].

d) The release of serotonin by [platelets](#) is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs and NSAIDs have been associated with an increased risk of bleeding [535].

3.5.1.EG| [Duloxetine](#)

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

2j) 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](#)[571].

3j) Severity: major

4j) Onset: unspecified

5j) Substantiation: probable

6j) 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[571].

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

3.5.1.EH| [Edoxaban](#)

1j) Interaction Effect: increased risk of bleeding

- 2) Summary: Concomitant use of edoxaban and SSRIs may increase the risk of bleeding. If coadministration is necessary, promptly evaluate any signs or symptoms of blood loss[295].
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Concomitant use of edoxaban and SSRIs may increase the risk of bleeding. If coadministration is necessary, promptly evaluate any signs or symptoms of blood loss[295].
- 7) Probable Mechanism: unknown

3.5.1.EI] Efavirenz

- 1) Interaction Effect: increased risk of QT interval prolongation
- 2) Summary: Consider alternatives to efavirenz when used concomitantly with another drug that prolongs the QT interval or has a known risk of *torsade de pointes*, because additive effects on the QT interval may occur. In a QT study of 58 healthy subjects, the mean C_{max} in patients with the CYP2B6 *6/*6 genotype was 2.25-fold higher than the mean C_{max} in those with the CYP2B6 *1/*1 genotype and the mean QTc interval prolongation was 8.7 milliseconds in subjects with the CYP2B6 *6/*6 genotype[128].
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Consider alternatives to efavirenz when used concomitantly with another drug that prolongs the QT interval or has a known risk of *torsade de pointes*, because additive effects on the QT interval may occur[128].
- 7) Probable Mechanism: additive effects on the QT interval
- 8) Literature Reports

a) In a QT study of healthy subjects (N=58) enriched for CYP2B6 polymorphisms, a positive association between efavirenz concentration and QTc prolongation was observed. Following administration of efavirenz 600 mg/day for 14 days, the mean C_{max} in subjects with the CYP2B6 *6/*6 genotype was 2.25-fold higher than the mean C_{max} in subjects with the CYP2B6 *1/*1 genotype and the mean QTc interval prolongation was 8.7 milliseconds in subjects with the CYP2B6 *6/*6 genotype [128].

3.5.1.EJ] Eletriptan

- 1) Interaction Effect: increased risk of serotonin syndrome
- 2) Summary: Concomitant use of eletriptan with an SSRI may result in serotonin syndrome due to additive serotonergic effects. Cases of life-threatening serotonin syndrome have been reported following coadministration of triptans and SSRIs. Symptoms may include agitation, hallucinations, coma, incoordination, tachycardia, labile blood pressure, hyperthermia, hyperreflexia, nausea, vomiting, and diarrhea. If treatment with eletriptan and an SSRI is required, the patient should be monitored closely for signs and symptoms of serotonin syndrome, particularly during treatment initiation and dose increases[586].
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Concomitant use of eletriptan and an SSRI may result in serotonin syndrome. Cases of life-threatening serotonin syndrome have been reported following coadministration of triptans and SSRIs. If concomitant use is warranted, closely observe the patient for signs and symptoms of serotonin syndrome, especially during treatment initiation and dose increases[586].
- 7) Probable Mechanism: additive serotonergic effects

3.5.1.EK] Eliglustat

- 1) Interaction Effect: increased eliglustat exposure and subsequent prolongation of the QT interval
- 2) Summary: Avoid coadministration of eliglustat with weak CYP3A4 inhibitors in poor CYP2D6 metabolizers with [Gaucher disease type 1](#), as resulting increases in eliglustat exposure can progress to serious [cardiac arrhythmias](#), including QT-interval prolongation. Although not specifically studied in poor metabolizers, eliglustat coadministration with a moderate CYP3A inhibitor was predicted to increase eliglustat Cmax by 2.5- to 2.8-fold and AUC by 2.9- to 3.2-fold among extensive and intermediate CYP2D6 metabolizers. Do not administer eliglustat with strong or moderate CYP3A4 inhibitors plus strong or moderate CYP2D6 inhibitors, as concurrent use is contraindicated for all patients[246].
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Coadministration of eliglustat with weak CYP3A4 inhibitors in poor CYP2D6 metabolizers with [Gaucher disease type 1](#) is not recommended, as resulting increases in eliglustat exposure can progress to serious [cardiac arrhythmias](#), including QT-interval prolongation. Do not administer eliglustat with strong or moderate CYP3A4 inhibitors plus strong or moderate CYP2D6 inhibitors, as concurrent use is contraindicated for all patients[246].
- 7) Probable Mechanism: inhibition of CYP3A4-mediated eliglustat metabolism
- 8) Literature Reports

a) Though not specifically studied in poor metabolizers with [Gaucher disease type 1](#), eliglustat use with the moderate CYP3A4 inhibitor, [fluconazole](#), was predicted to cause 2.8- and 3.2-fold increases in eliglustat Cmax and AUC, respectively, in extensive metabolizers and 2.5- and 2.9-fold increases in intermediate metabolizers [246]

b) Though not specifically studied among poor CYP2D6 metabolizers with [Gaucher disease type 1](#), simulations with extensive CYP2D6 metabolizers suggested that eliglustat Cmax and AUC would increase 16.7- and 24.2-fold, respectively, with concomitant use of [paroxetine](#) (a strong CYP2D6 inhibitor), plus [ketoconazole](#) (a strong CYP3A inhibitor). Among intermediate CYP2D6 metabolizers, the predicted eliglustat Cmax and AUC was 7.5- and 9.8-fold higher, respectively, with concurrent use of [paroxetine](#) plus [ketoconazole](#). Treatment with moderate CYP2D6 and CYP3A4 inhibitors would increase eliglustat Cmax and AUC an estimated 10.2- and 13.6-fold, respectively, with concomitant use of [terbinafine](#) (a moderate CYP2D6 inhibitor) plus [fluconazole](#) (a moderate CYP3A4 inhibitor) among extensive CYP2D6 metabolizers. Eliglustat Cmax and AUC were predicted to increased by 4.2- and 5-fold, respectively, among intermediate CYP2D6 metabolizers treated with [terbinafine](#) plus [fluconazole](#) [246].

3.5.1.EL] Enflurane

- 1) Interaction Effect: an increased risk of [cardiotoxicity](#) (QT prolongation, [torsades de pointes](#), [cardiac arrest](#))
- 2) Summary: Even though no formal drug interaction studies have been done, [enflurane](#) should be coadministered cautiously with other drugs which are also known to prolong the QTc interval, including [fluoxetine](#)[214][215].
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: The concurrent administration of [enflurane](#) with other agents that can prolong the QT interval, such as [fluoxetine](#), is not recommended.

7) Probable Mechanism: additive effects on QT prolongation

3.5.1.EM] Enoxaparin

1) Interaction Effect: an increased risk of bleeding

2) Summary: The release of serotonin by [platelets](#) is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs and anticoagulants has been associated with an increased risk of bleeding[458][457]. Bleeding events reported have included [epistaxis](#), ecchymosis, [hematoma](#), [petechiae](#), and life-threatening hemorrhages. Altered anticoagulant effects (including increased bleeding) have been reported with the coadministration of SSRIs with anticoagulants [457].

3) Severity: major

4) Onset: delayed

5) Substantiation: probable

6) Clinical Management: When [fluoxetine](#) and an anticoagulant are given concurrently, monitor patient for signs of increased bleeding. Patients who are taking an anticoagulant should be monitored closely for altered anticoagulant effects, including increased bleeding, when [fluoxetine](#) therapy is initiated or discontinued[457].

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 a significant 1.7-fold increased risk for hospitalization for nongastrointestinal bleeding; however, the rate of [gastrointestinal bleeding](#) was not significantly different [458].

3.5.1.EN] Epoprostenol

1) Interaction Effect: increased risk of bleeding

2) Summary: Exercise caution when coadministering a SSRI and an antiplatelet agent or anticoagulant as this may increase the risk of bleeding events[272][173][385].

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Use caution with concomitant use of [fluoxetine](#) with anticoagulants or antiplatelet agents, as coadministration may increase bleeding risk[272][173][385].

7) Probable Mechanism: altered anticoagulant effects

8) Literature Reports

a) In a retrospective study of patients over 50 years of age with the diagnosis of acute [myocardial infarction](#) (N=27,058), SSRI use with any antiplatelet therapy significantly increased the risk of bleeding by 1.42-fold compared with [aspirin](#) use alone. Therapy with [aspirin](#), [clopidogrel](#), and an SSRI significantly increased risk by 2.35-fold compared with [aspirin](#) use alone and by 1.57-fold compared with [clopidogrel](#) and [aspirin](#) combination therapy [385].

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

Concomitant use of SSRIs and antiplatelet drugs was associated with a 2.48-fold increase in risk of UGIB (3 studies) [272].

3.5.1.EO| Eptifibatide

- 1) Interaction Effect: increased risk of bleeding
- 2) Summary: Exercise caution when coadministering a SSRI and an antiplatelet agent or anticoagulant as this may increase the risk of bleeding events[272][173][385].
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Use caution with concomitant use of [fluoxetine](#) with anticoagulants or antiplatelet agents, as coadministration may increase bleeding risk[272][173][385].
- 7) Probable Mechanism: altered anticoagulant effects
- 8) Literature Reports

a) In a retrospective study of patients over 50 years of age with the diagnosis of acute [myocardial infarction](#) (N=27,058), SSRI use with any antiplatelet therapy significantly increased the risk of bleeding by 1.42-fold compared with [aspirin](#) use alone. Therapy with [aspirin](#), [clopidogrel](#), and an SSRI significantly increased risk by 2.35-fold compared with [aspirin](#) use alone and by 1.57-fold compared with [clopidogrel](#) and [aspirin](#) combination therapy [385].

b) In a systematic review and meta-analysis of 22 observational studies, SSRI use was associated with a significant 1.55 fold increase in risk of [upper gastrointestinal bleeding](#) (UGIB). Concomitant use of SSRIs and antiplatelet drugs was associated with a 2.48-fold increase in risk of UGIB (3 studies) [272].

3.5.1.EP| Ergoloid Mesylates

- 1) Interaction Effect: increased plasma concentrations of ergot derivatives and increased risk of [ergotism](#) (nausea, vomiting, vasospastic ischemia)
- 2) Summary: Concomitant use of [fluoxetine](#), a weak CYP3A4 inhibitor, and an ergot derivative may result in increased plasma concentrations of the ergot derivative due to inhibition of CYP3A4-mediated ergot metabolism. Because of the potential for serious toxicity including [vasospasm](#) can occur, use caution with the concurrent use of [fluoxetine](#) and ergot derivatives[189][188].
- 3) Severity: moderate
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: [Fluoxetine](#) may increase the plasma concentrations of ergot derivatives. Use caution when [fluoxetine](#) is coadministered with an ergot derivative, such as [dihydroergotamine](#), [ergotamine](#), or [methylergonovine](#), due to the potential for serious toxicity including [vasospasm](#) that can occur[188][189].
- 7) Probable Mechanism: inhibition of CYP3A4-mediated ergot metabolism by [fluoxetine](#)

3.5.1.EQ| Ergonovine

- 1) Interaction Effect: increased plasma concentrations of ergot derivatives and increased risk of [ergotism](#) (nausea, vomiting, vasospastic ischemia)
- 2) Summary: Concomitant use of [fluoxetine](#), a weak CYP3A4 inhibitor, and an ergot derivative may result in increased plasma concentrations of the ergot derivative due to inhibition of CYP3A4-mediated ergot

metabolism. Because of the potential for serious toxicity including [vasospasm](#) can occur, use caution with the concurrent use of [fluoxetine](#) and ergot derivatives[189][188].

3) Severity: moderate

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: [Fluoxetine](#) may increase the plasma concentrations of ergot derivatives. Use caution when [fluoxetine](#) is coadministered with an ergot derivative, such as [dihydroergotamine](#), [ergotamine](#), or [methylergonovine](#), due to the potential for serious toxicity including [vasospasm](#) that can occur[188][189].

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

3.5.1.ER] [Ergotamine](#)

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

2) Summary: Concomitant use of [fluoxetine](#), a weak CYP3A4 inhibitor, and an ergot derivative may result in increased plasma concentrations of the ergot derivative due to inhibition of CYP3A4-mediated ergot metabolism. Because of the potential for serious toxicity including [vasospasm](#) can occur, use caution with the concurrent use of [fluoxetine](#) and ergot derivatives[189][188].

3) Severity: moderate

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: [Fluoxetine](#) may increase the plasma concentrations of ergot derivatives. Use caution when [fluoxetine](#) is coadministered with an ergot derivative, such as [dihydroergotamine](#), [ergotamine](#), or [methylergonovine](#), due to the potential for serious toxicity including [vasospasm](#) that can occur[188][189].

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

3.5.1.ES] [Erythromycin](#)

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

2) Summary: [Erythromycin](#) significantly increased the mean QTc interval versus baseline in a retrospective study of 49 patients[573]. [Erythromycin](#) has demonstrated QTc prolongation in combination with other drugs that prolong the QT interval [574]. [Fluoxetine](#) has been associated with QT prolongation [575]. Caution is advised with coadministration of drugs that potentially prolong the QTc interval.

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Caution is advised if [erythromycin](#) and [fluoxetine](#) are used concomitantly. Monitor QT interval at baseline and periodically during treatment.

7) Probable Mechanism: additive effects on QT prolongation

8) Literature Reports

a) [Erythromycin](#) significantly increased the QTc interval compared with baseline in a retrospective study of 49 patients. The [erythromycin](#) dose was 500 milligrams or 1 gram four times daily, with a mean of 15 doses received. Patients (n equal to 9) who received 60 mg/kg/day or more all developed increases in QT interval of 15% or greater. For all patients, the mean QTc interval increased from 432 milliseconds (msec) at baseline to 483 msec (p less than 0.01). In patients with delayed repolarization at baseline (n equal to 9), the QTc interval increased from 473 msec to 525 msec (p less than 0.01). In patients with [heart disease](#) (n equal to 30), all experienced an increase in

QTc interval (mean of 15%), compared with an increase of 8% in patients without [heart disease](#) (p less than 0.05). In 5 patients (10%), the QTc interval was severely prolonged. One patient developed [torsades de pointes](#) attributed to [erythromycin](#). Of 16 patients receiving cotrimoxazole concomitantly, 8 developed QT prolongation of 15% or greater [572].

3.5.1.ET] Escitalopram

- 1) Interaction Effect: increased risk of QT-interval prolongation
- 2) Summary: Escitalopram is a QT-interval-prolonging drug[148]. Use caution with concurrent use of other QT-interval-prolonging agents, due to increased risk of additive QT-interval prolongation.
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Escitalopram is a QT-interval-prolonging drug[148]. Use caution with concurrent use of other QT-interval-prolonging agents, due to increased risk of additive QT-interval prolongation.
- 7) Probable Mechanism: additive QT-interval prolongation

3.5.1.EU] Escitalopram

- 1) Interaction Effect: an increased risk of QT-interval prolongation and [serotonin syndrome](#) ([hypertension](#), [hyperthermia](#), myoclonus, mental status changes)
- 2) Summary: Avoid coadministration of [fluoxetine](#) and other drugs that prolong the QT interval, such as escitalopram, as this may result in additive effects on QT interval prolongation and an increased risk of serious [ventricular arrhythmias](#). Coadministration may also result in additive serotonergic effects and may increase the risk of [serotonin syndrome](#). If concomitant use is required, periodically monitor for QT interval prolongation and signs and symptoms of [serotonin syndrome](#)[173]. 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 [146].
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: The concomitant use of [fluoxetine](#) with other drugs that prolong the QT interval, such as escitalopram, should be avoided as coadministration may result in additive effects on QT interval and an increased risk of serious [ventricular arrhythmias](#). Coadministration may also result in additive serotonergic effects and may increase the risk of [serotonin syndrome](#). If concomitant use of escitalopram and [fluoxetine](#) is required, periodically monitor ECG and for signs and symptoms of [serotonin syndrome](#). Discontinue use if QT prolongation or [serotonin syndrome](#) occurs[173].
- 7) Probable Mechanism: additive effects on QT interval; additive serotonergic effects

3.5.1.EV] Etodolac

- 1) Interaction Effect: an increased risk of bleeding
- 2) Summary: Caution is recommended with the concomitant use of NSAIDs and antidepressants, including SSRIs due to an increased risk of [intracranial hemorrhage](#)[529] and [gastrointestinal bleeding](#) [533][534][530][531]. Bleeding events have included [epistaxis](#), ecchymosis, [hematoma](#), [petechiae](#), and life-threatening hemorrhages [536][535][537][538]. When an SSRI and an NSAID are given concurrently, monitor the patient for signs of increased bleeding.

- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: established
- 6) Clinical Management: Use caution if NSAIDs and SSRIs are coadministered. Concomitant use of NSAIDs and SSRIs may cause an increased risk of [intracranial hemorrhage](#)[529] and [gastrointestinal bleeding](#) [530][531]. When an SSRI and an NSAID are given concurrently, monitor the patient for signs of increased bleeding.
- 7) Probable Mechanism: depletion of [platelet](#) serotonin by SSRI; additive effects
- 8) Literature Reports

a) Concomitant use of NSAIDs and antidepressants, including tricyclic antidepressants, SSRIs, serotonin-norepinephrine reuptake inhibitors, and MAOIs, resulted in a 60% increased risk of [intracranial hemorrhage](#) within 30 days of concomitant use compared with antidepressant use alone. There was no significant difference between the antidepressant drug classes and the increased risk; however, there was an increased risk associated with male patients compared with female patients [529].

b) SSRIs increase the risk of upper gastrointestinal (GI) bleeding, and this effect is potentiated by concurrent use of NSAIDs or low-dose [aspirin](#). Hospitalizations for [upper GI bleeding](#) were searched among 26,005 users of antidepressant medications and compared with the number of hospitalizations in those patients who did not receive prescriptions for antidepressants. The amount of [upper GI bleeding](#) episodes was 3.6 times more than expected. Combined use of an SSRI and NSAIDs or low-dose [aspirin](#) increased the risk to 12.2 and 5.2 times, respectively. The findings of this study demonstrate an increased risk of [upper GI bleeding](#) during the use of SSRIs. Combined use of SSRIs and NSAIDs or low-dose [aspirin](#) increased the risk even further [532].

c) Two metaanalyses of incidents of upper GI bleed due to SSRIs, NSAIDs, and their combination found that SSRIs increased the risk by 1.73 [533] to 2.36 times [534], NSAIDs by 2.55 times [533], and the combination of SSRIs and NSAIDs by 4.02 [533] to 6.33 times [534].

d) The release of serotonin by [platelets](#) is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs and NSAIDs have been associated with an increased risk of bleeding [535].

3.5.1.EW] Etofenamate

- 1) Interaction Effect: an increased risk of bleeding
- 2) Summary: Caution is recommended with the concomitant use of NSAIDs and antidepressants, including SSRIs due to an increased risk of [intracranial hemorrhage](#)[529] and [gastrointestinal bleeding](#) [533][534][530][531]. Bleeding events have included [epistaxis](#), ecchymosis, [hematoma](#), [petechiae](#), and life-threatening hemorrhages [536][535][537][538]. When an SSRI and an NSAID are given concurrently, monitor the patient for signs of increased bleeding.
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: established
- 6) Clinical Management: Use caution if NSAIDs and SSRIs are coadministered. Concomitant use of NSAIDs and SSRIs may cause an increased risk of [intracranial hemorrhage](#)[529] and [gastrointestinal bleeding](#) [530][531]. When an SSRI and an NSAID are given concurrently, monitor the patient for signs of increased bleeding.
- 7) Probable Mechanism: depletion of [platelet](#) serotonin by SSRI; additive effects
- 8) Literature Reports

a) Concomitant use of NSAIDs and antidepressants, including tricyclic antidepressants, SSRIs, serotonin-norepinephrine reuptake inhibitors, and MAOIs, resulted in a 60% increased risk of [intracranial hemorrhage](#) within 30 days of concomitant use compared with antidepressant use alone. There was no significant difference between the antidepressant drug classes and the increased risk; however, there was an increased risk associated with male patients compared with female patients [529].

b) SSRIs increase the risk of upper gastrointestinal (GI) bleeding, and this effect is potentiated by concurrent use of NSAIDs or low-dose [aspirin](#). Hospitalizations for [upper GI bleeding](#) were searched among 26,005 users of antidepressant medications and compared with the number of hospitalizations in those patients who did not receive prescriptions for antidepressants. The amount of [upper GI bleeding](#) episodes was 3.6 times more than expected. Combined use of an SSRI and NSAIDs or low-dose [aspirin](#) increased the risk to 12.2 and 5.2 times, respectively. The findings of this study demonstrate an increased risk of [upper GI bleeding](#) during the use of SSRIs. Combined use of SSRIs and NSAIDs or low-dose [aspirin](#) increased the risk even further [532].

c) Two metaanalyses of incidents of upper GI bleed due to SSRIs, NSAIDs, and their combination found that SSRIs increased the risk by 1.73 [533] to 2.36 times [534], NSAIDs by 2.55 times [533], and the combination of SSRIs and NSAIDs by 4.02 [533] to 6.33 times [534].

d) The release of serotonin by [platelets](#) is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs and NSAIDs have been associated with an increased risk of bleeding [535].

3.5.1.EX] Etoricoxib

1) Interaction Effect: an increased risk of bleeding

2) Summary: Caution is recommended with the concomitant use of NSAIDs and antidepressants, including SSRIs due to an increased risk of [intracranial hemorrhage](#)[529] and [gastrointestinal bleeding](#) [533][534][530][531]. Bleeding events have included [epistaxis](#), ecchymosis, [hematoma](#), [petechiae](#), and life-threatening hemorrhages [536][535][537][538]. When an SSRI and an NSAID are given concurrently, monitor the patient for signs of increased bleeding.

3) Severity: major

4) Onset: unspecified

5) Substantiation: established

6) Clinical Management: Use caution if NSAIDs and SSRIs are coadministered. Concomitant use of NSAIDs and SSRIs may cause an increased risk of [intracranial hemorrhage](#)[529] and [gastrointestinal bleeding](#) [530][531]. When an SSRI and an NSAID are given concurrently, monitor the patient for signs of increased bleeding.

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

8) Literature Reports

a) Concomitant use of NSAIDs and antidepressants, including tricyclic antidepressants, SSRIs, serotonin-norepinephrine reuptake inhibitors, and MAOIs, resulted in a 60% increased risk of [intracranial hemorrhage](#) within 30 days of concomitant use compared with antidepressant use alone. There was no significant difference between the antidepressant drug classes and the increased risk; however, there was an increased risk associated with male patients compared with female patients [529].

b) SSRIs increase the risk of upper gastrointestinal (GI) bleeding, and this effect is potentiated by concurrent use of NSAIDs or low-dose [aspirin](#). Hospitalizations for [upper GI bleeding](#) were searched among 26,005 users of antidepressant medications and compared with the number of hospitalizations in those patients who did not receive prescriptions for antidepressants. The amount of [upper GI bleeding](#) episodes was 3.6 times more than expected. Combined use of an SSRI and NSAIDs or low-dose [aspirin](#) increased the risk to 12.2 and 5.2 times, respectively. The findings of this study demonstrate an increased risk of [upper GI bleeding](#) during the use of SSRIs. Combined use of SSRIs and NSAIDs or low-dose [aspirin](#) increased the risk even further [532].

c) Two metaanalyses of incidents of upper GI bleed due to SSRIs, NSAIDs, and their combination found that SSRIs increased the risk by 1.73 [533] to 2.36 times [534], NSAIDs by 2.55 times [533], and the combination of SSRIs and NSAIDs by 4.02 [533] to 6.33 times [534].

d) The release of serotonin by [platelets](#) is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs and NSAIDs have been associated with an increased risk of bleeding [535].

3.5.1.EY] Felbinac

1) Interaction Effect: an increased risk of bleeding

2) Summary: Caution is recommended with the concomitant use of NSAIDs and antidepressants, including SSRIs due to an increased risk of [intracranial hemorrhage](#)[529] and [gastrointestinal bleeding](#) [533][534][530][531]. Bleeding events have included [epistaxis](#), ecchymosis, [hematoma](#), [petechiae](#), and life-threatening hemorrhages [536][535][537][538]. When an SSRI and an NSAID are given concurrently, monitor the patient for signs of increased bleeding.

3) Severity: major

4) Onset: unspecified

5) Substantiation: established

6) Clinical Management: Use caution if NSAIDs and SSRIs are coadministered. Concomitant use of NSAIDs and SSRIs may cause an increased risk of [intracranial hemorrhage](#)[529] and [gastrointestinal bleeding](#) [530][531]. When an SSRI and an NSAID are given concurrently, monitor the patient for signs of increased bleeding.

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

8) Literature Reports

a) Concomitant use of NSAIDs and antidepressants, including tricyclic antidepressants, SSRIs, serotonin-norepinephrine reuptake inhibitors, and MAOIs, resulted in a 60% increased risk of [intracranial hemorrhage](#) within 30 days of concomitant use compared with antidepressant use alone. There was no significant difference between the antidepressant drug classes and the increased risk; however, there was an increased risk associated with male patients compared with female patients [529].

b) SSRIs increase the risk of upper gastrointestinal (GI) bleeding, and this effect is potentiated by concurrent use of NSAIDs or low-dose [aspirin](#). Hospitalizations for [upper GI bleeding](#) were searched among 26,005 users of antidepressant medications and compared with the number of hospitalizations in those patients who did not receive prescriptions for antidepressants. The amount of [upper GI bleeding](#) episodes was 3.6 times more than expected. Combined use of an SSRI and NSAIDs or low-dose [aspirin](#) increased the risk to 12.2 and 5.2 times, respectively. The findings of this study demonstrate an increased risk of [upper GI bleeding](#) during the use of SSRIs. Combined use of SSRIs and NSAIDs or low-dose [aspirin](#) increased the risk even further [532].

c) Two metaanalyses of incidents of upper GI bleed due to SSRIs, NSAIDs, and their combination found that SSRIs increased the risk by 1.73 [533] to 2.36 times [534], NSAIDs by 2.55 times [533], and the combination of SSRIs and NSAIDs by 4.02 [533] to 6.33 times [534].

d) The release of serotonin by [platelets](#) is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs and NSAIDs have been associated with an increased risk of bleeding [535].

3.5.1.EZ] [Fenfluramine](#)

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

2) Summary: [Fenfluramine](#) is a nonspecific serotonin agonist that both enhances the release of serotonin and inhibits serotonin reuptake. Combination therapy with [fenfluramine](#) and another selective serotonin reuptake inhibitor, such as [fluoxetine](#), has the potential to cause [serotonin syndrome](#)[454]. [Serotonin syndrome](#) is a hyperserotonergic state characterized by symptoms such as restlessness, myoclonus, changes in mental status, hyperreflexia, diaphoresis, shivering, and tremor. Serious, even fatal, reactions have been reported [455]. Until more data are available, [fenfluramine](#) should not be used in combination with [fluoxetine](#).

3) Severity: major

4) Onset: rapid

5) Substantiation: theoretical

6) Clinical Management: Concurrent use of [fenfluramine](#) and [fluoxetine](#) may result in an additive increase in serotonin levels in the central nervous system, and could result in [serotonin syndrome](#) ([hypertension](#), [hyperthermia](#), myoclonus, mental status changes). [Fenfluramine](#) should not be used in combination with [fluoxetine](#) or other serotonin specific reuptake inhibitors.

7) Probable Mechanism: additive serotonergic effects

3.5.1.FA] [Fenoprofen](#)

1) Interaction Effect: an increased risk of bleeding

2) Summary: Caution is recommended with the concomitant use of NSAIDs and antidepressants, including SSRIs due to an increased risk of [intracranial hemorrhage](#)[529] and [gastrointestinal bleeding](#) [533][534][530][531]. Bleeding events have included [epistaxis](#), ecchymosis, [hematoma](#), [petechiae](#), and life-threatening hemorrhages [536][535][537][538]. When an SSRI and an NSAID are given concurrently, monitor the patient for signs of increased bleeding.

3) Severity: major

4) Onset: unspecified

5) Substantiation: established

6) Clinical Management: Use caution if NSAIDs and SSRIs are coadministered. Concomitant use of NSAIDs and SSRIs may cause an increased risk of [intracranial hemorrhage](#)[529] and [gastrointestinal bleeding](#) [530][531]. When an SSRI and an NSAID are given concurrently, monitor the patient for signs of increased bleeding.

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

8) Literature Reports

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

increased risk; however, there was an increased risk associated with male patients compared with female patients [529].

b)) SSRIs increase the risk of upper gastrointestinal (GI) bleeding, and this effect is potentiated by concurrent use of NSAIDs or low-dose [aspirin](#). Hospitalizations for [upper GI bleeding](#) were searched among 26,005 users of antidepressant medications and compared with the number of hospitalizations in those patients who did not receive prescriptions for antidepressants. The amount of [upper GI bleeding](#) episodes was 3.6 times more than expected. Combined use of an SSRI and NSAIDs or low-dose [aspirin](#) increased the risk to 12.2 and 5.2 times, respectively. The findings of this study demonstrate an increased risk of [upper GI bleeding](#) during the use of SSRIs. Combined use of SSRIs and NSAIDs or low-dose [aspirin](#) increased the risk even further [532].

c)) Two metaanalyses of incidents of upper GI bleed due to SSRIs, NSAIDs, and their combination found that SSRIs increased the risk by 1.73 [533] to 2.36 times [534], NSAIDs by 2.55 times [533], and the combination of SSRIs and NSAIDs by 4.02 [533] to 6.33 times [534].

d)) The release of serotonin by [platelets](#) is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs and NSAIDs have been associated with an increased risk of bleeding [535].

3.5.1.FB| [Fentanyl](#)

1)) Interaction Effect: increased risk of CNS depression

2)) Summary: Coadministration of [fentanyl](#), a CNS depressant, with other CNS depressants may cause additive CNS depression including [respiratory depression](#), hypotension, and profound sedation, which could potentially lead to coma or death[76]. Severe hypotension has been reported with coadministration of [fentanyl](#) and [midazolam](#) in neonates, including those maintained on an infusion of either drug who subsequently received rapid injections of either [fentanyl](#) or [midazolam](#) [77]. Due to the risk of additive CNS effects, use caution, monitor patients closely, and reduce the dose of one or both when these agents are administered concomitantly [76].

3)) Severity: major

4)) Onset: unspecified

5)) Substantiation: theoretical

6)) Clinical Management: Concomitant use of [fentanyl](#), which is a CNS depressant, with another CNS depressant may result in [respiratory depression](#), hypotension, and profound sedation, potentially leading to coma or death. Due to the added CNS depressant effects, exercise caution if coadministration of [fentanyl](#) and another CNS depressant is required. Carefully monitor patients receiving concomitant [fentanyl](#) and other CNS depressants and adjust dosage of one or both agents[76].

7)) Probable Mechanism: additive CNS depression

3.5.1.FC| [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[545], including SSRIs [547][546][548]. [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 [545]. 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 [146].

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**) [545]. 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 [146].

7) Probable Mechanism: additive serotonergic effect

8) Literature Reports

a) **Serotonin syndrome** associated with **fentanyl** use during an **esophagogastroduodenoscopy** was reported in a 39-year-old woman also taking **sertraline** 100 mg daily as an outpatient. The patient initially presented with **hematemesis** and a history of **alcoholic cirrhosis**. Prior to the **esophagogastroduodenoscopy**, an **octreotide** and **pantoprazole** drip was started, 2 doses of **fentanyl** 50 micrograms, and 2 doses of **midazolam** 1 mg were administered. The patient became somnolent and extremely rigid in all four extremities following the procedure, and vecuronium and **etomidate** were given for immediate intubation. The rigidity progressed with diffuse diaphoresis, horizontal **roving eye movements**, and a fever of 105 degrees F. Due to the potential for seizure activity, **lorazepam** 2 mg IV was given with no improvement and a **propofol** drip was started for continued sedation during intubation. A CPK value of 2800 units/L and an ammonia level of 340 micromols/L indicated **rhabdomyolysis**. An acute intracranial process was ruled out on a **CT scan** of the brain and the neurology team made the diagnosis of **serotonin syndrome** secondary to an interaction between **fentanyl** and **sertraline**. **Propofol** was continued for sedation and the patient received supportive treatment with a cooling blanket and **cypheptadine**. After 3 days, the patient's temperature and CPK level normalized and she later extubated with no further complications [546].

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

examination the patient was agitated and diaphoretic, had patellar hyperreflexia and a bilateral 3 to 4 beat ankle clonus. Laboratory evaluation was remarkable for a peak [creatinine kinase](#) of 1161 units/L on postoperative day 2. The patient was treated with [lorazepam](#) and [cyproheptadine](#) with resolution of symptoms after 3 days [547].

c) A case of postoperative [serotonin syndrome](#) following the administration of [fentanyl](#) for general [anesthesia](#) and post operative analgesia was reported in a 60-year-old woman also receiving [paroxetine](#). Outpatient medications included only [paroxetine](#) and thyroxine for a history of depression and [hypothyroidism](#). The patient was admitted for an extensive resection of a recurrent left chest wall [myxofibrosarcoma](#) and given [propofol](#) and 200 micrograms (mcg) of [fentanyl](#) for the [induction of anesthesia](#). The patient also received an additional 800 mcg of [fentanyl](#) (intermittent 50 mcg boluses) intraoperatively and a subsequent [fentanyl](#) infusion (100 to 200 mcg/hr) for postoperative sedation and analgesia (2545 mcg of [fentanyl](#) received over 36 hours). The [fentanyl](#) infusion was continued 36 hours postoperatively, at which time intermittent agitation, bilateral hypertonia and hyperreflexia, and bilateral inducible ankle clonus were observed on neurological examination. Symptoms were more severe in the lower limbs and on the right side of the body. A [CT scan](#) of the brain was unremarkable and all other examination findings, including a [thyroid function test](#), were within normal limits with the exception of elevated blood pressure (180/90 mmHg), which spontaneously resolved 24 hours after the procedure. [Fentanyl](#) was discontinued, and 24 hours later, there was marked improvement in neurological symptoms and complete recovery by postoperative day 4. The patient was ultimately discharged home with no further complications [548].

3.5.1.FD] Fepradinol

1) Interaction Effect: an increased risk of bleeding

2) Summary: Caution is recommended with the concomitant use of NSAIDs and antidepressants, including SSRIs due to an increased risk of [intracranial hemorrhage](#)[529] and [gastrointestinal bleeding](#) [533][534][530][531]. Bleeding events have included [epistaxis](#), ecchymosis, [hematoma](#), [petechiae](#), and life-threatening hemorrhages [536][535][537][538]. When an SSRI and an NSAID are given concurrently, monitor the patient for signs of increased bleeding.

3) Severity: major

4) Onset: unspecified

5) Substantiation: established

6) Clinical Management: Use caution if NSAIDs and SSRIs are coadministered. Concomitant use of NSAIDs and SSRIs may cause an increased risk of [intracranial hemorrhage](#)[529] and [gastrointestinal bleeding](#) [530][531]. When an SSRI and an NSAID are given concurrently, monitor the patient for signs of increased bleeding.

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

8) Literature Reports

a) Concomitant use of NSAIDs and antidepressants, including tricyclic antidepressants, SSRIs, serotonin-norepinephrine reuptake inhibitors, and MAOIs, resulted in a 60% increased risk of [intracranial hemorrhage](#) within 30 days of concomitant use compared with antidepressant use alone. There was no significant difference between the antidepressant drug classes and the increased risk; however, there was an increased risk associated with male patients compared with female patients [529].

b) SSRIs increase the risk of upper gastrointestinal (GI) bleeding, and this effect is potentiated by concurrent use of NSAIDs or low-dose [aspirin](#). Hospitalizations for [upper GI bleeding](#) were searched among 26,005 users of antidepressant medications and compared with the number

of hospitalizations in those patients who did not receive prescriptions for antidepressants. The amount of [upper GI bleeding](#) episodes was 3.6 times more than expected. Combined use of an SSRI and NSAIDs or low-dose [aspirin](#) increased the risk to 12.2 and 5.2 times, respectively. The findings of this study demonstrate an increased risk of [upper GI bleeding](#) during the use of SSRIs. Combined use of SSRIs and NSAIDs or low-dose [aspirin](#) increased the risk even further [532].

c) Two metaanalyses of incidents of upper GI bleed due to SSRIs, NSAIDs, and their combination found that SSRIs increased the risk by 1.73 [533] to 2.36 times [534], NSAIDs by 2.55 times [533], and the combination of SSRIs and NSAIDs by 4.02 [533] to 6.33 times [534].

d) The release of serotonin by [platelets](#) is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs and NSAIDs have been associated with an increased risk of bleeding [535].

3.5.1.FE] Feprazone

1) Interaction Effect: an increased risk of bleeding

2) Summary: Caution is recommended with the concomitant use of NSAIDs and antidepressants, including SSRIs due to an increased risk of [intracranial hemorrhage](#)[529] and [gastrointestinal bleeding](#) [533][534][530][531]. Bleeding events have included [epistaxis](#), ecchymosis, [hematoma](#), [petechiae](#), and life-threatening hemorrhages [536][535][537][538]. When an SSRI and an NSAID are given concurrently, monitor the patient for signs of increased bleeding.

3) Severity: major

4) Onset: unspecified

5) Substantiation: established

6) Clinical Management: Use caution if NSAIDs and SSRIs are coadministered. Concomitant use of NSAIDs and SSRIs may cause an increased risk of [intracranial hemorrhage](#)[529] and [gastrointestinal bleeding](#) [530][531]. When an SSRI and an NSAID are given concurrently, monitor the patient for signs of increased bleeding.

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

8) Literature Reports

a) Concomitant use of NSAIDs and antidepressants, including tricyclic antidepressants, SSRIs, serotonin-norepinephrine reuptake inhibitors, and MAOIs, resulted in a 60% increased risk of [intracranial hemorrhage](#) within 30 days of concomitant use compared with antidepressant use alone. There was no significant difference between the antidepressant drug classes and the increased risk; however, there was an increased risk associated with male patients compared with female patients [529].

b) SSRIs increase the risk of upper gastrointestinal (GI) bleeding, and this effect is potentiated by concurrent use of NSAIDs or low-dose [aspirin](#). Hospitalizations for [upper GI bleeding](#) were searched among 26,005 users of antidepressant medications and compared with the number of hospitalizations in those patients who did not receive prescriptions for antidepressants. The amount of [upper GI bleeding](#) episodes was 3.6 times more than expected. Combined use of an SSRI and NSAIDs or low-dose [aspirin](#) increased the risk to 12.2 and 5.2 times, respectively. The findings of this study demonstrate an increased risk of [upper GI bleeding](#) during the use of SSRIs. Combined use of SSRIs and NSAIDs or low-dose [aspirin](#) increased the risk even further [532].

c) Two metaanalyses of incidents of upper GI bleed due to SSRIs, NSAIDs, and their combination found that SSRIs increased the risk by 1.73 [533] to 2.36 times [534], NSAIDs by 2.55 times [533], and the combination of SSRIs and NSAIDs by 4.02 [533] to 6.33 times [534].

d)) The release of serotonin by [platelets](#) is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs and NSAIDs have been associated with an increased risk of bleeding [535].

3.5.1.FF] [Flecainide](#)

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

2)) Summary: Avoid coadministration of [flecainide](#), a CYP2D6 substrate[453], and [fluoxetine](#), a CYP2D6 inhibitor, as this may increase [flecainide](#) exposure and increase the risk for QT interval prolongation [173]. Both [flecainide](#) [453] and [fluoxetine](#), as single agents, prolong the QT interval. Additionally, [flecainide](#) has a narrow therapeutic index. If concomitant use is required, obtain a baseline ECG and periodically monitor ECG during therapy. Consider discontinuation of [fluoxetine](#) if signs or symptoms of [ventricular arrhythmia](#) occur and obtain a cardiac evaluation. Agents that have a narrow therapeutic index should be initiated at the low end of the dosing range if the patient is already taking [fluoxetine](#) or has used [fluoxetine](#) in the previous 5 weeks. If [fluoxetine](#) is initiated, consider dose reduction of the CYP2D6 substrate (eg, [flecainide](#)) [173].

3)) Severity: major

4)) Onset: unspecified

5)) Substantiation: theoretical

6)) Clinical Management: Concomitant use of [flecainide](#) and [fluoxetine](#) should be avoided because concomitant use may increase [flecainide](#) exposure, cause additive effects on the QT interval, and increase the risk for [ventricular arrhythmias](#) and [torsade de pointes](#). [173]. Both [flecainide](#) [453] and [fluoxetine](#), as single agents, prolong the QT interval. Additionally, [flecainide](#) has a narrow therapeutic index. If concomitant use is required, obtain a baseline ECG and periodically monitor ECG during therapy. Consider discontinuation of [fluoxetine](#) if signs or symptoms of [ventricular arrhythmia](#) occur and obtain a cardiac evaluation. Agents that have a narrow therapeutic index should be initiated at the low end of the dosing range if the patient is already taking [fluoxetine](#) or has used [fluoxetine](#) in the previous 5 weeks. If [fluoxetine](#) is initiated, consider dose reduction of the CYP2D6 substrate (eg, [flecainide](#)) [173].

7)) Probable Mechanism: inhibition of CYP2D6-mediated [flecainide](#) metabolism by [fluoxetine](#); additive QT interval prolongation

3.5.1.FG] [Flibanserin](#)

1)) Interaction Effect: additive CNS depression

2)) Summary: The concomitant use of flibanserin with CNS depressants may increase the risk of CNS depression (eg, somnolence and sedation) compared with the use of flibanserin alone. Advise the patient of the risks of CNS depressant use while using flibanserin[135].

3)) Severity: major

4)) Onset: unspecified

5)) Substantiation: theoretical

6)) Clinical Management: The concomitant use of flibanserin with CNS depressants may increase the risk of CNS depression (eg, somnolence and sedation) compared with the use of flibanserin alone. Advise the patient of the risks of CNS depressant use while using flibanserin[135].

7)) Probable Mechanism: additive CNS depression

3.5.1.FH] [Floctafenine](#)

1)) Interaction Effect: an increased risk of bleeding

2)) Summary: Caution is recommended with the concomitant use of NSAIDs and antidepressants, including SSRIs due to an increased risk of [intracranial hemorrhage](#)[529] and [gastrointestinal bleeding](#)

[533][534][530][531]. Bleeding events have included [epistaxis](#), ecchymosis, [hematoma](#), [petechiae](#), and life-threatening hemorrhages [536][535][537][538]. When an SSRI and an NSAID are given concurrently, monitor the patient for signs of increased bleeding.

3) Severity: major

4) Onset: unspecified

5) Substantiation: established

6) Clinical Management: Use caution if NSAIDs and SSRIs are coadministered. Concomitant use of NSAIDs and SSRIs may cause an increased risk of [intracranial hemorrhage](#)[529] and [gastrointestinal bleeding](#) [530][531]. When an SSRI and an NSAID are given concurrently, monitor the patient for signs of increased bleeding.

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

8) Literature Reports

a) Concomitant use of NSAIDs and antidepressants, including tricyclic antidepressants, SSRIs, serotonin-norepinephrine reuptake inhibitors, and MAOIs, resulted in a 60% increased risk of [intracranial hemorrhage](#) within 30 days of concomitant use compared with antidepressant use alone. There was no significant difference between the antidepressant drug classes and the increased risk; however, there was an increased risk associated with male patients compared with female patients [529].

b) SSRIs increase the risk of upper gastrointestinal (GI) bleeding, and this effect is potentiated by concurrent use of NSAIDs or low-dose [aspirin](#). Hospitalizations for [upper GI bleeding](#) were searched among 26,005 users of antidepressant medications and compared with the number of hospitalizations in those patients who did not receive prescriptions for antidepressants. The amount of [upper GI bleeding](#) episodes was 3.6 times more than expected. Combined use of an SSRI and NSAIDs or low-dose [aspirin](#) increased the risk to 12.2 and 5.2 times, respectively. The findings of this study demonstrate an increased risk of [upper GI bleeding](#) during the use of SSRIs. Combined use of SSRIs and NSAIDs or low-dose [aspirin](#) increased the risk even further [532].

c) Two metaanalyses of incidents of upper GI bleed due to SSRIs, NSAIDs, and their combination found that SSRIs increased the risk by 1.73 [533] to 2.36 times [534], NSAIDs by 2.55 times [533], and the combination of SSRIs and NSAIDs by 4.02 [533] to 6.33 times [534].

d) The release of serotonin by [platelets](#) is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs and NSAIDs have been associated with an increased risk of bleeding [535].

3.5.1.FI] [Fluconazole](#)

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

2) Summary: Case reports have described QT prolongation and [torsades de pointes](#) associated with [fluconazole](#)[289][290]. [Fluoxetine](#) has been shown to prolong the QTc interval at the recommended therapeutic dose [291]. Even though no formal drug interaction studies have been done, caution is advised if drugs known to prolong the QT interval are used concomitantly.

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Caution is advised if [fluconazole](#) and [fluoxetine](#) are used concomitantly.

7) Probable Mechanism: additive effects on QT prolongation

3.5.1.FJ] Flufenamic Acid

- 1) Interaction Effect: an increased risk of bleeding
- 2) Summary: Caution is recommended with the concomitant use of NSAIDs and antidepressants, including SSRIs due to an increased risk of [intracranial hemorrhage](#)[529] and [gastrointestinal bleeding](#) [533][534][530][531]. Bleeding events have included [epistaxis](#), ecchymosis, [hematoma](#), [petechiae](#), and life-threatening hemorrhages [536][535][537][538]. When an SSRI and an NSAID are given concurrently, monitor the patient for signs of increased bleeding.
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: established
- 6) Clinical Management: Use caution if NSAIDs and SSRIs are coadministered. Concomitant use of NSAIDs and SSRIs may cause an increased risk of [intracranial hemorrhage](#)[529] and [gastrointestinal bleeding](#) [530][531]. When an SSRI and an NSAID are given concurrently, monitor the patient for signs of increased bleeding.
- 7) Probable Mechanism: depletion of [platelet](#) serotonin by SSRI; additive effects
- 8) Literature Reports

a) Concomitant use of NSAIDs and antidepressants, including tricyclic antidepressants, SSRIs, serotonin-norepinephrine reuptake inhibitors, and MAOIs, resulted in a 60% increased risk of [intracranial hemorrhage](#) within 30 days of concomitant use compared with antidepressant use alone. There was no significant difference between the antidepressant drug classes and the increased risk; however, there was an increased risk associated with male patients compared with female patients [529].

b) SSRIs increase the risk of upper gastrointestinal (GI) bleeding, and this effect is potentiated by concurrent use of NSAIDs or low-dose [aspirin](#). Hospitalizations for [upper GI bleeding](#) were searched among 26,005 users of antidepressant medications and compared with the number of hospitalizations in those patients who did not receive prescriptions for antidepressants. The amount of [upper GI bleeding](#) episodes was 3.6 times more than expected. Combined use of an SSRI and NSAIDs or low-dose [aspirin](#) increased the risk to 12.2 and 5.2 times, respectively. The findings of this study demonstrate an increased risk of [upper GI bleeding](#) during the use of SSRIs. Combined use of SSRIs and NSAIDs or low-dose [aspirin](#) increased the risk even further [532].

c) Two metaanalyses of incidents of upper GI bleed due to SSRIs, NSAIDs, and their combination found that SSRIs increased the risk by 1.73 [533] to 2.36 times [534], NSAIDs by 2.55 times [533], and the combination of SSRIs and NSAIDs by 4.02 [533] to 6.33 times [534].

d) The release of serotonin by [platelets](#) is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs and NSAIDs have been associated with an increased risk of bleeding [535].

3.5.1.FK] Fluoxetine

- 1) Interaction Effect: increased risk of QT-interval prolongation
- 2) Summary: [Fluoxetine](#) use is associated with reports of QT interval prolongation and [ventricular arrhythmia](#), included [torsade de pointes](#). Concomitant use of [fluoxetine](#) and QT-prolonging drugs may result in additive prolongation of the QT interval. Therefore, coadministration should be avoided[173]. If coadministration with [fluoxetine](#) is necessary, consider a baseline ECG and on-treatment monitoring.
- 3) Severity: major

- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Avoid the concomitant use of [fluoxetine](#) with other drugs known to prolong the QT interval[173]. If coadministration with [fluoxetine](#) is necessary, consider a baseline ECG and on-treatment monitoring.
- 7) Probable Mechanism: additive QT-interval prolonging effects

3.5.1.FL] [Fluphenazine](#)

- 1) Interaction Effect: increased risk of [fluoxetine](#) toxicity, QT interval prolongation, and [serotonin syndrome](#)
- 2) Summary: Coadministration of [fluphenazine](#) (a CYP2D6 inhibitor) and [fluoxetine](#) (a CYP2D6 substrate) may increase [fluoxetine](#) exposure, and increase the risk for [serotonin syndrome](#), and QT interval prolongation.[173]. Additionally, a case of acute severe [parkinsonism](#) was reported with concomitant use of [fluoxetine](#) and [fluphenazine](#) [554]. If concomitant use is clinically warranted, monitor patients for development of [serotonin syndrome](#), particularly with initiation of therapy and dose increases. If [serotonin syndrome](#) occurs, immediately discontinue [fluoxetine](#) and any concomitant agents contributing to [serotonin syndrome](#). If [ventricular arrhythmias](#) develop, consider [fluoxetine](#) discontinuation and cardiac evaluation [173].
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: probable
- 6) Clinical Management: Use caution when coadministering [fluoxetine](#) with [fluphenazine](#), as concurrent use may increase [fluoxetine](#) exposure and increase the risk of [fluoxetine](#) toxicity, [serotonin syndrome](#), and QT interval prolongation. Monitor patients for development of [serotonin syndrome](#), particularly with initiation of therapy and dose increases. If [serotonin syndrome](#) occurs, immediately discontinue [fluoxetine](#) and any concomitant agents contributing to [serotonin syndrome](#). If [ventricular arrhythmias](#) develop, consider [fluoxetine](#) discontinuation and cardiac evaluation[173].
- 7) Probable Mechanism: inhibition of CYP2D6-mediated metabolism of [fluoxetine](#) by [fluphenazine](#)
- 8) Literature Reports

a) A 63-year-old female with chronic, multiple motor and vocal tics was successfully treated with [fluphenazine](#) 2.5 mg daily. When [nortriptyline](#) therapy for depression failed, the patient was started on [fluoxetine](#) 20 mg daily. After two weeks, she developed acute, severe [parkinsonism](#) manifesting as resting tremor, rigidity, bradykinesia, postural imbalance, and stooped posture. The [parkinsonism](#) resolved within three weeks of discontinuing the [fluphenazine](#) and the [fluoxetine](#), but the tics reappeared [553].

3.5.1.FM] [Flurbiprofen](#)

- 1) Interaction Effect: an increased risk of bleeding
- 2) Summary: Caution is recommended with the concomitant use of NSAIDs and antidepressants, including SSRIs due to an increased risk of [intracranial hemorrhage](#)[529] and [gastrointestinal bleeding](#) [533][534][530][531]. Bleeding events have included [epistaxis](#), ecchymosis, [hematoma](#), [petechiae](#), and life-threatening hemorrhages [536][535][537][538]. When an SSRI and an NSAID are given concurrently, monitor the patient for signs of increased bleeding.
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: established
- 6) Clinical Management: Use caution if NSAIDs and SSRIs are coadministered. Concomitant use of NSAIDs and SSRIs may cause an increased risk of [intracranial hemorrhage](#)[529] and [gastrointestinal](#)

[bleeding](#) [530][531]. When an SSRI and an NSAID are given concurrently, monitor the patient for signs of increased bleeding.

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

8) Literature Reports

a) Concomitant use of NSAIDs and antidepressants, including tricyclic antidepressants, SSRIs, serotonin-norepinephrine reuptake inhibitors, and MAOIs, resulted in a 60% increased risk of [intracranial hemorrhage](#) within 30 days of concomitant use compared with antidepressant use alone. There was no significant difference between the antidepressant drug classes and the increased risk; however, there was an increased risk associated with male patients compared with female patients [529].

b) SSRIs increase the risk of upper gastrointestinal (GI) bleeding, and this effect is potentiated by concurrent use of NSAIDs or low-dose [aspirin](#). Hospitalizations for [upper GI bleeding](#) were searched among 26,005 users of antidepressant medications and compared with the number of hospitalizations in those patients who did not receive prescriptions for antidepressants. The amount of [upper GI bleeding](#) episodes was 3.6 times more than expected. Combined use of an SSRI and NSAIDs or low-dose [aspirin](#) increased the risk to 12.2 and 5.2 times, respectively. The findings of this study demonstrate an increased risk of [upper GI bleeding](#) during the use of SSRIs. Combined use of SSRIs and NSAIDs or low-dose [aspirin](#) increased the risk even further [532].

c) Two metaanalyses of incidents of upper GI bleed due to SSRIs, NSAIDs, and their combination found that SSRIs increased the risk by 1.73 [533] to 2.36 times [534], NSAIDs by 2.55 times [533], and the combination of SSRIs and NSAIDs by 4.02 [533] to 6.33 times [534].

d) The release of serotonin by [platelets](#) is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs and NSAIDs have been associated with an increased risk of bleeding [535].

3.5.1.FN] [Fluvoxamine](#)

1) Interaction Effect: an increased risk of [olanzapine](#) adverse effects

2) Summary: Fluvoxamine inhibits cytochrome P450 1A2 enzymes and may inhibit [olanzapine](#) elimination[118]. The clinical significance of this interaction is unknown since [olanzapine](#) is metabolized by multiple enzyme systems.

3) Severity: moderate

4) Onset: delayed

5) Substantiation: probable

6) Clinical Management: Monitor patients for excessive [olanzapine](#) adverse effects (orthostatic hypotension, [tachycardia](#), transaminase elevations, seizures).

7) Probable Mechanism: inhibition of [olanzapine](#) elimination

8) Literature Reports

a) A patient experienced elevated [olanzapine](#) plasma levels during coadministration of [fluvoxamine](#). The patient was taking [fluvoxamine](#) and [olanzapine](#) for several months for [schizophrenia](#) and secondary depression. She appeared to move rigidly, had a slight tremor of both hands and mydriasis. [Olanzapine](#) concentration was 120 mcg/L and [fluvoxamine](#) concentration was 70 mcg/L. [Olanzapine](#) was decreased in increments from 15 mg/day to 5 mg/day. Fourteen days after the last decrease in dose, [olanzapine](#) plasma levels were 38 mcg/L. Tremor and rigidity disappeared, however, mydriasis persisted. [Fluvoxamine](#) was replaced by [paroxetine](#) which

resulted in [paroxetine](#) concentration of 0.027 mg/L and [olanzapine](#) concentration of 22 mcg/L [116].

b) Addition of [fluvoxamine](#) to [olanzapine](#) therapy may result in olanzapine-induced side effects or intoxication. Eight chronic schizophrenic patients were being treated for not less than 3 months with 10-20 mg/day of [olanzapine](#). The dose of [olanzapine](#) was unchanged for not less than 8 weeks prior to the study and remained stable throughout the study period. [Fluvoxamine](#) 100 mg/day was added to [olanzapine](#) treatment at the start of the study (week 0) and continued for 8 weeks. [Olanzapine](#) concentrations increased during [fluvoxamine](#) treatment 1.58-fold from week 0 to week 1, 1.42-fold from week 0 to week 4, and 1.81-fold from week 0 to week 8. Percentage change from week 0 to week 8 ranged from 12% to 112%. Mean concentrations of the N-demethylated metabolite were not significantly changed. Even though all eight patients had higher [olanzapine](#) blood serum concentrations on week 8 than on week 1, the ratio of increase of [olanzapine](#) blood serum concentrations from week 0 to week 8 did not correlate significantly with [fluvoxamine](#) serum levels (p greater than 0.05). This study confirmed that the addition of [fluvoxamine](#) to a stable dose of [olanzapine](#) increased [olanzapine](#) concentrations in the blood serum. Combined [olanzapine](#) and [fluvoxamine](#) should be used cautiously and controlled clinically and by therapeutic drug monitoring to avoid olanzapine-induced side effects or intoxication [117].

3.5.1.FO] [Fluvoxamine](#)

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

2) Summary: Concurrent use of [fluoxetine](#) (an SSRI and potent CYP2D6 inhibitor) with [fluvoxamine](#) (an SSRI and CYP2D6 substrate) may increase [fluvoxamine](#) exposure, result in additive serotonergic effects, and increase the risk of [serotonin syndrome](#). If concomitant use of [fluoxetine](#) and [fluvoxamine](#) is required, monitor for signs and symptoms of [serotonin syndrome](#)[173][275]. 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 [146]. If [serotonin syndrome](#) develops, discontinue [fluoxetine](#) and [fluvoxamine](#) and provide supportive care as necessary [173][275][146]

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: The concomitant use of [fluoxetine](#), a potent CYP2D6 inhibitor, with [fluvoxamine](#), a CYP2D6 substrate, should be undertaken with caution as this may increase [fluvoxamine](#) exposure. Coadministration of these 2 SSRIs may also result in additive serotonergic effects and may increase the risk of [serotonin syndrome](#). If concomitant use is necessary, discuss the risks of [serotonin syndrome](#) with the patient and monitor closely for symptoms of [serotonin syndrome](#) (mental status changes, autonomic instability, neuromuscular symptoms, seizures, and gastrointestinal symptoms), especially during treatment initiation and dose increases. If [serotonin syndrome](#) develops, discontinue [fluoxetine](#) and [fluvoxamine](#) and initiate supportive care[173][275].

7) Probable Mechanism: inhibition of CYP2D6-mediated metabolism of [fluvoxamine](#) by [fluoxetine](#); additive serotonergic effect

3.5.1.FP] [Fondaparinux](#)

1) Interaction Effect: an increased risk of bleeding

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

with an increased risk of bleeding[458][457]. Bleeding events reported have included [epistaxis](#), ecchymosis, [hematoma](#), [petechiae](#), and life-threatening hemorrhages. Altered anticoagulant effects (including increased bleeding) have been reported with the coadministration of SSRIs with anticoagulants [457].

3) Severity: major

4) Onset: delayed

5) Substantiation: probable

6) Clinical Management: When [fluoxetine](#) and an anticoagulant are given concurrently, monitor patient for signs of increased bleeding. Patients who are taking an anticoagulant should be monitored closely for altered anticoagulant effects, including increased bleeding, when [fluoxetine](#) therapy is initiated or discontinued[457].

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 a significant 1.7-fold increased risk for hospitalization for nongastrointestinal bleeding; however, the rate of [gastrointestinal bleeding](#) was not significantly different [458].

3.5.1.FQ] [Fosamprenavir](#)

1) Interaction Effect: reduced [olanzapine](#) exposure

2) Summary: Coadministration of [olanzapine](#) (CYP1A2 and UGT substrate) and [fosamprenavir](#) boosted with [ritonavir](#) (CYP1A2 and UGT inducer) may result in decreased [olanzapine](#) exposure[54] [55]. Increasing the [olanzapine](#) dose by 50% (from 10 to 15 mg/day) when coadministered with [fosamprenavir/ritonavir](#) compensated for the induction of CYP1A2- and UGT-mediated [olanzapine](#) metabolism and resulted in [olanzapine](#) exposure that was comparable to when [olanzapine](#) was administered alone in a randomized trial in 20 healthy volunteers [54].

3) Severity: moderate

4) Onset: unspecified

5) Substantiation: established

6) Clinical Management: Coadministration of [olanzapine](#) (CYP1A2 and UGT substrate) and [fosamprenavir](#) boosted with [ritonavir](#) (CYP1A2 and UGT inducer) may result in decreased [olanzapine](#) exposure[54][55]. Increasing the [olanzapine](#) dose by 50% (from 10 to 15 mg/day) when coadministered with [fosamprenavir/ritonavir](#) compensated for the induction of CYP1A2- and UGT-mediated [olanzapine](#) metabolism and resulted in [olanzapine](#) exposure that was comparable to when [olanzapine](#) was administered alone in a randomized trial in 20 healthy volunteers [54].

7) Probable Mechanism: induction of CYP1A2- and glucuronosyl transferase-mediated metabolism of [olanzapine](#) by [fosamprenavir](#) boosted with [ritonavir](#)

8) Literature Reports

a) Increasing the [olanzapine](#) dose by 50% when coadministered with [fosamprenavir/ritonavir](#) compensated for the induction of CYP1A2- and UGT-mediated [olanzapine](#) metabolism and resulted in [olanzapine](#) exposure that was comparable to when [olanzapine](#) was administered alone in a randomized, crossover trial in 20 healthy volunteers. [Fosamprenavir](#) 700 mg/[ritonavir](#) 100 mg twice daily (for 16 days) was given with a single [olanzapine](#) 15 mg (on day 13), and when compared with [olanzapine](#) 10 mg alone resulted in similar AUC (438.3 vs 436.9 mcg x hr/L), increased Cmax

by 32% (17.4 vs 13.2 mcg/L), and decreased the $t(1/2)$ by 32% (22.7 vs 33.4 hours). A higher C_{max} is due to induction by fosamprenavir/ritonavir having no effect on the absorption phase and was not associated with a higher incidence of olanzapine-associated adverse events in the combination group [54].

b) An open-label study involving 14 healthy volunteers revealed a significant alteration in pharmacokinetic parameters and a reduction in systemic exposure of olanzapine when administered in the presence of ritonavir. Each volunteer received a single dose of olanzapine 10 mg. After a 14-day washout period, subjects received ritonavir 300 mg BID for 3 days, then 400 mg BID for 4 days, then 500 mg BID for 4 days. Significant reductions were seen in the mean olanzapine AUC by 53% (501 to 235 nanograms x hr/mL), $t(1/2)$ by 50% (from 32 to 16 hours), and C_{max} by 40% (from 15 to 9 nanograms/mL). The oral clearance of olanzapine increased by 115% (from 20 to 43 L/hr) [55].

3.5.1.FR| Foscarnet

- 1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
- 2) Summary: Foscarnet can prolong the QT interval in some patients, which may result in ventricular tachycardia, ventricular fibrillation, and torsades de pointes. Because fluoxetine may also prolong the QT interval and increase the risk of arrhythmias, the concurrent administration of foscarnet and fluoxetine is not recommended[186][187].
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: The concurrent administration of foscarnet and fluoxetine is not recommended.
- 7) Probable Mechanism: additive cardiac effects

3.5.1.FS| Fosphenytoin

- 1) Interaction Effect: increased risk of phenytoin toxicity; increased risk of QT-interval prolongation
- 2) Summary: Fluoxetine should be used cautiously with other drugs known to prolong the QT interval, such as fosphenytoin; concurrent use may lead to an increased risk of serious cardiac adverse events, including ventricular arrhythmias[173]. Additionally, fosphenytoin is a prodrug rapidly converted to phenytoin via phosphatases [576]. The addition of concurrent fluoxetine in patients receiving stable doses of phenytoin has resulted in elevated phenytoin plasma concentrations and clinical toxicity. Consider baseline and periodic ECG monitoring during coadministration [173]. Phenytoin serum level monitoring is also warranted as lower fosphenytoin dosage may be required during concurrent use. Serum phenytoin levels should also be monitored following the discontinuation of fluoxetine; however, because of the long half-life of fluoxetine, decreases in phenytoin levels may not be clinically significant for a few weeks.
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Fluoxetine should be used cautiously with other drugs known to prolong the QT interval, such as fosphenytoin; concurrent use may lead to an increased risk of serious cardiac adverse events, including ventricular arrhythmias[173]. Additionally, fosphenytoin is a prodrug rapidly converted to phenytoin via phosphatases [576]. The addition of concurrent fluoxetine in patients receiving stable doses of phenytoin has resulted in elevated phenytoin plasma concentrations and clinical toxicity. Consider baseline and periodic ECG monitoring during coadministration [173]. Phenytoin serum level monitoring is also warranted as lower fosphenytoin dosage may be required during concurrent use. Serum phenytoin

levels should also be monitored following the discontinuation of [fluoxetine](#); however, because of the long half-life of [fluoxetine](#), decreases in [phenytoin](#) levels may not be clinically significant for a few weeks.

7) Probable Mechanism: decreased [phenytoin](#) metabolism; additive effects on QT interval

8) Literature Reports

a) A 42-year-old man receiving [phenytoin](#) 200 mg daily and [carbamazepine](#) 600 mg daily for grand mal seizures remained symptomatic with a [phenytoin](#) level of 2 nanograms/milliliter (ng/mL; 8 nanomol/L). [Phenytoin](#) was subsequently increased to 400 mg daily, [fluoxetine](#) 20 mg daily was added for aggression, and the patient experienced resolution of his behavioral problems and a cessation of his seizure activity. The [phenytoin](#) level ranged between 10.9 ng/mL and 15.7 ng/mL (43.2 nanomol/L and 62.2 nanomol/L) during [fluoxetine](#) therapy. However, the patient discontinued [fluoxetine](#) on his own and after a month experienced a recurrence of problems. [Phenytoin](#) concentration was measured at 6.6 ng/mL (26.2 nanomol/L) 6 weeks after the discontinuation of [fluoxetine](#), despite no change in his [phenytoin](#) dose. This case report illustrates the need for close monitoring of [phenytoin](#) levels when [fluoxetine](#) is initiated and discontinued, since subtherapeutic levels of [phenytoin](#) may result if doses of [phenytoin](#) are not readjusted following the cessation of [fluoxetine](#) [449].

b) During an in vitro study, the inhibitory effects of [fluoxetine](#) on CYP2C9 were evaluated using p-hydroxylation of [phenytoin](#) as an established index reaction reflecting CYP2C9 activity. In vivo, p-hydroxylation of [phenytoin](#) depends on the formation of 5-(p-hydroxy-phenyl)-5-phenylhydantoin (HPPH). [Fluoxetine](#), specifically the R-enantiomer, impaired the formation of HPPH, which can lead to an increase in steady-state [phenytoin](#) levels [450].

c) Twenty-three reported cases of fluoxetine-phenytoin interactions have resulted in large increases in serum [phenytoin](#) levels and/or symptoms of [phenytoin](#) toxicity. On the average, the adverse effects began within 2 weeks after [fluoxetine](#) was added to existing [phenytoin](#) therapy. The average increase in plasma levels in 9 evaluable cases was 161% (range 75 to 309%) and the maximum [phenytoin](#) serum concentration in 16 evaluable cases ranged from 22 to 53.5 mcg/mL (87.2 to 212.1 mcg/mL; therapeutic level, 10 to 20 mcg/mL [40 to 79 mcg/mL]) [451].

d) An 84-year-old woman experienced [phenytoin](#) toxicity within 5 days of adding [fluoxetine](#) to stabilized [phenytoin](#) therapy. After 2 months of [phenytoin](#) 300 mg/day, [fluoxetine](#) 20 mg daily was added and increased to 40 mg daily after 10 days. Within five days of starting [fluoxetine](#), she developed vertigo, gait ataxia, [diplopia](#), and altered mental status; her [phenytoin](#) serum level had increased from 15 to 35 mcg/mL (59 to 139 mcg/mL). Both [phenytoin](#) and [fluoxetine](#) were gradually reduced and the signs and symptoms of toxicity abated. Four weeks later she was rechallenged with the same dose of [fluoxetine](#) without a return of toxicity [452].

e) A 57-year-old woman experienced [phenytoin](#) toxicity within 10 days of adding [fluoxetine](#) to stabilized [phenytoin](#) therapy. After [phenytoin](#) 400 mg daily for a year (serum level, 11.5 mcg/mL [45.6 mcg/mL]), [fluoxetine](#) 20 mg daily was added. Ten days later she developed vomiting, vertigo, trunk ataxia, limb dysmetria, and [multidirectional nystagmus](#), and the [phenytoin](#) serum level was 47 mcg/mL (186 mcg/mL). [Fluoxetine](#) was discontinued and all signs and symptoms of toxicity disappeared over a 3-week period. At 4 weeks post-fluoxetine, the [phenytoin](#) serum level was 20 mcg/mL (79 mcg/mL) [452].

3.5.1.FT] [Frovatriptan](#)

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

2) Summary: There have been case reports of weakness, hyperreflexia, and incoordination following concomitant use of [sumatriptan](#), a 5-hydroxytryptamine-1 (5HT-1) agonist, and a serotonin specific reuptake inhibitor (SSRI)[584]. Because [frovatriptan](#) is a 5HT 1B/1D agonist, a similar interaction between SSRIs and [frovatriptan](#) may occur [585]. Concurrent use of [frovatriptan](#) and an SSRI may result in [serotonin syndrome](#) which may be life-threatening. Symptoms of [serotonin syndrome](#) may include restlessness, hallucinations, loss of coordination, fast heart beat, rapid changes in blood pressure, increased body temperature, overreactive reflexes, nausea, vomiting, and diarrhea. Clinicians should be aware that triptans may be commonly used intermittently and that either the triptan or the SSRI may be prescribed by a different physician. Discuss the risks of [serotonin syndrome](#) with patients who are prescribed this combination and monitor them closely for symptoms of [serotonin syndrome](#) [199].

3) Severity: major

4) Onset: delayed

5) Substantiation: probable

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

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

3.5.1.FU] [Furazolidone](#)

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

2) Summary: Concomitant use of [fluoxetine](#) and an MAOI is contraindicated. Concurrent administration or overlapping therapy with [fluoxetine](#) and an MAOI 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 SSRIs and MAOIs. A minimum of 14 days should elapse after discontinuing an MAOI intended to treat psychiatric disorders before initiating therapy with [fluoxetine](#), and a minimum of 5 weeks should elapse after discontinuing [fluoxetine](#) before initiating therapy with an MAOI intended to treat psychiatric disorders[283].

3) Severity: contraindicated

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Concurrent use of [fluoxetine](#) and an MAOI is contraindicated. Wait at least 14 days after discontinuing an MAOI intended to treat psychiatric disorders before initiating [fluoxetine](#). Wait at least 5 weeks after discontinuing [fluoxetine](#) before initiating therapy with an MAOI intended to treat psychiatric disorders[283].

7) Probable Mechanism: additive serotonergic effect

3.5.1.FV] [Galantamine](#)

1) Interaction Effect: increased [galantamine](#) plasma concentrations; increased risk of QT-interval prolongation

2) Summary: Coadministration of [fluoxetine](#), a CYP2D6 inhibitor and QT prolonging drug, and [galantamine](#), a CYP2D6 substrate and QT prolonging drug, may result in increased [galantamine](#) exposure and additive effects on the QT-interval[173]. If concomitant use is required, monitor for [galantamine](#) toxicity including anorexia, nausea, vomiting, dizziness, [arrhythmias](#) or [gastrointestinal bleeding](#) [220] and consider periodic [ECG monitoring](#). Discontinue use if symptoms of [ventricular arrhythmia](#) occur [173].

- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: probable
- 6) Clinical Management: Concomitant administration of [fluoxetine](#), a CYP2D6 inhibitor and QT prolonging drug, and [galantamine](#), a CYP2D6 substrate and QT prolonging drug, should be avoided as this may result in increased [galantamine](#) exposure. Additionally, concomitant administration of [fluoxetine](#) and [galantamine](#) may result in additive effects on the QT interval[173][220]. If coadministration is required, monitor for [galantamine](#) toxicity including anorexia, nausea, vomiting, dizziness, [arrhythmias](#), or [gastrointestinal bleeding](#) [220] and consider periodic [ECG monitoring](#). Discontinue use if symptoms of [ventricular arrhythmia](#) occur [173].
- 7) Probable Mechanism: inhibition of CYP2D6-mediated [galantamine](#) metabolism; additive QT-interval prolongation effects
- 8) Literature Reports

a) Based upon in vitro studies, the major enzymes involved in [galantamine](#) metabolism are CYP3A4 and CYP2D6. [Fluoxetine](#) is a known inhibitor of CYP2D6. In a population pharmacokinetic analysis using a database of 852 [Alzheimer's disease](#) patients, several drugs which inhibit CYP2D6, including [fluoxetine](#) (n=48), demonstrated a 25-33% decrease in [galantamine](#) clearance [220].

3.5.1.FW] Gemifloxacin

- 1) Interaction Effect: an increased risk of [cardiotoxicity](#) (QT prolongation, [torsades de pointes](#), [cardiac arrest](#))
- 2) Summary: Gemifloxacin should be avoided in patients receiving [fluoxetine](#). Gemifloxacin has the potential to prolong the QT interval in some patients[326]. Additive effects on QT prolongation may occur with the concomitant use of [fluoxetine](#) and gemifloxacin [327].
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: probable
- 6) Clinical Management: The concurrent administration of two drugs that prolong the QT interval, such as gemifloxacin and [fluoxetine](#), is not recommended.
- 7) Probable Mechanism: additive effects on QT prolongation

3.5.1.FX] Ginkgo

- 1) Interaction Effect: increased risk of [serotonin syndrome](#) ([hypertension](#), [hyperthermia](#), myoclonus, mental status changes)
- 2) Summary: The addition of Ginkgo biloba and/or St. John's Wort to therapy with [buspirone](#) and [fluoxetine](#) may have precipitated a hypomanic episode in a case report[375]. It is unclear if Ginkgo or St. John's Wort, the combination of both, or other patient factors, contributed to the effect. Theoretically, Ginkgo may increase the risk of [serotonin syndrome](#) when taken with selective serotonin reuptake inhibitors (SSRIs). Caution is advised, especially when ginkgo is taken to counteract sexual dysfunction associated with SSRIs. Ginkgo may inhibit monoamine oxidase [376][377], and has demonstrated serotonergic activity in animals [378] which might increase the risk of [serotonin syndrome](#) when ginkgo is combined with SSRIs. The potential MAO inhibitory activity of ginkgo is questionable. A human study did not show MAO inhibition in the brain following oral consumption [379]. Ginkgo biloba extract inhibited MAO-A/MAO-B in the rat brain in vitro [376][377] and MAO-B in human [platelets](#) in vitro [377]. No significant MAO inhibition was found in mice following oral consumption [380].
- 3) Severity: moderate
- 4) Onset: delayed

- 5) Substantiation: probable
- 6) Clinical Management: Monitor patients closely for symptoms of [serotonin syndrome](#) if ginkgo is combined with selective serotonin reuptake inhibitors (SSRIs).
- 7) Probable Mechanism: additive pharmacologic effects resulting in excessive serotonergic stimulation
- 8) Literature Reports

a) A 42-year-old female experienced symptoms consistent with a mixed hypomanic episode following concomitant use of [fluoxetine](#), [buspirone](#), Ginkgo biloba, and St. John's Wort. The symptoms resolved following discontinuation of Ginkgo and St. John's Wort. The patient was being treated for depression following a mild [traumatic brain injury](#) with [fluoxetine](#) 20 milligrams (mg) twice daily and [buspirone](#) 15 mg twice daily. Several weeks prior to presentation, [buspirone](#) was increased to 20 mg twice daily for persistent anxiety and the patient began taking Ginkgo biloba, [melatonin](#), and St. John's Wort in unspecified doses. [Melatonin](#) was considered unlikely to have contributed to her symptoms. Ginkgo and St. John's Wort were considered possible contributors since they may potentiate antidepressants, and considering the temporal relationship between the use of the herbs and onset of symptoms and discontinuation of the herbs and resolution of symptoms. However, the [brain injury](#) was considered a possible contributor [374].

3.5.1.FY| [Glimepiride](#)

- 1) Interaction Effect: excessive [hypoglycemia](#)
- 2) Summary: The hypoglycemic potential of [glimepiride](#) may be increased with concomitant [fluoxetine](#) therapy. The mechanism of this interaction is unknown. During concurrent therapy, monitor blood glucose levels closely and observe for signs and symptoms of [hypoglycemia](#) (eg, fatigue, restlessness, malaise, irritability, weakness, increased perspiration). Lower doses of [glimepiride](#) may be required to avoid excessive [hypoglycemia](#). When [fluoxetine](#) therapy is withdrawn, careful monitoring of the patient is recommended to observe for loss of glucose control[428].
- 3) Severity: moderate
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: During concurrent therapy, monitor blood glucose levels closely and observe for signs and symptoms of [hypoglycemia](#) (eg, fatigue, restlessness, malaise, irritability, weakness, increased perspiration). Lower doses of [glimepiride](#) may be required to avoid excessive [hypoglycemia](#). When [fluoxetine](#) therapy is withdrawn, careful monitoring of the patient is recommended to observe for loss of glucose control[428].
- 7) Probable Mechanism: unknown

3.5.1.FZ| [Glyburide](#)

- 1) Interaction Effect: excessive [hypoglycemia](#)
- 2) Summary: The hypoglycemic potential of [glyBURIDE](#) may be increased with concomitant [fluoxetine](#) therapy. The mechanism of this interaction is unknown. Blood glucose levels should be closely monitored when [fluoxetine](#) is added in a patient receiving [glyBURIDE](#). Lower doses of [glyBURIDE](#) may be required to avoid excessive [hypoglycemia](#). When [fluoxetine](#) therapy is withdrawn, careful monitoring of the patient is recommended to observe for loss of glucose control[217].
- 3) Severity: moderate
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: The hypoglycemic potential of [glyBURIDE](#) may be increased with concomitant [fluoxetine](#) therapy. Blood glucose levels should be closely monitored when [fluoxetine](#) is added in a patient receiving [glyBURIDE](#). Lower doses of [glyBURIDE](#) may be required to avoid excessive [hypoglycemia](#).

When [fluoxetine](#) therapy is withdrawn, careful monitoring of the patient is recommended to observe for loss of glucose control[217].

7) Probable Mechanism: unknown

3.5.1.GA] [Gonadorelin](#)

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

2) Summary: Use caution with coadministration of gonadotropin-releasing hormone (GnRH) agonists with QT-interval prolonging drugs. Androgen deprivation caused by GnRH agonists may prolong the QT interval and cause additive effects when administered with QT-interval prolonging drugs[141][142][143]. If concurrent therapy is necessary, monitor patients closely for signs and symptoms of [cardiac toxicity](#), including changes in the ECG.

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Use caution with coadministration of gonadotropin-releasing hormone (GnRH) agonists with QT-interval prolonging drugs, as additive effects on the QT interval may occur[141][142][143].

7) Probable Mechanism: additive effects on the QT interval

3.5.1.GB] [Goserelin](#)

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

2) Summary: Use caution with coadministration of gonadotropin-releasing hormone (GnRH) agonists with QT-interval prolonging drugs. Androgen deprivation caused by GnRH agonists may prolong the QT interval and cause additive effects when administered with QT-interval prolonging drugs[141][142][143]. If concurrent therapy is necessary, monitor patients closely for signs and symptoms of [cardiac toxicity](#), including changes in the ECG.

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Use caution with coadministration of gonadotropin-releasing hormone (GnRH) agonists with QT-interval prolonging drugs, as additive effects on the QT interval may occur[141][142][143].

7) Probable Mechanism: additive effects on the QT interval

3.5.1.GC] [Granisetron](#)

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

2) Summary: Concomitant use of [granisetron](#) with a drug that is a serotonergic and QT-interval prolonging drug may increase the risk of [serotonin syndrome](#)[318] and the risk of QT-interval prolongation [319]. [Serotonin syndrome](#) has been reported with the cocurrent use of 5-hydroxytryptamine-3 antagonists and serotonergic drugs, primarily in infusion centers or in post-anesthesia care units. Inform patients of this increased risk. Monitor for the emergence of [serotonin syndrome](#) and discontinue treatment with [granisetron](#) and institute supportive therapy if symptoms of [serotonin syndrome](#) occur [318]. Coadministration with other drugs that prolong the QT-interval may result in additive effects on the QT-interval, therefore use with caution [319].

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Concomitant use of [granisetron](#) with a drug that is a serotonergic and QT-interval prolonging drug may increase the risk of [serotonin syndrome](#)[318] and the risk of QT-interval prolongation [319]. Inform patients of the increased risk of [serotonin syndrome](#). Monitor for the emergence of [serotonin syndrome](#) and discontinue treatment with [granisetron](#) and institute supportive therapy if symptoms of [serotonin syndrome](#) occur [318]. Coadministration with other drugs that prolong the QT-interval may result in additive effects on the QT-interval, therefore use with caution [319].

7) Probable Mechanism: unknown; additive QT-interval prolongation

3.5.1.GD] [Halofantrine](#)

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

2) Summary: [Halofantrine](#) can prolong the QT interval in some patients, which may result in [ventricular tachycardia](#), [ventricular fibrillation](#), and [torsades de pointes](#). Because [fluoxetine](#) has demonstrated QT prolongation at therapeutic doses and may increase the risk of [arrhythmias](#), the concurrent administration of [halofantrine](#) with [fluoxetine](#) is not recommended[466][467].

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

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

7) Probable Mechanism: additive cardiac effects

3.5.1.GE] [Haloperidol](#)

1) Interaction Effect: an increased risk of [parkinsonism](#) (cogwheeling rigidity, unstable gait)

2) Summary: A patient receiving [haloperidol](#) experienced extreme [parkinsonism](#) following the addition of [olanzapine](#) therapy. Possible explanations include a pharmacokinetic interaction between [olanzapine](#), a weak cytochrome P450 2D6 (CYP2D6) inhibitor, and [haloperidol](#), a CYP2D6 substrate. Pharmacodynamically, the small amount of [dopamine](#) (D2) blockade from [olanzapine](#) may have been enough to increase the patient's [parkinsonism](#)[178].

3) Severity: moderate

4) Onset: delayed

5) Substantiation: probable

6) Clinical Management: Patients should be closely monitored for signs and symptoms of increased parkinsonian adverse effects when [olanzapine](#) is added to [haloperidol](#) therapy. Doses of [haloperidol](#) may need to be decreased.

7) Probable Mechanism: competitive inhibition of cytochrome P450 2D6-mediated [haloperidol](#) metabolism; increased [dopamine](#) D2 blockade

8) Literature Reports

a) A 67-year-old hospitalized male with [bipolar disorder](#) who had stopped taking his medications was restarted on [haloperidol](#) 10 mg nightly, [benztropine](#) 1 mg nightly, and [valproate](#) 750 mg twice daily. He had been experiencing some mild parkinsonian symptoms at baseline, but these symptoms did not worsen when [haloperidol](#) was reinstituted. Following stabilization on this regimen, it was decided to change his antipsychotic medication to [olanzapine](#) to minimize any [parkinsonism](#) that was a result of his medications. While tapering the [haloperidol](#) and initiating [olanzapine](#), the patient experienced extreme [parkinsonism](#) that resulted in an inability to walk. His mental status remained unchanged. [Haloperidol](#) was discontinued on day 7 of combination therapy, and two days later the patient's [parkinsonism](#) side effects had resolved back to baseline.

[Benztropine](#) was then discontinued, and the parkinsonian symptoms did not reoccur while on [olanzapine](#) [177].

3.5.1.GF] [Haloperidol](#)

1)) Interaction Effect: increased [haloperidol](#) exposure and risk of [haloperidol](#) toxicity; increased risk of QT prolongation and [torsades de pointes](#)

2)) Summary: Use caution with coadministration of [fluoxetine](#) and [haloperidol](#), as concurrent use increases the risk of QT interval prolongation (including [torsades de pointes](#)) inherent in both drugs[173][408]. Coadministration with [fluoxetine](#) may also increase [haloperidol](#) plasma concentrations [173] and increase the risk of [haloperidol](#) toxicity [409][410][411].

3)) Severity: major

4)) Onset: unspecified

5)) Substantiation: probable

6)) Clinical Management: Use caution with coadministration of [fluoxetine](#) and [haloperidol](#), as concurrent use increases the risk of QT interval prolongation (including [torsades de pointes](#)) inherent in both drugs[173][408]. Coadministration with [fluoxetine](#) may also increase [haloperidol](#) plasma concentrations [173] and increase the risk of [haloperidol](#) toxicity [409][410][411].

7)) Probable Mechanism: inhibition CYP2D6-mediated metabolism of [haloperidol](#) by [fluoxetine](#); additive effects of QT interval prolongation

8)) Literature Reports

a)) A 40-year-old man developed urinary retention while taking [fluoxetine](#) and [haloperidol](#). During a recurrence of depression, the patient was treated with [fluoxetine](#) 20 mg/day, [alprazolam](#) 1.5 mg per day, and [haloperidol](#) 1 mg per day. The patient had previously taken [fluoxetine](#) and [alprazolam](#) without incident. Approximately 1 week after beginning therapy, the patient developed difficulty in voiding urine, dilated pupils, dry mouth, palpitations, restlessness, hand tremors, and insomnia. After discontinuation of [haloperidol](#) and [alprazolam](#), side effects ceased within 1 week. The authors postulated that the interaction was due to [fluoxetine](#) inhibition of cytochrome CYP2D6, which metabolizes [haloperidol](#) [409].

b)) [Fluoxetine](#) increased plasma concentrations of [haloperidol](#) in 8 outpatients. Patients received [fluoxetine](#) 20 mg daily for 10 days with maintenance doses of [haloperidol](#) (average dose, 14 mg per day). After 10 days, mean plasma concentrations of [haloperidol](#) had increased by 20%. Extrapyramidal symptom scores did not change appreciably after the addition of [fluoxetine](#) although 1 patient developed mild [akathisia](#) and another developed tremors. Extrapyramidal symptoms were expected to increase because of indirect inhibition of [dopamine](#) synthesis by [fluoxetine](#) [412].

c)) A 39-year-old man experienced [tardive dyskinesia](#) with concomitant [fluoxetine](#) and [haloperidol](#) therapy. He was taking [fluoxetine](#) 20 mg daily for 2 months, then [haloperidol](#) 2 mg twice daily was started and later lowered to 1 mg per day. Five months later during a routine examination, [tardive dyskinesia](#) was diagnosed. The suggested mechanism was the down-regulation of [dopamine](#) activity [410].

d)) A 39-year-old woman developed [tardive dyskinesia](#) associated with concomitant [fluoxetine](#) and [haloperidol](#) therapy. She had been taking [haloperidol](#) 2 to 5 mg a day for two years (both with and without [benztropine](#)) with occasional mild, reversible extrapyramidal symptoms. Five days before stopping [haloperidol](#), she started taking [fluoxetine](#), which was increased over several days to 40 mg twice a day. After two weeks of [fluoxetine](#) she took [haloperidol](#) 5 mg each on two consecutive days (along with continuation of [fluoxetine](#)). She then experienced severe tongue

stiffness, [parkinsonism](#), and [akathisia](#). Both [fluoxetine](#) and [haloperidol](#) were withdrawn. During the next 7 days her extrapyramidal symptoms gradually disappeared [411].

3.5.1.GG| [Halothane](#)

- 1) Interaction Effect: an increased risk of [cardiotoxicity](#) (QT prolongation, [torsades de pointes](#), [cardiac arrest](#))
- 2) Summary: Even though no formal drug interaction studies have been done, [halothane](#) should be administered cautiously with other drugs which are also known to prolong the QTc interval, including [fluoxetine](#)[459][460].
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: The concurrent administration of [halothane](#) with other agents that can prolong the QT interval, such as [fluoxetine](#), is not recommended.
- 7) Probable Mechanism: additive effect on QT interval

3.5.1.GH| [Heparin](#)

- 1) Interaction Effect: an increased risk of bleeding
- 2) Summary: The release of serotonin by [platelets](#) is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs and anticoagulants has been associated with an increased risk of bleeding[458][457]. Bleeding events reported have included [epistaxis](#), ecchymosis, [hematoma](#), [petechiae](#), and life-threatening hemorrhages. Altered anticoagulant effects (including increased bleeding) have been reported with the coadministration of SSRIs with anticoagulants [457].
- 3) Severity: major
- 4) Onset: delayed
- 5) Substantiation: probable
- 6) Clinical Management: When [fluoxetine](#) and an anticoagulant are given concurrently, monitor patient for signs of increased bleeding. Patients who are taking an anticoagulant should be monitored closely for altered anticoagulant effects, including increased bleeding, when [fluoxetine](#) therapy is initiated or discontinued[457].
- 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 a significant 1.7-fold increased risk for hospitalization for nongastrointestinal bleeding; however, the rate of [gastrointestinal bleeding](#) was not significantly different [458].

3.5.1.GI| [Histrelin](#)

- 1) Interaction Effect: increased risk of QT-interval prolongation
- 2) Summary: Use caution with coadministration of gonadotropin-releasing hormone (GnRH) agonists with QT-interval prolonging drugs. Androgen deprivation caused by GnRH agonists may prolong the QT interval and cause additive effects when administered with QT-interval prolonging drugs[141][142][143].

If concurrent therapy is necessary, monitor patients closely for signs and symptoms of [cardiac toxicity](#), including changes in the ECG.

3J) Severity: major

4J) Onset: unspecified

5J) Substantiation: theoretical

6J) Clinical Management: Use caution with coadministration of gonadotropin-releasing hormone (GnRH) agonists with QT-interval prolonging drugs, as additive effects on the QT interval may occur[141][142] [143].

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

3.5.1.GJ] [Hydrocodone](#)

1J) Interaction Effect: increased risk of CNS depression (ie, [respiratory depression](#), profound sedation, coma)

2J) Summary: Use caution with the concomitant use of [hydrocodone](#) and a CNS depressant as this may result in additive CNS effects and increase the risk of [respiratory depression](#), profound sedation, coma, and/or death. If combination therapy is required, reduce the initial [hydrocodone](#) dose by 20% to 30% and consider using a lower dose of the concomitant CNS depressant. Monitor patients for signs of [respiratory depression](#), sedation, or hypotension[84]. Avoid concomitant use of [hydrocodone cough](#) medications with CNS depressants [78].

3J) Severity: major

4J) Onset: unspecified

5J) Substantiation: theoretical

6J) Clinical Management: The concomitant use of [hydrocodone](#) and a CNS depressant may result in additive CNS effects and increase the risk of [respiratory depression](#), profound sedation, coma, and/or death. If combination therapy is required, reduce the initial [hydrocodone](#) dose by 20% to 30% and use a lower dose of the concomitant CNS depressant. Monitor patients for signs of [respiratory depression](#), sedation, or hypotension[84]. Avoid concomitant use of [hydrocodone cough](#) medications with CNS depressants [78].

7J) Probable Mechanism: additive CNS depression

3.5.1.GK] [Hydromorphone](#)

1J) Interaction Effect: an increase in CNS or [respiratory depression](#)

2J) Summary: The concomitant use of [HYDROmorphine](#) and other CNS depressants, such as antipsychotics, may result in additive CNS depressant effects, including [respiratory depression](#), hypotension, profound sedation, and coma. When administering [HYDROmorphine](#) and an antipsychotic together, dose reduction of one or both of the medications should be considered[101].

3J) Severity: major

4J) Onset: unspecified

5J) Substantiation: theoretical

6J) Clinical Management: Concomitant use of [HYDROmorphine](#) and other CNS depressants, such as antipsychotics, may result in [respiratory depression](#), hypotension, profound sedation, and coma. When concomitant use is required, dose reduction of one or both medications should be considered[101].

7J) Probable Mechanism: additive CNS depression

3.5.1.GL] [Hydroquinidine](#)

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

- 2)) Summary: Even though no formal drug interaction studies have been done, the coadministration of Class Ia antiarrhythmics and other drugs known to prolong the QTc interval is not recommended[343]. [Fluoxetine](#) has demonstrated QT prolongation at therapeutic doses [344].
- 3)) Severity: major
- 4)) Onset: unspecified
- 5)) Substantiation: theoretical
- 6)) Clinical Management: The concurrent administration of class Ia antiarrhythmic agents and agents that prolong the QT interval, such as [fluoxetine](#), is not recommended.
- 7)) Probable Mechanism: additive effects on QT prolongation

3.5.1.GM] [Hydroxychloroquine](#)

- 1)) Interaction Effect: increased risk of QT-interval prolongation
- 2)) Summary: [Hydroxychloroquine](#) has been associated with QT interval prolongation[56][57], [ventricular premature contractions](#), and [torsade de pointes](#) [57]. Therefore, use caution with coadministration of [hydroxychloroquine](#) and other QT interval-prolonging drugs, as life-threatening additive effects on the QT interval, including [torsades de pointes](#), may occur. Consider close [ECG monitoring](#) at baseline and during concurrent therapy with QT-interval prolonging drugs.
- 3)) Severity: major
- 4)) Onset: unspecified
- 5)) Substantiation: probable
- 6)) Clinical Management: [Hydroxychloroquine](#) has been associated with QT interval prolongation[56][57]. Therefore, use caution with coadministration of [hydroxychloroquine](#) and other QT interval-prolonging drugs, as life-threatening additive effects on the QT interval, including [torsades de pointes](#), may occur. Consider close [ECG monitoring](#) at baseline and during concurrent therapy with QT-interval prolonging drugs.
- 7)) Probable Mechanism: additive QT interval effects
- 8)) Literature Reports

a)) Hydroxychloroquine-associated QT interval prolongation was reported in a 41-year-old woman with [congestive heart failure](#) with [systolic left ventricular dysfunction](#). Her comorbidities included [hypertension](#), [systemic lupus erythematosus](#), and [stage 5 chronic kidney disease](#). One week after reinitiation of [hydroxychloroquine](#) therapy, a significant prolongation of the QT interval (QTc 614 msec) was observed during a routine ECG. Following treatment discontinuation of [hydroxychloroquine](#), serial ECGs demonstrated a shortening of the QTc interval. The patient's QTc was 473 msec at a follow up 1 year after discharge [56].

b)) QT prolongation and refractory [ventricular arrhythmia](#) were reported with chronic [hydroxychloroquine](#) use in a 67-year-old woman with [systemic lupus erythematosus](#). The patient had been receiving [prednisolone](#), [theophylline](#), and [hydroxychloroquine](#) 200 mg/day for 1 year. The patient had a medical history of [cirrhosis](#), [hepatitis B](#) virus related [hepatoma](#) with portal vein [thrombosis](#), and [asthma](#). The patient experienced a sudden episode of unconsciousness and generalized rigidity while at home. Although the patient regained consciousness within minutes and had no complaints of chest pain, palpitation, limb weakness, incontinence, or confusion, the episode recurred several times. Upon admission the ECG showed multiple [ventricular premature contractions](#), [torsade de pointes](#), and prolongation of the QT interval. Treatment with [hydroxychloroquine](#) was discontinued. Following medical management, [ventricular arrhythmia](#) subsided after 4 days and the QT interval shortened [57].

3.5.1.GN] [Hydroxytryptophan](#)

- 1) Interaction Effect: an increased risk of [serotonin syndrome](#) ([hypertension](#), [hyperthermia](#), myoclonus, mental status changes)
- 2) Summary: Potentially life-threatening [serotonin syndrome](#) has been reported with SSRIs when used concomitantly with other serotonergic drugs, such as hydroxytryptophan or tryptophan. If coadministration is clinically warranted, monitor for the development of [serotonin syndrome](#), especially during treatment initiation and dose increases[237].
- 3) Severity: major
- 4) Onset: rapid
- 5) Substantiation: theoretical
- 6) Clinical Management: Potentially life-threatening [serotonin syndrome](#) has been reported with SSRIs when used concomitantly with other serotonergic drugs, such as hydroxytryptophan or tryptophan. If coadministration is clinically warranted, monitor for the development of [serotonin syndrome](#), especially during treatment initiation and dose increases[237].
- 7) Probable Mechanism: additive serotonergic effect
- 8) Literature Reports

a) In a case series, the concurrent use of [fluoxetine](#) 50 to 100 mg daily and L-tryptophan 1 to 4 g daily resulted in all five patients experiencing central nervous system toxicity (agitation, poor concentration, nausea, diarrhea, paresthesias, palpitations, chills, headaches, aggressive behavior, and severe insomnia) within a few days. Tryptophan was discontinued and the symptoms disappeared [238].

3.5.1.GO| [Hydroxyzine](#)

- 1) Interaction Effect: increased risk of QT interval prolongation
- 2) Summary: [Hydroxyzine](#) has been associated with QT interval prolongation and development of [Torsade de Pointes](#). Caution is advised if [hydroxyzine](#) is used concomitantly with this drug as additive effects on QT prolongation may occur[139]. Consider close [ECG monitoring](#) at baseline and during concurrent therapy with QT-interval prolonging drugs.
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: [Hydroxyzine](#) has been associated with QT interval prolongation and development of [Torsade de Pointes](#). Caution is advised if [hydroxyzine](#) is used concomitantly with this drug as additive effects on QT prolongation may occur[139]. Consider close [ECG monitoring](#) at baseline and during concurrent therapy with QT-interval prolonging drugs.
- 7) Probable Mechanism: additive effects on the QT interval

3.5.1.GP| [Ibuprofen](#)

- 1) Interaction Effect: an increased risk of bleeding
- 2) Summary: Caution is recommended with the concomitant use of NSAIDs and antidepressants, including SSRIs due to an increased risk of [intracranial hemorrhage](#)[529] and [gastrointestinal bleeding](#) [533][534][530][531]. Bleeding events have included [epistaxis](#), ecchymosis, [hematoma](#), [petechiae](#), and life-threatening hemorrhages [536][535][537][538]. When an SSRI and an NSAID are given concurrently, monitor the patient for signs of increased bleeding.
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: established
- 6) Clinical Management: Use caution if NSAIDs and SSRIs are coadministered. Concomitant use of NSAIDs and SSRIs may cause an increased risk of [intracranial hemorrhage](#)[529] and [gastrointestinal](#)

bleeding [530][531]. When an SSRI and an NSAID are given concurrently, monitor the patient for signs of increased bleeding.

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

8) Literature Reports

a) Concomitant use of NSAIDs and antidepressants, including tricyclic antidepressants, SSRIs, serotonin-norepinephrine reuptake inhibitors, and MAOIs, resulted in a 60% increased risk of intracranial hemorrhage within 30 days of concomitant use compared with antidepressant use alone. There was no significant difference between the antidepressant drug classes and the increased risk; however, there was an increased risk associated with male patients compared with female patients [529].

b) SSRIs increase the risk of upper gastrointestinal (GI) bleeding, and this effect is potentiated by concurrent use of NSAIDs or low-dose aspirin. Hospitalizations for upper GI bleeding were searched among 26,005 users of antidepressant medications and compared with the number of hospitalizations in those patients who did not receive prescriptions for antidepressants. The amount of upper GI bleeding episodes was 3.6 times more than expected. Combined use of an SSRI and NSAIDs or low-dose aspirin increased the risk to 12.2 and 5.2 times, respectively. The findings of this study demonstrate an increased risk of upper GI bleeding during the use of SSRIs. Combined use of SSRIs and NSAIDs or low-dose aspirin increased the risk even further [532].

c) Two metaanalyses of incidents of upper GI bleed due to SSRIs, NSAIDs, and their combination found that SSRIs increased the risk by 1.73 [533] to 2.36 times [534], NSAIDs by 2.55 times [533], and the combination of SSRIs and NSAIDs by 4.02 [533] to 6.33 times [534].

d) The release of serotonin by platelets is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs and NSAIDs have been associated with an increased risk of bleeding [535].

3.5.1.GQI Ibuprofen Lysine

1) Interaction Effect: an increased risk of bleeding

2) Summary: Caution is recommended with the concomitant use of NSAIDs and antidepressants, including SSRIs due to an increased risk of intracranial hemorrhage[529] and gastrointestinal bleeding [533][534][530][531]. Bleeding events have included epistaxis, ecchymosis, hematoma, petechiae, and life-threatening hemorrhages [536][535][537][538]. When an SSRI and an NSAID are given concurrently, monitor the patient for signs of increased bleeding.

3) Severity: major

4) Onset: unspecified

5) Substantiation: established

6) Clinical Management: Use caution if NSAIDs and SSRIs are coadministered. Concomitant use of NSAIDs and SSRIs may cause an increased risk of intracranial hemorrhage[529] and gastrointestinal bleeding [530][531]. When an SSRI and an NSAID are given concurrently, monitor the patient for signs of increased bleeding.

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

8) Literature Reports

a) Concomitant use of NSAIDs and antidepressants, including tricyclic antidepressants, SSRIs, serotonin-norepinephrine reuptake inhibitors, and MAOIs, resulted in a 60% increased risk of intracranial hemorrhage within 30 days of concomitant use compared with antidepressant use alone. There was no significant difference between the antidepressant drug classes and the

increased risk; however, there was an increased risk associated with male patients compared with female patients [529].

b) SSRIs increase the risk of upper gastrointestinal (GI) bleeding, and this effect is potentiated by concurrent use of NSAIDs or low-dose [aspirin](#). Hospitalizations for [upper GI bleeding](#) were searched among 26,005 users of antidepressant medications and compared with the number of hospitalizations in those patients who did not receive prescriptions for antidepressants. The amount of [upper GI bleeding](#) episodes was 3.6 times more than expected. Combined use of an SSRI and NSAIDs or low-dose [aspirin](#) increased the risk to 12.2 and 5.2 times, respectively. The findings of this study demonstrate an increased risk of [upper GI bleeding](#) during the use of SSRIs. Combined use of SSRIs and NSAIDs or low-dose [aspirin](#) increased the risk even further [532].

c) Two metaanalyses of incidents of upper GI bleed due to SSRIs, NSAIDs, and their combination found that SSRIs increased the risk by 1.73 [533] to 2.36 times [534], NSAIDs by 2.55 times [533], and the combination of SSRIs and NSAIDs by 4.02 [533] to 6.33 times [534].

d) The release of serotonin by [platelets](#) is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs and NSAIDs have been associated with an increased risk of bleeding [535].

3.5.1.GR] [Ibutilide](#)

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

2) Summary: Even though no formal drug interaction studies have been done, the coadministration of Class III antiarrhythmics and other drugs known to prolong the QTc interval is not recommended[300] [301][302]. [Fluoxetine](#) has been shown to prolong the QTc interval at the recommended therapeutic dose [303].

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

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

7) Probable Mechanism: additive effects on QT prolongation

3.5.1.GS] [Iloperidone](#)

1) Interaction Effect: increased plasma concentrations of iloperidone and increased risk of QT prolongation

2) Summary: Coadministration of iloperidone, a CYP2D6 substrate, and [fluoxetine](#), a potent CYP2D6 inhibitor, results in increased plasma levels of iloperidone[216]. Concomitant use of [fluoxetine](#) and iloperidone may also result in additive effects on the QT interval. Therefore, coadministration should be avoided [173]. If coadministration with [fluoxetine](#) is necessary, reduce iloperidone doses by one-half. Upon withdrawal of [fluoxetine](#) from the combination therapy, resume the previous iloperidone dose [216].

3) Severity: major

4) Onset: unspecified

5) Substantiation: established

6) Clinical Management: Avoid the concomitant use of [fluoxetine](#) with other drugs known to prolong the QT interval, including iloperidone[173]. If coadministration with [fluoxetine](#) is necessary, reduce iloperidone doses by one-half. Upon withdrawal of [fluoxetine](#) from the combination therapy, resume the previous iloperidone dose [216].

- 7) Probable Mechanism: inhibition of the CYP2D6-mediated metabolism of iloperidone by [fluoxetine](#) and additive QT-interval prolongation
- 8) Literature Reports

a) Coadministration of [fluoxetine](#) 20 mg twice daily for 21 days and iloperidone 3 mg (single doses) in 23 healthy volunteers (ages 29 to 44 years) classified as CYP2D6 extensive metabolizers increased the AUC of iloperidone and the P88 metabolite by 2- to 3-fold, and decreased the AUC of the P95 metabolite by one-half [216].

3.5.1.GT] [Iloprost](#)

- 1) Interaction Effect: increased risk of bleeding
- 2) Summary: Exercise caution when coadministering a SSRI and an antiplatelet agent or anticoagulant as this may increase the risk of bleeding events[272][173][385].
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Use caution with concomitant use of [fluoxetine](#) with anticoagulants or antiplatelet agents, as coadministration may increase bleeding risk[272][173][385].
- 7) Probable Mechanism: altered anticoagulant effects
- 8) Literature Reports

a) In a retrospective study of patients over 50 years of age with the diagnosis of acute [myocardial infarction](#) (N=27,058), SSRI use with any antiplatelet therapy significantly increased the risk of bleeding by 1.42-fold compared with [aspirin](#) use alone. Therapy with [aspirin](#), [clopidogrel](#), and an SSRI significantly increased risk by 2.35-fold compared with [aspirin](#) use alone and by 1.57-fold compared with [clopidogrel](#) and [aspirin](#) combination therapy [385].

b) In a systematic review and meta-analysis of 22 observational studies, SSRI use was associated with a significant 1.55 fold increase in risk of [upper gastrointestinal bleeding](#) (UGIB). Concomitant use of SSRIs and antiplatelet drugs was associated with a 2.48-fold increase in risk of UGIB (3 studies) [272].

3.5.1.GU] [Imipramine](#)

- 1) Interaction Effect: increased risk of tricyclic antidepressant toxicity, QT prolongation and [serotonin syndrome](#)
- 2) Summary: [Fluoxetine](#), a potent CYP2D6 inhibitor, is associated with an increased risk of [serotonin syndrome](#), QT prolongation, and [ventricular arrhythmias](#) (including [torsade de pointes](#)). Concomitant therapy with CYP2D6-metabolized tricyclic antidepressants (TCAs) may potentiate these risks and introduce TCA toxicity[173]; concurrent use of [fluoxetine](#) and [desipramine](#), [nortriptyline](#), and [imipramine](#) has resulted in significant increases in TCA concentrations [517][523][524][525][526][527]. Use caution with concurrent administration of [fluoxetine](#) and TCAs. If [fluoxetine](#) is added to an existing TCA regimen, consider TCA dose reduction. If [fluoxetine](#) and a TCA are coadministered or [fluoxetine](#) has been recently discontinued, consider plasma TCA monitoring. If [serotonin syndrome](#) occurs, immediately discontinue [fluoxetine](#) and TCA. If [ventricular arrhythmias](#) develop, consider [fluoxetine](#) discontinuation and cardiac evaluation [173].
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical

6j) Clinical Management: Use caution with concurrent administration of [fluoxetine](#) and TCAs, as elevated TCA plasma concentrations may occur. If [fluoxetine](#) is added to an existing TCA regimen, consider TCA dose reduction. If [fluoxetine](#) and a TCA are coadministered or [fluoxetine](#) has been recently discontinued, consider plasma TCA monitoring. If [serotonin syndrome](#) occurs, immediately discontinue [fluoxetine](#) and TCA. If [ventricular arrhythmias](#) develop, consider [fluoxetine](#) discontinuation and cardiac evaluation[173]

7j) Probable Mechanism: decreased CYP2D6-mediated metabolism of tricyclic antidepressants by [fluoxetine](#); additive effects on QT prolongation; additive serotonergic effects

8j) Literature Reports

aj) Previously stable plasma levels of [imipramine](#) and [desipramine](#) rose more than 2- to 10-fold with [fluoxetine](#) coadministration in 2 clinical studies. This effect may persist for 3 weeks or more after [fluoxetine](#) discontinuation. Dose reduction and temporary monitoring of tricyclic antidepressant plasma concentrations may be indicated with concurrent [fluoxetine](#) treatment or recent [fluoxetine](#) discontinuation [173].

bj) [Fluoxetine](#) statistically and clinically significantly increased [desipramine](#) concentrations in 18 healthy subjects. When [fluoxetine](#) (20 mg daily) was added to [desipramine](#) (50 mg daily), the mean maximum concentration of [desipramine](#) increased by 278% and the AUC increased by 342%. [Desipramine](#) trough concentrations continued to be 198% above baseline 3 weeks after [fluoxetine](#) was discontinued. The same study compared pharmacokinetics of [desipramine](#) when combined with [sertraline](#). The impact of [sertraline](#) was modest, resulting in small and short-term increases in [desipramine](#) plasma concentrations [517].

cj) Concomitant administration of [fluoxetine](#) and [desipramine](#) was reported to result in an increased [desipramine](#) level and new onset of [delirium](#) in a 69-year-old male within 10 days of the addition of [fluoxetine](#) to the patient's regimen [518].

dj) [Fluoxetine](#) increased the level of tricyclic antidepressants ([nortriptyline](#), [imipramine](#), [desipramine](#)) in 4 patients. After the addition of [fluoxetine](#), the ratio of antidepressant level to dose increased by 109% to 486% in the patients. Three patients developed clinical symptoms (anticholinergic effects, constipation, urinary hesitancy, sedation, unstable gait) as a result of the increased levels [519].

ej) A 39-year-old female experienced symptomatic increases in her [desipramine](#) levels with concomitant [fluoxetine](#) therapy. Prior to [fluoxetine](#) therapy, the patient's measured levels of [desipramine](#) had ranged from 148 to 160 nanograms/milliliter (ng/mL; 556 to 601 nanomol/L) on a regimen of 300 mg daily. Five weeks after the addition of [fluoxetine](#) 20 mg daily, she reported anticholinergic symptoms, sedation, and confusion with a [desipramine](#) level of 527 ng/mL (1978 nanomol/L). The [desipramine](#) dose was lowered to 200 mg/day; 11 days later, the level was 244 ng/mL (916 nanomol/L); the patient reported decreased energy, impaired short-term memory, and some "garbled" speech, as well as an episode of nausea, dizziness, and syncope. The [desipramine](#) dose was reduced to 50 mg/day, and the adverse effects resolved in 6 days. Eight days later, the [desipramine](#) level was 122 ng/mL (458 nanomol/L) [520].

fj) A 33-year-old depressed male developed adverse effects of dry mouth, tinnitus, and difficulties with alertness and memory while receiving [fluoxetine](#) 40 mg daily and [desipramine](#) 150 mg daily for 5 weeks; [fluoxetine](#) was discontinued and the blood levels of [desipramine](#) decreased from 938 to 48 nanograms/mL (3521 to 180 nanomol/L) with resolution of clinical symptoms [521].

gj) A 75-year-old female experienced symptomatic increases in her [desipramine](#) serum concentrations when [fluoxetine](#) was added. [Desipramine](#) serum levels ranged from 109 to 150 ng/

mL (409 to 563 nanomol/L) with oral doses of 300 mg at bedtime prior to [fluoxetine](#) therapy. Following the addition of oral [fluoxetine](#) 20 mg daily to the regimen, the [desipramine](#) serum level increased to 212 ng/mL (796 nanomol/L) within five days. The [fluoxetine](#) dose was increased to 40 mg/day three days later, and the [desipramine](#) serum level was 419 ng/mL (1573 nanomol/L) after four days. A worsening of depression and severe fatigue coincided with the increases in [desipramine](#) serum levels. Withdrawal of [fluoxetine](#) and reduction in the [desipramine](#) dose to 200 mg daily reduced the [desipramine](#) serum level to 231 ng/mL (867 nanomol/L) within two weeks [522].

3.5.1.GV] [Indomethacin](#)

- 1) Interaction Effect: an increased risk of bleeding
- 2) Summary: Caution is recommended with the concomitant use of NSAIDs and antidepressants, including SSRIs due to an increased risk of [intracranial hemorrhage](#)[529] and [gastrointestinal bleeding](#) [533][534][530][531]. Bleeding events have included [epistaxis](#), ecchymosis, [hematoma](#), [petechiae](#), and life-threatening hemorrhages [536][535][537][538]. When an SSRI and an NSAID are given concurrently, monitor the patient for signs of increased bleeding.
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: established
- 6) Clinical Management: Use caution if NSAIDs and SSRIs are coadministered. Concomitant use of NSAIDs and SSRIs may cause an increased risk of [intracranial hemorrhage](#)[529] and [gastrointestinal bleeding](#) [530][531]. When an SSRI and an NSAID are given concurrently, monitor the patient for signs of increased bleeding.
- 7) Probable Mechanism: depletion of [platelet](#) serotonin by SSRI; additive effects
- 8) Literature Reports

a) Concomitant use of NSAIDs and antidepressants, including tricyclic antidepressants, SSRIs, serotonin-norepinephrine reuptake inhibitors, and MAOIs, resulted in a 60% increased risk of [intracranial hemorrhage](#) within 30 days of concomitant use compared with antidepressant use alone. There was no significant difference between the antidepressant drug classes and the increased risk; however, there was an increased risk associated with male patients compared with female patients [529].

b) SSRIs increase the risk of upper gastrointestinal (GI) bleeding, and this effect is potentiated by concurrent use of NSAIDs or low-dose [aspirin](#). Hospitalizations for [upper GI bleeding](#) were searched among 26,005 users of antidepressant medications and compared with the number of hospitalizations in those patients who did not receive prescriptions for antidepressants. The amount of [upper GI bleeding](#) episodes was 3.6 times more than expected. Combined use of an SSRI and NSAIDs or low-dose [aspirin](#) increased the risk to 12.2 and 5.2 times, respectively. The findings of this study demonstrate an increased risk of [upper GI bleeding](#) during the use of SSRIs. Combined use of SSRIs and NSAIDs or low-dose [aspirin](#) increased the risk even further [532].

c) Two metaanalyses of incidents of upper GI bleed due to SSRIs, NSAIDs, and their combination found that SSRIs increased the risk by 1.73 [533] to 2.36 times [534], NSAIDs by 2.55 times [533], and the combination of SSRIs and NSAIDs by 4.02 [533] to 6.33 times [534].

d) The release of serotonin by [platelets](#) is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs and NSAIDs have been associated with an increased risk of bleeding [535].

3.5.1.GW| Insulin

- 1) Interaction Effect: increased risk of [hypoglycemia](#)
- 2) Summary: Use caution when coadministering [fluoxetine](#) and [insulins](#) or [pramlintide](#), as this may increase the risk of [hypoglycemia](#). Monitor glucose levels more frequently and adjust the dose of [insulin](#) if necessary[355][356][357].
- 3) Severity: moderate
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Use caution when coadministering [fluoxetine](#) and [insulins](#) or [pramlintide](#), as this may increase the risk of [hypoglycemia](#). Monitor glucose levels more frequently and adjust the dose of [insulin](#) if necessary[355][356][357].
- 7) Probable Mechanism: unknown

3.5.1.GX| Insulin Aspart, Recombinant

- 1) Interaction Effect: increased risk of [hypoglycemia](#)
- 2) Summary: Use caution when coadministering [fluoxetine](#) and [insulins](#) or [pramlintide](#), as this may increase the risk of [hypoglycemia](#). Monitor glucose levels more frequently and adjust the dose of [insulin](#) if necessary[355][356][357].
- 3) Severity: moderate
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Use caution when coadministering [fluoxetine](#) and [insulins](#) or [pramlintide](#), as this may increase the risk of [hypoglycemia](#). Monitor glucose levels more frequently and adjust the dose of [insulin](#) if necessary[355][356][357].
- 7) Probable Mechanism: unknown

3.5.1.GY| Insulin Bovine

- 1) Interaction Effect: increased risk of [hypoglycemia](#)
- 2) Summary: Use caution when coadministering [fluoxetine](#) and [insulins](#) or [pramlintide](#), as this may increase the risk of [hypoglycemia](#). Monitor glucose levels more frequently and adjust the dose of [insulin](#) if necessary[355][356][357].
- 3) Severity: moderate
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Use caution when coadministering [fluoxetine](#) and [insulins](#) or [pramlintide](#), as this may increase the risk of [hypoglycemia](#). Monitor glucose levels more frequently and adjust the dose of [insulin](#) if necessary[355][356][357].
- 7) Probable Mechanism: unknown

3.5.1.GZ| Insulin Degludec

- 1) Interaction Effect: increased risk of [hypoglycemia](#)
- 2) Summary: Use caution when coadministering [fluoxetine](#) and [insulins](#) or [pramlintide](#), as this may increase the risk of [hypoglycemia](#). Monitor glucose levels more frequently and adjust the dose of [insulin](#) if necessary[355][356][357].
- 3) Severity: moderate
- 4) Onset: unspecified

- 5) Substantiation: theoretical
- 6) Clinical Management: Use caution when coadministering [fluoxetine](#) and [insulins](#) or [pramlintide](#), as this may increase the risk of [hypoglycemia](#). Monitor glucose levels more frequently and adjust the dose of [insulin](#) if necessary[355][356][357].
- 7) Probable Mechanism: unknown

3.5.1.HA] [Insulin Detemir](#)

- 1) Interaction Effect: increased risk of [hypoglycemia](#)
- 2) Summary: Use caution when coadministering [fluoxetine](#) and [insulins](#) or [pramlintide](#), as this may increase the risk of [hypoglycemia](#). Monitor glucose levels more frequently and adjust the dose of [insulin](#) if necessary[355][356][357].
- 3) Severity: moderate
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Use caution when coadministering [fluoxetine](#) and [insulins](#) or [pramlintide](#), as this may increase the risk of [hypoglycemia](#). Monitor glucose levels more frequently and adjust the dose of [insulin](#) if necessary[355][356][357].
- 7) Probable Mechanism: unknown

3.5.1.HB] [Insulin Glargine, Recombinant](#)

- 1) Interaction Effect: increased risk of [hypoglycemia](#)
- 2) Summary: Use caution when coadministering [fluoxetine](#) and [insulins](#) or [pramlintide](#), as this may increase the risk of [hypoglycemia](#). Monitor glucose levels more frequently and adjust the dose of [insulin](#) if necessary[355][356][357].
- 3) Severity: moderate
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Use caution when coadministering [fluoxetine](#) and [insulins](#) or [pramlintide](#), as this may increase the risk of [hypoglycemia](#). Monitor glucose levels more frequently and adjust the dose of [insulin](#) if necessary[355][356][357].
- 7) Probable Mechanism: unknown

3.5.1.HC] [Insulin Glulisine](#)

- 1) Interaction Effect: increased risk of [hypoglycemia](#)
- 2) Summary: Use caution when coadministering [fluoxetine](#) and [insulins](#) or [pramlintide](#), as this may increase the risk of [hypoglycemia](#). Monitor glucose levels more frequently and adjust the dose of [insulin](#) if necessary[355][356][357].
- 3) Severity: moderate
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Use caution when coadministering [fluoxetine](#) and [insulins](#) or [pramlintide](#), as this may increase the risk of [hypoglycemia](#). Monitor glucose levels more frequently and adjust the dose of [insulin](#) if necessary[355][356][357].
- 7) Probable Mechanism: unknown

3.5.1.HD] [Insulin Lispro, Recombinant](#)

- 1) Interaction Effect: increased risk of [hypoglycemia](#)

- 2) Summary: Use caution when coadministering [fluoxetine](#) and [insulins](#) or [pramlintide](#), as this may increase the risk of [hypoglycemia](#). Monitor glucose levels more frequently and adjust the dose of [insulin](#) if necessary[355][356][357].
- 3) Severity: moderate
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Use caution when coadministering [fluoxetine](#) and [insulins](#) or [pramlintide](#), as this may increase the risk of [hypoglycemia](#). Monitor glucose levels more frequently and adjust the dose of [insulin](#) if necessary[355][356][357].
- 7) Probable Mechanism: unknown

3.5.1.HE] [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[342].
- 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[342].
- 7) Probable Mechanism: inhibition of [norepinephrine](#) transporter function by antidepressants

3.5.1.HF] [Iproniazid](#)

- 1) Interaction Effect: an increased risk of [serotonin syndrome](#) ([hypertension](#), [tachycardia](#), [hyperthermia](#), [myoclonus](#), [mental status changes](#))
- 2) Summary: Concomitant use of [fluoxetine](#) and an MAOI is contraindicated. Concurrent administration or overlapping therapy with [fluoxetine](#) and an MAOI 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 SSRIs and MAOIs. A minimum of 14 days should elapse after discontinuing an MAOI intended to treat psychiatric disorders before initiating therapy with [fluoxetine](#), and a minimum of 5 weeks should elapse after discontinuing [fluoxetine](#) before initiating therapy with an MAOI intended to treat psychiatric disorders[283].
- 3) Severity: contraindicated
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Concurrent use of [fluoxetine](#) and an MAOI is contraindicated. Wait at least 14 days after discontinuing an MAOI intended to treat psychiatric disorders before initiating [fluoxetine](#).

Wait at least 5 weeks after discontinuing [fluoxetine](#) before initiating therapy with an MAOI intended to treat psychiatric disorders[283].

7J) Probable Mechanism: additive serotonergic effect

3.5.1.HGJ [Isocarboxazid](#)

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

2J) Summary: Concomitant use of [fluoxetine](#) and an MAOI is contraindicated. Concurrent administration or overlapping therapy with [fluoxetine](#) and an MAOI 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 SSRIs and MAOIs. A minimum of 14 days should elapse after discontinuing an MAOI intended to treat psychiatric disorders before initiating therapy with [fluoxetine](#), and a minimum of 5 weeks should elapse after discontinuing [fluoxetine](#) before initiating therapy with an MAOI intended to treat psychiatric disorders[283].

3J) Severity: contraindicated

4J) Onset: unspecified

5J) Substantiation: theoretical

6J) Clinical Management: Concurrent use of [fluoxetine](#) and an MAOI is contraindicated. Wait at least 14 days after discontinuing an MAOI intended to treat psychiatric disorders before initiating [fluoxetine](#). Wait at least 5 weeks after discontinuing [fluoxetine](#) before initiating therapy with an MAOI intended to treat psychiatric disorders[283].

7J) Probable Mechanism: additive serotonergic effect

3.5.1.HHJ [Isoflurane](#)

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

2J) Summary: Even though no formal drug interaction studies have been done, [isoflurane](#) should be administered cautiously with other drugs which are also known to prolong the QTc interval, including [fluoxetine](#)[340][341].

3J) Severity: major

4J) Onset: unspecified

5J) Substantiation: theoretical

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

7J) Probable Mechanism: additive effect on QT interval

3.5.1.HIJ [Isradipine](#)

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

2J) Summary: [Isradipine](#) can prolong the QT interval in some patients, which may result in [ventricular tachycardia](#), [ventricular fibrillation](#), and [torsades de pointes](#). Because [fluoxetine](#) may also prolong the QT interval and increase the risk of [arrhythmias](#), the concurrent administration of [isradipine](#) with [fluoxetine](#) is not recommended[386].

3J) Severity: major

4J) Onset: unspecified

5J) Substantiation: theoretical

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

7J) Probable Mechanism: additive cardiac effects

3.5.1.HJ] Ivabradine

1J) Interaction Effect: increased risk of QT prolongation

2J) Summary: Use caution with the concomitant administration of ivabradine and other drugs that prolong the QT interval due to the potential for additive QT prolongation[61].

3J) Severity: major

4J) Onset: unspecified

5J) Substantiation: theoretical

6J) Clinical Management: Use caution with the concomitant administration of ivabradine and other drugs that prolong the QT interval due to the potential for additive QT prolongation[61].

7J) Probable Mechanism: additive QT-interval prolongation

3.5.1.HK] Ketoconazole

1J) Interaction Effect: increased risk for QT prolongation

2J) Summary: [Ketoconazole](#) has been shown to prolong the QT interval[122]. Caution is advised when using [ketoconazole](#) together with another agent known to cause QT interval prolongation. Concomitant use of [ketoconazole](#) with this drug may result in additive effects on the QT interval, increasing the risk for serious [ventricular arrhythmias](#), including [torsades de pointes](#).

3J) Severity: major

4J) Onset: unspecified

5J) Substantiation: theoretical

6J) Clinical Management: [Ketoconazole](#) has been shown to prolong the QT interval[122]. Caution is advised when using [ketoconazole](#) together with another agent known to cause QT interval prolongation. Concomitant use of [ketoconazole](#) with this drug may result in additive effects on the QT interval, increasing the risk for serious [ventricular arrhythmias](#), including [torsades de pointes](#).

7J) Probable Mechanism: additive QT-interval prolongation

3.5.1.HL] Ketoprofen

1J) Interaction Effect: an increased risk of bleeding

2J) Summary: Caution is recommended with the concomitant use of NSAIDs and antidepressants, including SSRIs due to an increased risk of [intracranial hemorrhage](#)[529] and [gastrointestinal bleeding](#) [533][534][530][531]. Bleeding events have included [epistaxis](#), ecchymosis, [hematoma](#), [petechiae](#), and life-threatening hemorrhages [536][535][537][538]. When an SSRI and an NSAID are given concurrently, monitor the patient for signs of increased bleeding.

3J) Severity: major

4J) Onset: unspecified

5J) Substantiation: established

6J) Clinical Management: Use caution if NSAIDs and SSRIs are coadministered. Concomitant use of NSAIDs and SSRIs may cause an increased risk of [intracranial hemorrhage](#)[529] and [gastrointestinal bleeding](#) [530][531]. When an SSRI and an NSAID are given concurrently, monitor the patient for signs of increased bleeding.

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

8J) Literature Reports

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

use alone. There was no significant difference between the antidepressant drug classes and the increased risk; however, there was an increased risk associated with male patients compared with female patients [529].

b)) SSRIs increase the risk of upper gastrointestinal (GI) bleeding, and this effect is potentiated by concurrent use of NSAIDs or low-dose [aspirin](#). Hospitalizations for [upper GI bleeding](#) were searched among 26,005 users of antidepressant medications and compared with the number of hospitalizations in those patients who did not receive prescriptions for antidepressants. The amount of [upper GI bleeding](#) episodes was 3.6 times more than expected. Combined use of an SSRI and NSAIDs or low-dose [aspirin](#) increased the risk to 12.2 and 5.2 times, respectively. The findings of this study demonstrate an increased risk of [upper GI bleeding](#) during the use of SSRIs. Combined use of SSRIs and NSAIDs or low-dose [aspirin](#) increased the risk even further [532].

c)) Two metaanalyses of incidents of upper GI bleed due to SSRIs, NSAIDs, and their combination found that SSRIs increased the risk by 1.73 [533] to 2.36 times [534], NSAIDs by 2.55 times [533], and the combination of SSRIs and NSAIDs by 4.02 [533] to 6.33 times [534].

d)) The release of serotonin by [platelets](#) is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs and NSAIDs have been associated with an increased risk of bleeding [535].

3.5.1.HM] Ketorolac

1)) Interaction Effect: an increased risk of bleeding

2)) Summary: Caution is recommended with the concomitant use of NSAIDs and antidepressants, including SSRIs due to an increased risk of [intracranial hemorrhage](#)[529] and [gastrointestinal bleeding](#) [533][534][530][531]. Bleeding events have included [epistaxis](#), ecchymosis, [hematoma](#), [petechiae](#), and life-threatening hemorrhages [536][535][537][538]. When an SSRI and an NSAID are given concurrently, monitor the patient for signs of increased bleeding.

3)) Severity: major

4)) Onset: unspecified

5)) Substantiation: established

6)) Clinical Management: Use caution if NSAIDs and SSRIs are coadministered. Concomitant use of NSAIDs and SSRIs may cause an increased risk of [intracranial hemorrhage](#)[529] and [gastrointestinal bleeding](#) [530][531]. When an SSRI and an NSAID are given concurrently, monitor the patient for signs of increased bleeding.

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

8)) Literature Reports

a)) Concomitant use of NSAIDs and antidepressants, including tricyclic antidepressants, SSRIs, serotonin-norepinephrine reuptake inhibitors, and MAOIs, resulted in a 60% increased risk of [intracranial hemorrhage](#) within 30 days of concomitant use compared with antidepressant use alone. There was no significant difference between the antidepressant drug classes and the increased risk; however, there was an increased risk associated with male patients compared with female patients [529].

b)) SSRIs increase the risk of upper gastrointestinal (GI) bleeding, and this effect is potentiated by concurrent use of NSAIDs or low-dose [aspirin](#). Hospitalizations for [upper GI bleeding](#) were searched among 26,005 users of antidepressant medications and compared with the number of hospitalizations in those patients who did not receive prescriptions for antidepressants. The amount of [upper GI bleeding](#) episodes was 3.6 times more than expected. Combined use of an

SSRI and NSAIDs or low-dose [aspirin](#) increased the risk to 12.2 and 5.2 times, respectively. The findings of this study demonstrate an increased risk of [upper GI bleeding](#) during the use of SSRIs. Combined use of SSRIs and NSAIDs or low-dose [aspirin](#) increased the risk even further [532].

c) Two metaanalyses of incidents of upper GI bleed due to SSRIs, NSAIDs, and their combination found that SSRIs increased the risk by 1.73 [533] to 2.36 times [534], NSAIDs by 2.55 times [533], and the combination of SSRIs and NSAIDs by 4.02 [533] to 6.33 times [534].

d) The release of serotonin by [platelets](#) is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs and NSAIDs have been associated with an increased risk of bleeding [535].

3.5.1.HN] [Lepirudin](#)

- 1) Interaction Effect: increased risk of bleeding
- 2) Summary: Exercise caution when coadministering a SSRI and an antiplatelet agent or anticoagulant as this may increase the risk of bleeding events[272][173][385].
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Use caution with concomitant use of [fluoxetine](#) with anticoagulants or antiplatelet agents, as coadministration may increase bleeding risk[272][173][385].
- 7) Probable Mechanism: altered anticoagulant effects
- 8) Literature Reports

a) In a retrospective study of patients over 50 years of age with the diagnosis of acute [myocardial infarction](#) (N=27,058), SSRI use with any antiplatelet therapy significantly increased the risk of bleeding by 1.42-fold compared with [aspirin](#) use alone. Therapy with [aspirin](#), [clopidogrel](#), and an SSRI significantly increased risk by 2.35-fold compared with [aspirin](#) use alone and by 1.57-fold compared with [clopidogrel](#) and [aspirin](#) combination therapy [385].

b) In a systematic review and meta-analysis of 22 observational studies, SSRI use was associated with a significant 1.55 fold increase in risk of [upper gastrointestinal bleeding](#) (UGIB). Concomitant use of SSRIs and antiplatelet drugs was associated with a 2.48-fold increase in risk of UGIB (3 studies) [272].

3.5.1.HO] [Leuprolide](#)

- 1) Interaction Effect: increased risk of QT-interval prolongation
- 2) Summary: Use caution with coadministration of gonadotropin-releasing hormone (GnRH) agonists with QT-interval prolonging drugs. Androgen deprivation caused by GnRH agonists may prolong the QT interval and cause additive effects when administered with QT-interval prolonging drugs[141][142][143]. If concurrent therapy is necessary, monitor patients closely for signs and symptoms of [cardiac toxicity](#), including changes in the ECG.
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Use caution with coadministration of gonadotropin-releasing hormone (GnRH) agonists with QT-interval prolonging drugs, as additive effects on the QT interval may occur[141][142][143].
- 7) Probable Mechanism: additive effects on the QT interval

3.5.1.HP] Levodopa

- 1) Interaction Effect: decreased [levodopa](#) effectiveness
- 2) Summary: Concurrent use of [olanzapine](#) may antagonize the pharmacological effects of [levodopa](#)[107]. The clinical significance of this interaction is unknown.
- 3) Severity: moderate
- 4) Onset: rapid
- 5) Substantiation: theoretical
- 6) Clinical Management: Monitor patients for [levodopa](#) efficacy.
- 7) Probable Mechanism: pharmacological antagonism

3.5.1.HQ] Levofloxacin

- 1) Interaction Effect: increased risk of QT interval prolongation
- 2) Summary: The concomitant use of [levofloxacin](#) together with another agent known to cause QT-interval prolongation should be avoided. Concomitant use may result in additive effects on the QT interval and increase the risk of cardiac adverse events, including [arrhythmia](#) and [torsade de pointes](#). The elderly and patients with risk factors for [torsade de pointes](#) (known QT prolongation, uncorrected hypokalemia) may be more susceptible to QT interval effects[171].
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: The concomitant use of [levofloxacin](#) together with another agent known to cause QT-interval prolongation should be avoided. Concomitant use may result in additive effects on the QT interval and increase the risk of cardiac adverse events, including [arrhythmia](#) and [torsade de pointes](#). The elderly and patients with risk factors for [torsade de pointes](#) (known QT prolongation, uncorrected hypokalemia) may be more susceptible to QT interval effects[171].
- 7) Probable Mechanism: additive effects on QT interval

3.5.1.HR] Levomethadyl

- 1) Interaction Effect: an increased risk of [cardiotoxicity](#) (QT prolongation, [torsades de pointes](#), [cardiac arrest](#))
- 2) Summary: Any drug known to have the potential to prolong the QT interval should not be used with levomethadyl. Possible pharmacodynamic interactions can occur between levomethadyl and potentially arrhythmogenic agents such as [olanzapine](#) that prolong the QT interval[150].
- 3) Severity: contraindicated
- 4) Onset: delayed
- 5) Substantiation: theoretical
- 6) Clinical Management: Levomethadyl is contraindicated in patients being treated with [olanzapine](#) as it may precipitate QT prolongation and interact with levomethadyl.
- 7) Probable Mechanism: additive cardiac effects

3.5.1.HS] Levomethadyl

- 1) Interaction Effect: an increased risk of [cardiotoxicity](#) (QT prolongation, [torsades de pointes](#), [cardiac arrest](#))
- 2) Summary: Any drug known to have the potential to prolong the QT interval should not be used with levomethadyl. Possible pharmacodynamic interactions can occur between levomethadyl and potentially arrhythmogenic agents such as [fluoxetine](#) that prolong the QT interval[282].

- 3) Severity: contraindicated
- 4) Onset: delayed
- 5) Substantiation: theoretical
- 6) Clinical Management: Levomethadyl is contraindicated in patients being treated with fluoxetine as it may precipitate QT prolongation and interact with levomethadyl.
- 7) Probable Mechanism: unknown

3.5.1.HT] 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[577].
- 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[577].
- 7) Probable Mechanism: additive serotonergic effects

3.5.1.HU] Levothyroxine

- 1) Interaction Effect: increased levothyroxine requirements
- 2) Summary: Use caution with coadministration of levothyroxine and an SSRI. In patients stabilized on levothyroxine, administration of sertraline, for example, may require an increase in levothyroxine dose[549].
- 3) Severity: moderate
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Use caution with coadministration of levothyroxine and an SSRI. In patients stabilized on levothyroxine, administration of sertraline, for example, may require an increase in levothyroxine dose[549].
- 7) Probable Mechanism: unknown

3.5.1.HV] Lidoflazine

- 1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
- 2) Summary: Lidoflazine and fluoxetine have been shown to prolong the QTc interval at the recommended therapeutic dose[543][544]. Even though no formal drug interaction studies have been done, the coadministration of drugs known to prolong the QTc interval is not recommended.
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical

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

7) Probable Mechanism: additive effects on QT prolongation

3.5.1.HW] Linezolid

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

2) Summary: Concurrent use of fluoxetine and an MAOI, such as linezolid, is contraindicated. If urgent treatment with linezolid is necessary in a patient receiving fluoxetine, alternatives are not available, and risk/benefit has been evaluated, promptly discontinue fluoxetine and then linezolid may be administered. Monitor for serotonin syndrome for 5 weeks or until 24 hours after the last dose of linezolid, whichever comes first. Treatment with fluoxetine can be resumed 24 hours after the last dose of linezolid[283].

3) Severity: contraindicated

4) Onset: unspecified

5) Substantiation: probable

6) Clinical Management: Concurrent use of fluoxetine and an MAOI, such as linezolid, is contraindicated. If urgent treatment with linezolid is necessary in a patient receiving fluoxetine, alternatives are not available, and risk/benefit has been evaluated, promptly discontinue fluoxetine and then linezolid may be administered. Monitor for serotonin syndrome for 5 weeks or until 24 hours after the last linezolid dose, whichever comes first. Fluoxetine can be resumed 24 hours after the last linezolid dose[283].

7) Probable Mechanism: additive serotonergic effects

8) Literature Reports

a) A 4-year-old girl, weighing 12.8 kg, experienced serotonin syndrome-like symptoms following concomitant use of linezolid and fluoxetine. Eleven days after receiving fluoxetine 5 mg daily for acute stress disorder in response to a burn injury, the patient received oral linezolid 140 mg every 12 hours. Two days later, she was premedicated with oral fentanyl 200 mcg prior to a wound debridement procedure. Shortly afterwards, she became agitated and had myoclonus in her arms and legs. She also had mydriasis, was unable to visually track across midline, and her gaze deviated to the lower left quadrant. Discontinuation of fluoxetine and initiation of oral diphenhydramine 25 mg led to partial improvement in symptoms. Subsequently, linezolid was discontinued and replaced with an alternate antibiotic. Symptoms of agitation, myoclonic movements, and nystagmus resolved over the next 2 days [332].

b) The concomitant administration of fluoxetine and linezolid was associated with mild symptoms of serotonin syndrome in a 23-year-old man as described in a case report. The patient, who had recently achieved complete remission of acute myelogenous leukemia and was admitted for maintenance chemotherapy, routinely received treatment with oral fluoxetine 60 mg once daily, oral methadone 75 mg once daily, oral voriconazole 300 mg twice daily, transdermal nicotine patch 21 mg (changed daily), oral lorazepam 2 mg twice daily (with 1 mg doses as needed every 4 hours), and oral quetiapine 200 mg every evening. On day 9 of admission, the fluoxetine dose was increased to 80 mg daily for mood instability, and linezolid 600 mg every 12 hours was initiated on day 43. Within 12 hours of initiating linezolid, the patient experienced physical discomfort and severe abdominal pain (described as feeling like a "runner's cramp" and making it "difficult to breathe"). The discomfort continued following another 4 doses of linezolid over the next day. On day 47, linezolid was discontinued, after a total of 6 linezolid doses, and the pain and other symptoms resolved within 48 hours. During linezolid therapy, vital signs and laboratory results were unremarkable, except for chemotherapy-induced neutropenia, thrombocytopenia, and anemia [333].

c) A retrospective chart review identified one highly probable case of [serotonin syndrome](#) in a patient who received concomitant therapy with [linezolid](#) and [venlafaxine](#), followed by [citalopram](#). Charts of 72 inpatients who received [linezolid](#) and an SSRI or [venlafaxine](#) within 14 days of each other were reviewed for a diagnosis of [serotonin syndrome](#) (SS) using the Sternbach and the Hunter serotonin toxicity criteria. Of these patients, 52 (72%) were treated concomitantly with [linezolid](#) and an SSRI or [venlafaxine](#). Four patients met the criteria for having either high or low probability of SS. Of these, one case involved an 81-year-old woman who was determined to have a high probability of SS after receiving concomitant [linezolid](#) and [venlafaxine](#) followed by [citalopram](#). [Linezolid](#) was given for a vancomycin-resistant Enterococcus UTI. When the patient presented, she refused to eat, was confused as to time and place, and began shouting. Although she appeared to have met 6 of the Sternbach criteria and 4 of the Hunter criteria for SS, a diagnosis of SS was not documented in her chart. Her blood pressure was 180 mmHg with a heart rate of 120 beats/min and a respiratory rate of 50 breaths/min. The following day, she barely spoke and could not be aroused; additional symptoms included lethargy, extremity twitching and jerking, eyes rolled back in her head, and labored breathing. [Linezolid](#) was discontinued, and she was sedated and intubated. Five days following onset of symptoms and 2 days after [linezolid](#) was stopped, she was extubated and had returned to baseline mental status with the ability to communicate [334].

d) In one case report, a 39-year-old woman experienced symptoms of [serotonin syndrome](#) after concomitant treatment with [fluoxetine](#) and [linezolid](#). She was admitted to the emergency room after being found unresponsive at home. This patient had a history of depression, suicide attempts and alcohol dependency. Before admission, her medications consisted of [disulfiram](#), [fluoxetine](#), [buspirone](#), [cyclobenzaprine](#), and folate. All medications were discontinued upon admission. The patient was given 2 doses of [physostigmine](#) for anticholinergic symptoms believed to be caused by a [cyclobenzaprine](#) overdose. Two days after admission, the patient became sedated, developed [tachycardia](#), and had sporadic agitation presumably due to alcohol withdrawal. She was given [lorazepam](#) and [haloperidol](#) for the alcohol withdrawal and agitation. On day 5, she was intubated for [respiratory depression](#) thought to be from either [pneumonia](#) or respiratory suppression from [lorazepam](#). The patient received [vancomycin](#) for MRSA (sputum) and on day 13, was extubated and her mental status improved. On day 18, [vancomycin](#) was changed to [linezolid](#). Immediate changes in her mental status were apparent. She experienced convulsions, tremors, weakness, and perspiration. After 2 doses of [linezolid](#), the patient had a temperature of 98 degrees, blood pressure of 140/90 mmHg, a heart rate of 170, and respirations of 18. [Linezolid](#) was discontinued and the [vancomycin](#) regimen restarted. The patient was diagnosed with benzodiazepine withdrawal, neuroleptic syndrome, sepsis, [meningitis](#), and [serotonin syndrome](#). [Serotonin syndrome](#) was diagnosed as a likely drug interaction between [linezolid](#) and [fluoxetine](#) [335].

3.5.1.HX] 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[528].
- 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[528].

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

3.5.1.HY] [Lithium](#)

1) Interaction Effect: weakness, [dyskinesias](#), increased extrapyramidal symptoms, [encephalopathy](#), and brain damage

2) Summary: An encephalopathic syndrome followed by irreversible brain damage has occurred in a few patients treated with [lithium](#) plus a [DOPamine-2](#) antagonist, particularly [haloperidol](#). A causal relationship between these events and the concomitant administration of a [DOPamine-2](#) antagonist and [lithium](#) has not been established[163]. Coadministration of [lithium](#) and a number of antipsychotic drugs has caused a wide variety of encephalopathic symptoms, brain damage, extrapyramidal symptoms, and [dyskinesias](#) in isolated case reports. In most cases, these effects have occurred with therapeutic [lithium](#) levels [164][165][166]. However, many series and trials have reported using such combinations with no severe adverse consequences [167]. The mechanism is not fully understood, but chronic [lithium](#) treatment decreases neostriatal DOPaminergic activity, probably through a direct action on the G protein and the capacity of the G proteins, once activated, to stimulate adenylyl cyclase [168]. Hyperglycemic reactions have also occurred during combined phenothiazine and [lithium](#) use [169].

3) Severity: major

4) Onset: delayed

5) Substantiation: probable

6) Clinical Management: Monitor patients closely for any signs of toxicity or extrapyramidal symptoms, especially if high doses of [DOPamine-2](#) antagonists, particularly [haloperidol](#), and [lithium](#) are used. Serum [lithium](#) levels should be monitored periodically. Some clinicians advocate maintaining levels in the low therapeutic range.

7) Probable Mechanism: unknown

8) Literature Reports

a) Concomitant [haloperidol](#) and [lithium](#) therapy has resulted in symptoms of [encephalopathy](#), confusion, extrapyramidal symptoms, and fever in several patients with mania [152][153][154]. Irreversible [neurological injuries](#) have been reported [155][156].

b) Seizures, [encephalopathy](#), [delirium](#), and abnormal EEG occurred in four patients during combined [lithium](#) and [thioridazine](#) therapy [157]. Serum [lithium](#) levels were below 1 mEq/L at the time of the toxic reaction in all cases. All patients had previously tolerated [lithium](#) in combination with another phenothiazine. Three of these patients developed symptoms within eight days of initiating combination therapy.

c) The addition of [lithium](#) to [neuroleptic therapy](#) exacerbated extrapyramidal symptoms (EPS) in a small study [158]. The patients had received at least five days of treatment with either oral [thiothixene](#), [haloperidol](#), or [fluphenazine](#) in mean doses of 607.5 [chlorpromazine](#) equivalents prior to initiation of the [lithium](#) and were experiencing drug-induced extrapyramidal symptoms. Oral [lithium](#) was added when clinically indicated in sufficient doses to achieve a therapeutic serum

concentration. The maximum levels attained were 0.65 to 1.27 mEq/L. The EPS ratings increased in all ten patients following the addition of **lithium**. However, only three patients developed marked symptoms and no patient developed **lithium** toxicity. Significantly increased symptoms included gait, shoulder shaking, elbow rigidity, and tremor.

d) Ten patients treated with **clozapine** and **lithium** were studied [159]. Of the ten patients, four experienced significant neurologic effects, including jerking of limbs, **facial spasms** and tics, tremor of hands and arms, tongue twitching, and stumbling gait. One of these also experienced **delirium**. These effects reversed when **lithium** was discontinued or given at a lower dose. On rechallenge, one of two patients suffered recurrence of symptoms. By keeping serum **lithium** no greater than 0.5 mEq/L, **clozapine** could be safely coadministered.

e) **Chlorpromazine** serum levels can be significantly reduced in the presence of **lithium** treatment. If used concurrently, abrupt cessation of **lithium** may result in rebound elevation of **chlorpromazine** levels, resulting in **chlorpromazine** toxicity. In patients on a lithium-chlorpromazine combination, abrupt withdrawal of the **lithium** may precipitate **chlorpromazine cardiotoxicity**. In this report, such toxicity was manifested as sudden **ventricular fibrillation** associated with prolongation of the QTc interval. Hypotension and EPS are also possible in this situation [160].

f) However, other data do not support that such adverse events are frequent or indeed causally related to combination therapy. Combination of **DOPamine** antagonist antipsychotic drugs and **lithium** have been used successfully in many patients with **manic-depressive illness**. It has been proposed that the interaction may only become significant with very high doses of one or both drugs or with failure to discontinue dosing in the presence of toxic symptoms [161].

g) A 69-year-old patient with oxygen-dependent **chronic obstructive pulmonary disorder** and a 25-year history of **bipolar disorder** was started on **risperidone** 3 mg for the treatment of new-onset auditory and visual hallucinations. She had also been maintained on a regimen of **lithium** (450 mg daily) for more than 10 years. In addition, she was given **amantadine** (100 mg twice daily) for tremor. Three weeks after the start of **risperidone**, the patient experienced a decline in mental status in addition to dizziness, worsening tremors, nausea and vomiting, polyuria, depression, and visual and auditory hallucinations. She was then admitted to the hospital for **delirium**. Her **lithium** serum level was 1.36 mEq/L at the time of the admission. All medications were discontinued. Although her **lithium** level decreased to 0.41 mEq/L, she continued to experience profound **delirium**, tremors, lethargy, and hallucinations for almost one week. After she started to respond to commands, she was restarted on **lithium** (300 mg at bedtime) because of the onset of mild **hypomania**. Five days later, she was discharged with a regimen of **lithium** and low-dose **lorazepam** for treatment of insomnia. It is suggested that **delirium** could have been caused by the concurrent use of **lithium** and **risperidone**. Other factors could also have caused **delirium**, such as the patient's serum **lithium** level and the underlying **pulmonary pathology**. In addition, **amantadine**, which facilitates the release of presynaptic **DOPamine** and has a mild anticholinergic effect, may have contributed [162].

3.5.1.HZ] **Lithium**

1) Interaction Effect: possible increased **lithium** concentrations and/or an increased risk of SSRI-related **serotonin syndrome** (**hypertension**, **hyperthermia**, myoclonus, mental status changes)

2) Summary: Concomitant use of **lithium** and various SSRIs has been associated with enhanced side effects of either or both drugs, and with or without elevated **lithium** levels. The combination has resulted in **neurotoxicity** and increased **lithium** levels in one case report[483]. Signs and symptoms of **lithium** toxicity and **serotonin syndrome** have also been reported in patients who demonstrated therapeutic serum

lithium levels while on concurrent **fluoxetine** and **lithium** [484][485]. Two studies have failed to identify a pharmacokinetic interaction between **lithium** and **citalopram** [486][487]. Combined administration of **citalopram** (40 mg daily for 10 days) and **lithium** (30 mmol/day for 5 days) had no significant effect on the pharmacokinetics of **citalopram** or **lithium**. However, plasma **lithium** levels should be monitored with appropriate adjustment to the **lithium** dose in accordance with standard clinical practice. **Lithium** may enhance the serotonergic effects of **citalopram**, therefore caution should be exercised when **citalopram** and **lithium** are coadministered [488]. Concurrent use of **fluvoxamine** and **lithium** has led to case reports of increased **lithium** levels and **neurotoxicity**, **serotonin syndrome**, somnolence, and mania [483][489][490][491]. No pharmacokinetic interference was apparent during a multiple-dose study of coadministered **lithium** and **paroxetine** [492]. If these two agents are to be given concomitantly, the manufacturer suggests that caution be used until more clinical experience is available. Drug interactions leading to **lithium** toxicity have been reported when **lithium** was coadministered with **fluoxetine** and **fluvoxamine** (both in the same pharmacological class as **paroxetine**, eg, selective serotonin reuptake inhibitors) [489][483].

3) Severity: moderate

4) Onset: delayed

5) Substantiation: established

6) Clinical Management: Monitor patients on concurrent **lithium** and selective serotonin reuptake inhibitor therapy for increased plasma concentrations of **lithium**. In addition, monitor patients for signs and symptoms associated with **serotonin syndrome** (**hypertension**, **hyperthermia**, myoclonus, mental status changes).

7) Probable Mechanism: unknown

8) Literature Reports

a) Concomitant administration of oral **lithium** carbonate and oral **fluoxetine** resulted in increased **lithium** serum levels with **lithium** toxicity in a 44-year-old woman with a **bipolar affective disorder** [475]. **Fluoxetine** 20 mg daily was added to a regimen of **lithium** 1200 mg daily following patient complaints of weakness, tiredness, decreased concentration, and early morning awakening. **Lithium** serum levels increased to 1.7 mEq/L from a range of 0.75 to 1.15 mEq/L prior to **fluoxetine**. **Fluoxetine** was discontinued and the dose of **lithium** decreased; this resulted in a decrease in the **lithium** serum level within 48 hours to 1.2 mEq/L. The neurologic symptoms subsided within seven days as the **lithium** serum level decreased to 0.9 mEq/L. The contribution of **fluoxetine** to **lithium** toxicity in this patient was obscured by the fact that the **lithium** was reduced at the time of **fluoxetine** withdrawal.

b) A 53-year old woman who had been taking **fluoxetine** 20 mg daily and **lorazepam** 0.5 mg four times daily for a **major depressive disorder** had **lithium** 900 mg per day added to her **regimen in order** to augment her response to **fluoxetine**. Within 48 hours, the patient became confused, ataxic, and developed a coarse tremor in her right arm. Vital signs showed a rectal temperature of 101 degrees F, and laboratory values were normal except for an elevated **leukocyte** count and slightly elevated **bilirubin** level. After discontinuation of **lithium** and **fluoxetine**, the patient's symptoms resolved over the next four days. At no point did the **lithium** levels reach a toxic level, suggesting that the patient's symptoms were due to a toxic reaction between **fluoxetine** and **lithium** [476].

c) **Serotonin syndrome** was precipitated when **lithium** 300 mg twice daily was added to a three-month regimen of **fluoxetine** 40 mg per day. Five days later, the patient's **lithium** level was measured at 0.65 mEq/L and the dose was increased to 300 mg three times daily. Two days after this dosage change, the patient experienced **akathisia**, myoclonus, hyperreflexia, shivering, tremor, diarrhea, and incoordination. After discontinuation of **lithium** and initiation of **cyproheptadine** therapy, the patient's symptoms began to improve. The patient was discharged on a regimen of **fluoxetine** 40 mg per day without further symptoms of **serotonin syndrome** [477].

d) Eight healthy male volunteers completed three phases of an interaction study to determine the effects of coadministered [lithium](#) and [citalopram](#). All subjects were extensive metabolizers of sparteine, indicating normal cytochrome P450 2D6 enzyme activity. Although [lithium](#) is not influenced by drug oxidation, [citalopram](#) metabolites are excreted by the kidney, as is [lithium](#). Each subject received [citalopram](#) 40 mg alone as a single daily dose for 10 days, [lithium](#) 30 mmol (1980 mg) alone daily for five days, and [lithium](#) coadministered with [citalopram](#) on days 3-7. At least two weeks separated each treatment phase. Results showed that the concurrent administration of [citalopram](#) and [lithium](#) did not significantly alter the pharmacokinetics of [lithium](#) [478].

e) Twenty-four patients experiencing depression (DSM III criteria) were randomized under double-blind conditions to receive [citalopram](#) (40 mg to 60 mg daily) and [lithium](#) carbonate (800 mg daily) or placebo. All of the subjects had failed to respond to four weeks of [citalopram](#) monotherapy. [Lithium](#) was coadministered on days 29 to 42. No evidence of a pharmacokinetic interaction between [lithium](#) and [citalopram](#) was noted, and [cotherapy](#) was well tolerated [479].

f) [Serotonin syndrome](#) was described in a 53-year-old patient who was stabilized on [lithium](#) 1400 mg daily (serum level 0.71 mmol/L) and was given [fluvoxamine](#) 50 mg daily. Over a 10-day period the [fluvoxamine](#) dose was increased to 200 mg daily; tremor and difficulty with fine hand movements developed. After two weeks, tremor, impaired motor function coordination, marked bilateral hyperreflexia of biceps and knee jerks, and clonus in both ankles were seen. After 12 weeks of continued therapy, during which time no further deterioration occurred, [nortriptyline](#) 100 mg daily replaced [fluvoxamine](#), and the neuromuscular symptoms abated over a 2-week period. After four weeks the patient's neurological exam was normal [480].

g) Three cases of mania were reported in patients who were treated with [lithium](#) and [fluvoxamine](#). The mania appeared 10 days, four weeks, and five weeks, respectively, after [cotherapy](#) was begun. [Fluvoxamine](#) was discontinued and, in two of the three patients, the mania resolved, and successful treatment of depression occurred with [lithium](#) alone. The third patient improved, but depression reappeared within a month of [fluvoxamine](#) discontinuation [481].

h) In an open-labeled, placebo-controlled study, [lithium](#) 600 mg was administered to 16 subjects orally twice daily on days one through eight and once in the morning on day nine. In addition, oral [sertraline](#) 100 mg or placebo was given twice, ten hours and two hours prior to [lithium](#) dosing on day nine. The steady-state [lithium](#) level was only decreased by 1.4% (0.01 mEq/L) and the [lithium](#) renal clearance increased by 6.9% (0.11 L/hour) when [sertraline](#) was coadministered. Seven subjects experienced side effects, mainly tremors, after receiving [lithium](#) and [sertraline](#), whereas no subjects who ingested placebo and [lithium](#) experienced side effects [482].

3.5.1.1A) Lofepramine

1) Interaction Effect: increased risk of tricyclic antidepressant toxicity, QT prolongation and [serotonin syndrome](#)

2) Summary: [Fluoxetine](#), a potent CYP2D6 inhibitor, is associated with an increased risk of [serotonin syndrome](#), QT prolongation, and [ventricular arrhythmias](#) (including [torsade de pointes](#)). Concomitant therapy with CYP2D6-metabolized tricyclic antidepressants (TCAs) may potentiate these risks and introduce TCA toxicity[173]; concurrent use of [fluoxetine](#) and [desipramine](#), [nortriptyline](#), and [imipramine](#) has resulted in significant increases in TCA concentrations [517][523][524][525][526][527]. Use caution with concurrent administration of [fluoxetine](#) and TCAs. If [fluoxetine](#) is added to an existing TCA regimen, consider TCA dose reduction. If [fluoxetine](#) and a TCA are coadministered or [fluoxetine](#) has been recently

discontinued, consider plasma TCA monitoring. If [serotonin syndrome](#) occurs, immediately discontinue [fluoxetine](#) and TCA. If [ventricular arrhythmias](#) develop, consider [fluoxetine](#) discontinuation and cardiac evaluation [173].

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Use caution with concurrent administration of [fluoxetine](#) and TCAs, as elevated TCA plasma concentrations may occur. If [fluoxetine](#) is added to an existing TCA regimen, consider TCA dose reduction. If [fluoxetine](#) and a TCA are coadministered or [fluoxetine](#) has been recently discontinued, consider plasma TCA monitoring. If [serotonin syndrome](#) occurs, immediately discontinue [fluoxetine](#) and TCA. If [ventricular arrhythmias](#) develop, consider [fluoxetine](#) discontinuation and cardiac evaluation[173]

7) Probable Mechanism: decreased CYP2D6-mediated metabolism of tricyclic antidepressants by [fluoxetine](#); additive effects on QT prolongation; additive serotonergic effects

8) Literature Reports

a) Previously stable plasma levels of [imipramine](#) and [desipramine](#) rose more than 2- to 10-fold with [fluoxetine](#) coadministration in 2 clinical studies. This effect may persist for 3 weeks or more after [fluoxetine](#) discontinuation. Dose reduction and temporary monitoring of tricyclic antidepressant plasma concentrations may be indicated with concurrent [fluoxetine](#) treatment or recent [fluoxetine](#) discontinuation [173].

b) [Fluoxetine](#) statistically and clinically significantly increased [desipramine](#) concentrations in 18 healthy subjects. When [fluoxetine](#) (20 mg daily) was added to [desipramine](#) (50 mg daily), the mean maximum concentration of [desipramine](#) increased by 278% and the AUC increased by 342%. [Desipramine](#) trough concentrations continued to be 198% above baseline 3 weeks after [fluoxetine](#) was discontinued. The same study compared pharmacokinetics of [desipramine](#) when combined with [sertraline](#). The impact of [sertraline](#) was modest, resulting in small and short-term increases in [desipramine](#) plasma concentrations [517].

c) Concomitant administration of [fluoxetine](#) and [desipramine](#) was reported to result in an increased [desipramine](#) level and new onset of [delirium](#) in a 69-year-old male within 10 days of the addition of [fluoxetine](#) to the patient's regimen [518].

d) [Fluoxetine](#) increased the level of tricyclic antidepressants ([nortriptyline](#), [imipramine](#), [desipramine](#)) in 4 patients. After the addition of [fluoxetine](#), the ratio of antidepressant level to dose increased by 109% to 486% in the patients. Three patients developed clinical symptoms (anticholinergic effects, constipation, urinary hesitancy, sedation, unstable gait) as a result of the increased levels [519].

e) A 39-year-old female experienced symptomatic increases in her [desipramine](#) levels with concomitant [fluoxetine](#) therapy. Prior to [fluoxetine](#) therapy, the patient's measured levels of [desipramine](#) had ranged from 148 to 160 nanograms/milliliter (ng/mL; 556 to 601 nanomol/L) on a regimen of 300 mg daily. Five weeks after the addition of [fluoxetine](#) 20 mg daily, she reported anticholinergic symptoms, sedation, and confusion with a [desipramine](#) level of 527 ng/mL (1978 nanomol/L). The [desipramine](#) dose was lowered to 200 mg/day; 11 days later, the level was 244 ng/mL (916 nanomol/L); the patient reported decreased energy, impaired short-term memory, and some "garbled" speech, as well as an episode of nausea, dizziness, and syncope. The [desipramine](#) dose was reduced to 50 mg/day, and the adverse effects resolved in 6 days. Eight days later, the [desipramine](#) level was 122 ng/mL (458 nanomol/L) [520].

f) A 33-year-old depressed male developed adverse effects of dry mouth, tinnitus, and difficulties with alertness and memory while receiving [fluoxetine](#) 40 mg daily and [desipramine](#) 150 mg daily for 5 weeks; [fluoxetine](#) was discontinued and the blood levels of [desipramine](#) decreased from 938 to 48 nanograms/mL (3521 to 180 nanomol/L) with resolution of clinical symptoms [521].

g) A 75-year-old female experienced symptomatic increases in her [desipramine](#) serum concentrations when [fluoxetine](#) was added. [Desipramine](#) serum levels ranged from 109 to 150 ng/mL (409 to 563 nanomol/L) with oral doses of 300 mg at bedtime prior to [fluoxetine](#) therapy. Following the addition of oral [fluoxetine](#) 20 mg daily to the regimen, the [desipramine](#) serum level increased to 212 ng/mL (796 nanomol/L) within five days. The [fluoxetine](#) dose was increased to 40 mg/day three days later, and the [desipramine](#) serum level was 419 ng/mL (1573 nanomol/L) after four days. A worsening of depression and severe fatigue coincided with the increases in [desipramine](#) serum levels. Withdrawal of [fluoxetine](#) and reduction in the [desipramine](#) dose to 200 mg daily reduced the [desipramine](#) serum level to 231 ng/mL (867 nanomol/L) within two weeks [522].

3.5.1.IB] Lomitapide

1) Interaction Effect: increased exposure of lomitapide

2) Summary: The concomitant use of lomitapide (a CYP3A4 substrate) and a weak CYP3A4 inhibitor may cause increased exposure to lomitapide. When the weak CYP3A4 inhibitor, [atorvastatin](#) was coadministered with lomitapide, the systemic exposure of lomitapide increased by approximately 2-fold. If concurrent use is required, the maximum lomitapide dosage is 30 mg daily. When initiating a weak CYP3A4 inhibitor in patients already taking lomitapide 10 mg/day or more, decrease the lomitapide dose by 50%. Then carefully titrate based on response and tolerability to a maximum of 30 mg/day[212].

3) Severity: moderate

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: The concomitant use of lomitapide (a CYP3A4 substrate) with a weak CYP3A4 inhibitor may cause increased exposure to lomitapide. If concurrent use is required, the maximum lomitapide dosage is 30 mg daily. When initiating a weak CYP3A4 inhibitor in patients already taking lomitapide 10 mg/day or more, decrease the lomitapide dose by 50%. Then carefully titrate based on response and tolerability to a maximum of 30 mg/day[212]

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

8) Literature Reports

a) The concomitant administration of the weak CYP3A4 inhibitor [atorvastatin](#) 80 mg daily with a single 20-mg dose of lomitapide increased the AUC of lomitapide 2-fold and Cmax 2.1-fold compared with lomitapide administered alone [212].

3.5.1.IC] Lorazepam

1) Interaction Effect: potentiation of excessive sedation and cardiorespiratory depression

2) Summary: The concomitant use of intramuscularly administered [olanzapine](#) and parenteral benzodiazepines ([diazepam](#), [lorazepam](#), [midazolam](#)) is not recommended due to the potentiation of excessive sedation and cardiorespiratory depression[68].

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: The concomitant use of intramuscularly administered [olanzapine](#) and parenteral benzodiazepines ([diazepam](#), [lorazepam](#), [midazolam](#)) is not recommended due to additive CNS depression[68].

7) Probable Mechanism: additive CNS depression

3.5.1.ID] Lorcaserin

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

2) Summary: Lorcaserin is a serotonergic drug and concomitant use with another agent that affects the serotonergic neurotransmitter system, such as an SSRI, serotonin-norepinephrine reuptake inhibitor, or tricyclic antidepressant, may result in an increased risk of [serotonin syndrome](#) and should be approached with extreme caution. [Serotonin syndrome](#) may be life threatening and symptoms may include mental status changes (eg, agitation, hallucinations, coma), autonomic instability (eg, [tachycardia](#), labile blood pressure, [hyperthermia](#)), neuromuscular aberrations (eg, hyperreflexia, incoordination), and/or gastrointestinal symptoms (eg, nausea, vomiting, diarrhea). If coadministration is required, monitor closely for signs and symptoms of [serotonin syndrome](#), especially during initiation of the coadministered drug and during dosage increases of either drug. If [serotonin syndrome](#) develops, discontinue both agents and initiate supportive symptomatic therapy[269].

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Use extreme caution with concomitant administration of lorcaserin and another serotonergic drug, such as an SSRI, serotonin-norepinephrine reuptake inhibitor, or tricyclic antidepressant, as this may result in additive serotonergic effects and may increase the risk of [serotonin syndrome](#). If coadministration is required, careful monitoring is recommended, especially during treatment initiation and dose increases. Drug discontinuation and supportive symptomatic treatment is recommended if [serotonin syndrome](#) develops[269].

7) Probable Mechanism: additive serotonergic effects

3.5.1.IE] Lornoxicam

1) Interaction Effect: an increased risk of bleeding

2) Summary: Caution is recommended with the concomitant use of NSAIDs and antidepressants, including SSRIs due to an increased risk of [intracranial hemorrhage](#)[529] and [gastrointestinal bleeding](#) [533][534][530][531]. Bleeding events have included [epistaxis](#), ecchymosis, [hematoma](#), [petechiae](#), and life-threatening hemorrhages [536][535][537][538]. When an SSRI and an NSAID are given concurrently, monitor the patient for signs of increased bleeding.

3) Severity: major

4) Onset: unspecified

5) Substantiation: established

6) Clinical Management: Use caution if NSAIDs and SSRIs are coadministered. Concomitant use of NSAIDs and SSRIs may cause an increased risk of [intracranial hemorrhage](#)[529] and [gastrointestinal bleeding](#) [530][531]. When an SSRI and an NSAID are given concurrently, monitor the patient for signs of increased bleeding.

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

8) Literature Reports

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

use alone. There was no significant difference between the antidepressant drug classes and the increased risk; however, there was an increased risk associated with male patients compared with female patients [529].

b)) SSRIs increase the risk of upper gastrointestinal (GI) bleeding, and this effect is potentiated by concurrent use of NSAIDs or low-dose [aspirin](#). Hospitalizations for [upper GI bleeding](#) were searched among 26,005 users of antidepressant medications and compared with the number of hospitalizations in those patients who did not receive prescriptions for antidepressants. The amount of [upper GI bleeding](#) episodes was 3.6 times more than expected. Combined use of an SSRI and NSAIDs or low-dose [aspirin](#) increased the risk to 12.2 and 5.2 times, respectively. The findings of this study demonstrate an increased risk of [upper GI bleeding](#) during the use of SSRIs. Combined use of SSRIs and NSAIDs or low-dose [aspirin](#) increased the risk even further [532].

c)) Two metaanalyses of incidents of upper GI bleed due to SSRIs, NSAIDs, and their combination found that SSRIs increased the risk by 1.73 [533] to 2.36 times [534], NSAIDs by 2.55 times [533], and the combination of SSRIs and NSAIDs by 4.02 [533] to 6.33 times [534].

d)) The release of serotonin by [platelets](#) is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs and NSAIDs have been associated with an increased risk of bleeding [535].

3.5.1.IF] Loxoprofen

1)) Interaction Effect: an increased risk of bleeding

2)) Summary: Caution is recommended with the concomitant use of NSAIDs and antidepressants, including SSRIs due to an increased risk of [intracranial hemorrhage](#)[529] and [gastrointestinal bleeding](#) [533][534][530][531]. Bleeding events have included [epistaxis](#), ecchymosis, [hematoma](#), [petechiae](#), and life-threatening hemorrhages [536][535][537][538]. When an SSRI and an NSAID are given concurrently, monitor the patient for signs of increased bleeding.

3)) Severity: major

4)) Onset: unspecified

5)) Substantiation: established

6)) Clinical Management: Use caution if NSAIDs and SSRIs are coadministered. Concomitant use of NSAIDs and SSRIs may cause an increased risk of [intracranial hemorrhage](#)[529] and [gastrointestinal bleeding](#) [530][531]. When an SSRI and an NSAID are given concurrently, monitor the patient for signs of increased bleeding.

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

8)) Literature Reports

a)) Concomitant use of NSAIDs and antidepressants, including tricyclic antidepressants, SSRIs, serotonin-norepinephrine reuptake inhibitors, and MAOIs, resulted in a 60% increased risk of [intracranial hemorrhage](#) within 30 days of concomitant use compared with antidepressant use alone. There was no significant difference between the antidepressant drug classes and the increased risk; however, there was an increased risk associated with male patients compared with female patients [529].

b)) SSRIs increase the risk of upper gastrointestinal (GI) bleeding, and this effect is potentiated by concurrent use of NSAIDs or low-dose [aspirin](#). Hospitalizations for [upper GI bleeding](#) were searched among 26,005 users of antidepressant medications and compared with the number of hospitalizations in those patients who did not receive prescriptions for antidepressants. The amount of [upper GI bleeding](#) episodes was 3.6 times more than expected. Combined use of an

SSRI and NSAIDs or low-dose [aspirin](#) increased the risk to 12.2 and 5.2 times, respectively. The findings of this study demonstrate an increased risk of [upper GI bleeding](#) during the use of SSRIs. Combined use of SSRIs and NSAIDs or low-dose [aspirin](#) increased the risk even further [532].

c) Two metaanalyses of incidents of upper GI bleed due to SSRIs, NSAIDs, and their combination found that SSRIs increased the risk by 1.73 [533] to 2.36 times [534], NSAIDs by 2.55 times [533], and the combination of SSRIs and NSAIDs by 4.02 [533] to 6.33 times [534].

d) The release of serotonin by [platelets](#) is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs and NSAIDs have been associated with an increased risk of bleeding [535].

3.5.1.1.G) Lumiracoxib

1) Interaction Effect: an increased risk of bleeding

2) Summary: Caution is recommended with the concomitant use of NSAIDs and antidepressants, including SSRIs due to an increased risk of [intracranial hemorrhage](#)[529] and [gastrointestinal bleeding](#) [533][534][530][531]. Bleeding events have included [epistaxis](#), ecchymosis, [hematoma](#), [petechiae](#), and life-threatening hemorrhages [536][535][537][538]. When an SSRI and an NSAID are given concurrently, monitor the patient for signs of increased bleeding.

3) Severity: major

4) Onset: unspecified

5) Substantiation: established

6) Clinical Management: Use caution if NSAIDs and SSRIs are coadministered. Concomitant use of NSAIDs and SSRIs may cause an increased risk of [intracranial hemorrhage](#)[529] and [gastrointestinal bleeding](#) [530][531]. When an SSRI and an NSAID are given concurrently, monitor the patient for signs of increased bleeding.

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

8) Literature Reports

a) Concomitant use of NSAIDs and antidepressants, including tricyclic antidepressants, SSRIs, serotonin-norepinephrine reuptake inhibitors, and MAOIs, resulted in a 60% increased risk of [intracranial hemorrhage](#) within 30 days of concomitant use compared with antidepressant use alone. There was no significant difference between the antidepressant drug classes and the increased risk; however, there was an increased risk associated with male patients compared with female patients [529].

b) SSRIs increase the risk of upper gastrointestinal (GI) bleeding, and this effect is potentiated by concurrent use of NSAIDs or low-dose [aspirin](#). Hospitalizations for [upper GI bleeding](#) were searched among 26,005 users of antidepressant medications and compared with the number of hospitalizations in those patients who did not receive prescriptions for antidepressants. The amount of [upper GI bleeding](#) episodes was 3.6 times more than expected. Combined use of an SSRI and NSAIDs or low-dose [aspirin](#) increased the risk to 12.2 and 5.2 times, respectively. The findings of this study demonstrate an increased risk of [upper GI bleeding](#) during the use of SSRIs. Combined use of SSRIs and NSAIDs or low-dose [aspirin](#) increased the risk even further [532].

c) Two metaanalyses of incidents of upper GI bleed due to SSRIs, NSAIDs, and their combination found that SSRIs increased the risk by 1.73 [533] to 2.36 times [534], NSAIDs by 2.55 times [533], and the combination of SSRIs and NSAIDs by 4.02 [533] to 6.33 times [534].

d)) The release of serotonin by [platelets](#) is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs and NSAIDs have been associated with an increased risk of bleeding [535].

3.5.1.IH) [Meclizine](#)

- 1)) Interaction Effect: increased [meclizine](#) exposure
- 2)) Summary: CYP2D6 is the primary pathway for [meclizine](#) metabolism in vitro[329][330][331]. Coadministration of [meclizine](#) with certain CYP2D6 inhibitors may result in increased [meclizine](#) exposure and risk of adverse effects. If concomitant use is necessary, use caution and consider monitoring patients for increased [meclizine](#) adverse effects.
- 3)) Severity: moderate
- 4)) Onset: unspecified
- 5)) Substantiation: theoretical
- 6)) Clinical Management: Concomitant use of [meclizine](#), an in vitro CYP2D6 substrate[329][330][331], and certain CYP2D6 inhibitors may result in increased [meclizine](#) exposure and risk of adverse effects. If coadministration is necessary, use caution and consider monitoring patients for increased [meclizine](#) adverse effects.
- 7)) Probable Mechanism: inhibition of CYP2D6-mediated [meclizine](#) metabolism

3.5.1.II) [Meclofenamate](#)

- 1)) Interaction Effect: an increased risk of bleeding
- 2)) Summary: Caution is recommended with the concomitant use of NSAIDs and antidepressants, including SSRIs due to an increased risk of [intracranial hemorrhage](#)[529] and [gastrointestinal bleeding](#) [533][534][530][531]. Bleeding events have included [epistaxis](#), ecchymosis, [hematoma](#), [petechiae](#), and life-threatening hemorrhages [536][535][537][538]. When an SSRI and an NSAID are given concurrently, monitor the patient for signs of increased bleeding.
- 3)) Severity: major
- 4)) Onset: unspecified
- 5)) Substantiation: established
- 6)) Clinical Management: Use caution if NSAIDs and SSRIs are coadministered. Concomitant use of NSAIDs and SSRIs may cause an increased risk of [intracranial hemorrhage](#)[529] and [gastrointestinal bleeding](#) [530][531]. When an SSRI and an NSAID are given concurrently, monitor the patient for signs of increased bleeding.
- 7)) Probable Mechanism: depletion of [platelet](#) serotonin by SSRI; additive effects
- 8)) Literature Reports

a)) Concomitant use of NSAIDs and antidepressants, including tricyclic antidepressants, SSRIs, serotonin-norepinephrine reuptake inhibitors, and MAOIs, resulted in a 60% increased risk of [intracranial hemorrhage](#) within 30 days of concomitant use compared with antidepressant use alone. There was no significant difference between the antidepressant drug classes and the increased risk; however, there was an increased risk associated with male patients compared with female patients [529].

b)) SSRIs increase the risk of upper gastrointestinal (GI) bleeding, and this effect is potentiated by concurrent use of NSAIDs or low-dose [aspirin](#). Hospitalizations for [upper GI bleeding](#) were searched among 26,005 users of antidepressant medications and compared with the number of hospitalizations in those patients who did not receive prescriptions for antidepressants. The amount of [upper GI bleeding](#) episodes was 3.6 times more than expected. Combined use of an

SSRI and NSAIDs or low-dose [aspirin](#) increased the risk to 12.2 and 5.2 times, respectively. The findings of this study demonstrate an increased risk of [upper GI bleeding](#) during the use of SSRIs. Combined use of SSRIs and NSAIDs or low-dose [aspirin](#) increased the risk even further [532].

c) Two metaanalyses of incidents of upper GI bleed due to SSRIs, NSAIDs, and their combination found that SSRIs increased the risk by 1.73 [533] to 2.36 times [534], NSAIDs by 2.55 times [533], and the combination of SSRIs and NSAIDs by 4.02 [533] to 6.33 times [534].

d) The release of serotonin by [platelets](#) is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs and NSAIDs have been associated with an increased risk of bleeding [535].

3.5.1.IJ] Mefenamic Acid

1) Interaction Effect: an increased risk of bleeding

2) Summary: Caution is recommended with the concomitant use of NSAIDs and antidepressants, including SSRIs due to an increased risk of [intracranial hemorrhage](#)[529] and [gastrointestinal bleeding](#) [533][534][530][531]. Bleeding events have included [epistaxis](#), ecchymosis, [hematoma](#), [petechiae](#), and life-threatening hemorrhages [536][535][537][538]. When an SSRI and an NSAID are given concurrently, monitor the patient for signs of increased bleeding.

3) Severity: major

4) Onset: unspecified

5) Substantiation: established

6) Clinical Management: Use caution if NSAIDs and SSRIs are coadministered. Concomitant use of NSAIDs and SSRIs may cause an increased risk of [intracranial hemorrhage](#)[529] and [gastrointestinal bleeding](#) [530][531]. When an SSRI and an NSAID are given concurrently, monitor the patient for signs of increased bleeding.

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

8) Literature Reports

a) Concomitant use of NSAIDs and antidepressants, including tricyclic antidepressants, SSRIs, serotonin-norepinephrine reuptake inhibitors, and MAOIs, resulted in a 60% increased risk of [intracranial hemorrhage](#) within 30 days of concomitant use compared with antidepressant use alone. There was no significant difference between the antidepressant drug classes and the increased risk; however, there was an increased risk associated with male patients compared with female patients [529].

b) SSRIs increase the risk of upper gastrointestinal (GI) bleeding, and this effect is potentiated by concurrent use of NSAIDs or low-dose [aspirin](#). Hospitalizations for [upper GI bleeding](#) were searched among 26,005 users of antidepressant medications and compared with the number of hospitalizations in those patients who did not receive prescriptions for antidepressants. The amount of [upper GI bleeding](#) episodes was 3.6 times more than expected. Combined use of an SSRI and NSAIDs or low-dose [aspirin](#) increased the risk to 12.2 and 5.2 times, respectively. The findings of this study demonstrate an increased risk of [upper GI bleeding](#) during the use of SSRIs. Combined use of SSRIs and NSAIDs or low-dose [aspirin](#) increased the risk even further [532].

c) Two metaanalyses of incidents of upper GI bleed due to SSRIs, NSAIDs, and their combination found that SSRIs increased the risk by 1.73 [533] to 2.36 times [534], NSAIDs by 2.55 times [533], and the combination of SSRIs and NSAIDs by 4.02 [533] to 6.33 times [534].

d)) The release of serotonin by [platelets](#) is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs and NSAIDs have been associated with an increased risk of bleeding [535].

3.5.1.IK] [Mefloquine](#)

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

2)) Summary: [Fluoxetine](#) has been shown to prolong the QTc interval at the recommended therapeutic dose[323]. Even though no formal drug interaction studies have been done, caution is advised if [mefloquine](#) is used with other drugs which can prolong the QTc interval [324].

3)) Severity: major

4)) Onset: unspecified

5)) Substantiation: theoretical

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

7)) Probable Mechanism: additive effects on QT prolongation

3.5.1.IL] [Melitracen](#)

1)) Interaction Effect: increased risk of tricyclic antidepressant toxicity, QT prolongation and [serotonin syndrome](#)

2)) Summary: [Fluoxetine](#), a potent CYP2D6 inhibitor, is associated with an increased risk of [serotonin syndrome](#), QT prolongation, and [ventricular arrhythmias](#) (including [torsade de pointes](#)). Concomitant therapy with CYP2D6-metabolized tricyclic antidepressants (TCAs) may potentiate these risks and introduce TCA toxicity[173]; concurrent use of [fluoxetine](#) and [desipramine](#), [nortriptyline](#), and [imipramine](#) has resulted in significant increases in TCA concentrations [517][523][524][525][526][527]. Use caution with concurrent administration of [fluoxetine](#) and TCAs. If [fluoxetine](#) is added to an existing TCA regimen, consider TCA dose reduction. If [fluoxetine](#) and a TCA are coadministered or [fluoxetine](#) has been recently discontinued, consider plasma TCA monitoring. If [serotonin syndrome](#) occurs, immediately discontinue [fluoxetine](#) and TCA. If [ventricular arrhythmias](#) develop, consider [fluoxetine](#) discontinuation and cardiac evaluation [173].

3)) Severity: major

4)) Onset: unspecified

5)) Substantiation: theoretical

6)) Clinical Management: Use caution with concurrent administration of [fluoxetine](#) and TCAs, as elevated TCA plasma concentrations may occur. If [fluoxetine](#) is added to an existing TCA regimen, consider TCA dose reduction. If [fluoxetine](#) and a TCA are coadministered or [fluoxetine](#) has been recently discontinued, consider plasma TCA monitoring. If [serotonin syndrome](#) occurs, immediately discontinue [fluoxetine](#) and TCA. If [ventricular arrhythmias](#) develop, consider [fluoxetine](#) discontinuation and cardiac evaluation[173]

7)) Probable Mechanism: decreased CYP2D6-mediated metabolism of tricyclic antidepressants by [fluoxetine](#); additive effects on QT prolongation; additive serotonergic effects

8)) Literature Reports

a)) Previously stable plasma levels of [imipramine](#) and [desipramine](#) rose more than 2- to 10-fold with [fluoxetine](#) coadministration in 2 clinical studies. This effect may persist for 3 weeks or more after [fluoxetine](#) discontinuation. Dose reduction and temporary monitoring of tricyclic antidepressant plasma concentrations may be indicated with concurrent [fluoxetine](#) treatment or recent [fluoxetine](#) discontinuation [173].

b) **Fluoxetine** statistically and clinically significantly increased **desipramine** concentrations in 18 healthy subjects. When **fluoxetine** (20 mg daily) was added to **desipramine** (50 mg daily), the mean maximum concentration of **desipramine** increased by 278% and the AUC increased by 342%. **Desipramine** trough concentrations continued to be 198% above baseline 3 weeks after **fluoxetine** was discontinued. The same study compared pharmacokinetics of **desipramine** when combined with **sertraline**. The impact of **sertraline** was modest, resulting in small and short-term increases in **desipramine** plasma concentrations [517].

c) Concomitant administration of **fluoxetine** and **desipramine** was reported to result in an increased **desipramine** level and new onset of **delirium** in a 69-year-old male within 10 days of the addition of **fluoxetine** to the patient's regimen [518].

d) **Fluoxetine** increased the level of tricyclic antidepressants (**nortriptyline**, **imipramine**, **desipramine**) in 4 patients. After the addition of **fluoxetine**, the ratio of antidepressant level to dose increased by 109% to 486% in the patients. Three patients developed clinical symptoms (anticholinergic effects, constipation, urinary hesitancy, sedation, unstable gait) as a result of the increased levels [519].

e) A 39-year-old female experienced symptomatic increases in her **desipramine** levels with concomitant **fluoxetine** therapy. Prior to **fluoxetine** therapy, the patient's measured levels of **desipramine** had ranged from 148 to 160 nanograms/milliliter (ng/mL; 556 to 601 nanomol/L) on a regimen of 300 mg daily. Five weeks after the addition of **fluoxetine** 20 mg daily, she reported anticholinergic symptoms, sedation, and confusion with a **desipramine** level of 527 ng/mL (1978 nanomol/L). The **desipramine** dose was lowered to 200 mg/day; 11 days later, the level was 244 ng/mL (916 nanomol/L); the patient reported decreased energy, impaired short-term memory, and some "garbled" speech, as well as an episode of nausea, dizziness, and syncope. The **desipramine** dose was reduced to 50 mg/day, and the adverse effects resolved in 6 days. Eight days later, the **desipramine** level was 122 ng/mL (458 nanomol/L) [520].

f) A 33-year-old depressed male developed adverse effects of dry mouth, tinnitus, and difficulties with alertness and memory while receiving **fluoxetine** 40 mg daily and **desipramine** 150 mg daily for 5 weeks; **fluoxetine** was discontinued and the blood levels of **desipramine** decreased from 938 to 48 nanograms/mL (3521 to 180 nanomol/L) with resolution of clinical symptoms [521].

g) A 75-year-old female experienced symptomatic increases in her **desipramine** serum concentrations when **fluoxetine** was added. **Desipramine** serum levels ranged from 109 to 150 ng/mL (409 to 563 nanomol/L) with oral doses of 300 mg at bedtime prior to **fluoxetine** therapy. Following the addition of oral **fluoxetine** 20 mg daily to the regimen, the **desipramine** serum level increased to 212 ng/mL (796 nanomol/L) within five days. The **fluoxetine** dose was increased to 40 mg/day three days later, and the **desipramine** serum level was 419 ng/mL (1573 nanomol/L) after four days. A worsening of depression and severe fatigue coincided with the increases in **desipramine** serum levels. Withdrawal of **fluoxetine** and reduction in the **desipramine** dose to 200 mg daily reduced the **desipramine** serum level to 231 ng/mL (867 nanomol/L) within two weeks [522].

3.5.1.IM] **Meloxicam**

1) Interaction Effect: an increased risk of bleeding

2) Summary: Caution is recommended with the concomitant use of NSAIDs and antidepressants, including SSRIs due to an increased risk of **intracranial hemorrhage**[529] and **gastrointestinal bleeding**

[533][534][530][531]. Bleeding events have included [epistaxis](#), ecchymosis, [hematoma](#), [petechiae](#), and life-threatening hemorrhages [536][535][537][538]. When an SSRI and an NSAID are given concurrently, monitor the patient for signs of increased bleeding.

3) Severity: major

4) Onset: unspecified

5) Substantiation: established

6) Clinical Management: Use caution if NSAIDs and SSRIs are coadministered. Concomitant use of NSAIDs and SSRIs may cause an increased risk of [intracranial hemorrhage](#)[529] and [gastrointestinal bleeding](#) [530][531]. When an SSRI and an NSAID are given concurrently, monitor the patient for signs of increased bleeding.

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

8) Literature Reports

a) Concomitant use of NSAIDs and antidepressants, including tricyclic antidepressants, SSRIs, serotonin-norepinephrine reuptake inhibitors, and MAOIs, resulted in a 60% increased risk of [intracranial hemorrhage](#) within 30 days of concomitant use compared with antidepressant use alone. There was no significant difference between the antidepressant drug classes and the increased risk; however, there was an increased risk associated with male patients compared with female patients [529].

b) SSRIs increase the risk of upper gastrointestinal (GI) bleeding, and this effect is potentiated by concurrent use of NSAIDs or low-dose [aspirin](#). Hospitalizations for [upper GI bleeding](#) were searched among 26,005 users of antidepressant medications and compared with the number of hospitalizations in those patients who did not receive prescriptions for antidepressants. The amount of [upper GI bleeding](#) episodes was 3.6 times more than expected. Combined use of an SSRI and NSAIDs or low-dose [aspirin](#) increased the risk to 12.2 and 5.2 times, respectively. The findings of this study demonstrate an increased risk of [upper GI bleeding](#) during the use of SSRIs. Combined use of SSRIs and NSAIDs or low-dose [aspirin](#) increased the risk even further [532].

c) Two metaanalyses of incidents of upper GI bleed due to SSRIs, NSAIDs, and their combination found that SSRIs increased the risk by 1.73 [533] to 2.36 times [534], NSAIDs by 2.55 times [533], and the combination of SSRIs and NSAIDs by 4.02 [533] to 6.33 times [534].

d) The release of serotonin by [platelets](#) is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs and NSAIDs have been associated with an increased risk of bleeding [535].

3.5.1.IN] [Meperidine](#)

1) Interaction Effect: increased risk of CNS depression (ie, [respiratory depression](#), profound sedation, coma)

2) Summary: The concomitant use of [meperidine](#) with other CNS depressants may result in profound sedation, [respiratory depression](#), coma, and/or death. Reserve concomitant use to clinical settings where alternative treatment options are inadequate. If combination therapy is required, reduce the initial dose of the newly prescribed medication and titrate to clinical response while monitoring for [respiratory depression](#) and sedation[78].

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Reserve concomitant use of [meperidine](#) with other CNS depressants to clinical settings where alternative treatment options are inadequate. If combination therapy is required, reduce

the initial dose of the newly prescribed medication and titrate to clinical response while monitoring for [respiratory depression](#) and sedation[78].

7J) Probable Mechanism: additive CNS depression

3.5.1.IOJ [Meperidine](#)

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

2J) Summary: A 43-year-old male on [fluoxetine](#) every other day experienced [serotonin syndrome](#) immediately after intravenous [meperidine](#) was administered[185]. If [fluoxetine](#) and [meperidine](#) are used concomitantly, monitor closely for symptoms of [serotonin syndrome](#). [Serotonin syndrome](#) can be life-threatening. If [serotonin syndrome](#) develops, discontinue the offending agents and provide supportive care and other therapy as necessary [146].

3J) Severity: major

4J) Onset: rapid

5J) Substantiation: probable

6J) Clinical Management: A case of [serotonin syndrome](#) was reported with coadministration of [fluoxetine](#) and [meperidine](#) and therefore, concomitant use is discouraged[185]. If [fluoxetine](#) and [meperidine](#) are used concomitantly, monitor closely for symptoms of [serotonin syndrome](#) such as neuromuscular abnormalities (including hyper-reflexia, tremor, muscle rigidity, clonus, peripheral hypertonicity, and shivering), autonomic hyperactivity (including [tachycardia](#), mydriasis, diaphoresis, the presence of bowel sounds, and diarrhea), and mental status changes (including agitation and [delirium](#)). [Serotonin syndrome](#) can be life-threatening. If [serotonin syndrome](#) develops, discontinue the offending agents and provide supportive care and other therapy as necessary [146].

7J) Probable Mechanism: additive pharmacologic effects

8J) Literature Reports

aJ) A 43-year-old male on [fluoxetine](#) every other day experienced [serotonin syndrome](#) immediately after intravenous [meperidine](#) was administered. His other medications were [rosiglitazone](#) and [fenofibrate](#). His medical history includes [type 2 diabetes](#), [dyslipidemia](#), and recurrent episodes of [pancreatitis](#). Prior to this adverse event he received [meperidine](#) and [midazolam](#), while not on [fluoxetine](#), without any sequela. Before an [endoscopy](#) procedure he was administered intravenous [midazolam](#) and 50 mg of intravenous [meperidine](#). He immediately became agitated and restless. He was unable to follow verbal commands because of confusion. Blood pressure (180/100 mm Hg) and heart rate (130 bpm) increased and [oxygen saturation](#) decreased to 95%. He had diaphoresis and dilated pupils. Within 10 minutes his blood pressure started to decrease. He had an episode of diarrhea. Over the next 10 to 15 minutes, his agitation subsided, he remained sleepy and confused, and blood pressure and heart continued to decrease to baseline. His temperature was 98.4 degrees Fahrenheit. After 60 to 90 minutes his sensorium appeared to clear and diaphoresis resolved. The patient remained afebrile with stable vital signs over the next 24 hours. He was treated with [hydromorphone](#) for abdominal pain without any adverse reaction. Several weeks later he received [fentanyl](#), [midazolam](#), and [propofol](#) pre-endoscopy without any event, but had not taken [fluoxetine](#) for 2 weeks before the procedure [185].

3.5.1.IPJ [Mesoridazine](#)

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

2J) Summary: The concomitant use of [mesoridazine](#) with drugs that cause QT-interval prolongation is contraindicated, as coadministration may increase the risk of QT prolongation and serious [ventricular arrhythmias](#)[96].

3J) Severity: contraindicated

4J) Onset: unspecified

- 5) Substantiation: established
- 6) Clinical Management: The concomitant use of [mesoridazine](#) with drugs that cause QT-interval prolongation is contraindicated, as coadministration may increase the risk of QT prolongation and serious [ventricular arrhythmias](#)[96].
- 7) Probable Mechanism: additive QT-interval prolongation

3.5.1.IQ] [Methadone](#)

- 1) Interaction Effect: increased risk of CNS depression
- 2) Summary: Concomitant use of [methadone](#), which is a CNS depressant, with another CNS depressant may result in additive effects including [respiratory depression](#), hypotension, and profound sedation, potentially leading to coma or death. Assess the duration of use and the patients degree of tolerance to CNS depressants. If [methadone](#) is coadministered with a CNS depressant, initiate the dose of [methadone](#) at 2.5 mg every 12 hours, and consider lowering the dose of the concomitant CNS depressant. Monitor for signs and symptoms of [respiratory depression](#), hypotension, and sedation[106].
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Concomitant use of [methadone](#), which is a CNS depressant, with another CNS depressant may result in additive effects including [respiratory depression](#), hypotension, and profound sedation, potentially leading to coma or death. Assess the duration of use and the patients degree of tolerance to CNS depressants. If [methadone](#) is coadministered with a CNS depressant, initiate the dose of [methadone](#) at 2.5 mg every 12 hours, and consider lowering the dose of the concomitant CNS depressant. Monitor for signs and symptoms of [respiratory depression](#), hypotension, and sedation[106].
- 7) Probable Mechanism: additive CNS depression effects

3.5.1.IR] [Methadone](#)

- 1) Interaction Effect: an increased risk of QT interval prolongation and [serotonin syndrome](#) ([hypertension](#), [hyperthermia](#), myoclonus, mental status changes)
- 2) Summary: Coadministration of [fluoxetine](#) and other drugs that prolong the QT interval, such as [methadone](#)[373], may result in additive effects on QT interval prolongation and an increased risk of serious [ventricular arrhythmias](#). Coadministration may also result in additive serotonergic effects and may increase the risk of [serotonin syndrome](#). Avoid concomitant administration if possible. If concomitant use is required, periodically monitor for QT interval prolongation and signs and symptoms of [serotonin syndrome](#) [173]. 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 [146].
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: The concomitant use of [fluoxetine](#) with other drugs that prolong the QT interval, such as [methadone](#)[373], should be avoided as coadministration may result in additive effects on QT interval prolongation and an increased risk of serious [ventricular arrhythmias](#). Coadministration may also result in additive serotonergic effects and may increase the risk of [serotonin syndrome](#). If concomitant use of [methadone](#) and [trazodone](#) is required, periodically monitor ECG and for signs and symptoms of [serotonin syndrome](#). Discontinue use if QT prolongation or [serotonin syndrome](#) occurs [173].

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

3.5.1.IS] Methamphetamine

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

2J) Summary: Coadministration of an [amphetamine](#) and a serotonergic agent that inhibits CYP2D6 may result in increased [amphetamine](#) exposure and additional risk for [serotonin syndrome](#). If concomitant use of an [amphetamine](#) and such an agent is clinically required, initiate with lower doses and monitor patients carefully, especially during treatment initiation and dosage adjustment. Discontinue both drugs if [serotonin syndrome](#) is suspected[528].

3J) Severity: major

4J) Onset: unspecified

5J) Substantiation: theoretical

6J) Clinical Management: Coadministration of an [amphetamine](#) and another serotonergic agent may result in [serotonin syndrome](#), because both drugs affect the serotonergic neurotransmitter system. Additionally, coadministration of an [amphetamine](#) with a CYP2D6 inhibitor may increase [amphetamine](#) exposure, because [amphetamines](#) and their derivatives are metabolized to some degree by CYP2D6. An increase in [amphetamine](#) exposure may further increase risk of [serotonin syndrome](#). If concomitant use of an [amphetamine](#) and a serotonergic agent that inhibits CYP2D6 is clinically required, initiate with lower doses and monitor patients carefully, especially during treatment initiation and dosage adjustment. Discontinue both drugs if [serotonin syndrome](#) is suspected[528].

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

3.5.1.IT] Methylene Blue

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

2J) Summary: Concurrent use of [fluoxetine](#) and IV methylene blue, an MAOI, is contraindicated due to reports of [serotonin syndrome](#) with concurrent use of an SSRI and methylene blue 1 to 8 mg/kg administered IV[308]. No cases have been identified in patients receiving methylene blue up to 5 mg for lymphatic mapping in [breast cancer](#) [310]. While the risk of concurrent [fluoxetine](#) with other forms of methylene blue is unclear, interactions are possible with methylene blue administered orally, by injection, or in IV doses lower than 1 mg/kg. If urgent treatment with IV methylene blue is necessary in a patient receiving [fluoxetine](#), and alternatives are not available, and risk/benefit has been evaluated, promptly discontinue [fluoxetine](#) and then IV methylene blue may be administered [308]. Use the lowest possible dose of methylene blue [309]. Monitor for 5 weeks or 24 hours after the last dose of IV methylene blue, whichever comes first. [Fluoxetine](#) may be resumed 24 hours after the last methylene blue dose [308].

3J) Severity: contraindicated

4J) Onset: unspecified

5J) Substantiation: theoretical

6J) Clinical Management: Concurrent use of [fluoxetine](#) and IV methylene blue (an MAOI) is contraindicated. If urgent treatment with IV methylene blue is necessary in a patient receiving [fluoxetine](#), and alternatives are not available, and risk/benefit has been evaluated, promptly discontinue [fluoxetine](#) and then IV methylene blue may be administered[308]. Use the lowest possible dose of methylene blue [309]. Monitor for [serotonin syndrome](#) for 5 weeks or until 24 hours after the last dose of IV methylene blue, whichever comes first. [Fluoxetine](#) can be resumed 24 hours after the last dose of methylene blue. While the risk of concurrent [fluoxetine](#) with other forms of methylene blue is unclear, interactions are possible with methylene blue administered orally, by injection, or in IV doses lower than 1 mg/kg [308].

7J) Probable Mechanism: additive serotonergic effects

8) Literature Reports

a) Patients treated with SSRIs who are undergoing lymphatic mapping for [breast cancer](#) are not expected to experience an interaction with concomitant use of methylene blue. Doses of methylene blue used in lymphatic mapping are many times lower (5 mg total) compared with doses used when [serotonin syndrome](#) occurred with concomitant use of an SSRI and methylene blue (eg, 1 to 8 mg/kg). No case reports of [serotonin syndrome](#) have been reported in patients taking SSRIs who received methylene blue in lymphatic mapping; however, health care providers should still be aware of the potential for an interaction between methylene blue and SSRIs in this setting [310].

3.5.1.IU] [Methylergonovine](#)

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

2) Summary: Concomitant use of [fluoxetine](#), a weak CYP3A4 inhibitor, and an ergot derivative may result in increased plasma concentrations of the ergot derivative due to inhibition of CYP3A4-mediated ergot metabolism. Because of the potential for serious toxicity including [vasospasm](#) can occur, use caution with the concurrent use of [fluoxetine](#) and ergot derivatives[189][188].

3) Severity: moderate

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: [Fluoxetine](#) may increase the plasma concentrations of ergot derivatives. Use caution when [fluoxetine](#) is coadministered with an ergot derivative, such as [dihydroergotamine](#), [ergotamine](#), or [methylergonovine](#), due to the potential for serious toxicity including [vasospasm](#) that can occur[188][189].

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

3.5.1.IV] [Methylphenidate](#)

1) Interaction Effect: increased selective serotonin reuptake inhibitor plasma concentrations

2) Summary: Human pharmacologic studies have demonstrated that [methylphenidate](#) may inhibit the metabolism of selective serotonin reuptake inhibitors (SSRIs). Downward dose adjustments of the SSRI may be necessary when it is used concurrently with [methylphenidate](#). Additionally, when initiating or discontinuing [methylphenidate](#), the SSRI dose may need to be adjusted as needed[402].

3) Severity: moderate

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Use caution when prescribing [methylphenidate](#) to patients who take an selective serotonin reuptake inhibitor (SSRI). Concomitant use of [methylphenidate](#) and an SSRI may cause elevated SSRI plasma concentrations. Consider a decrease in the dose of SSRI when these agents are coadministered. Additionally, consider adjusting the SSRI dose if necessary when initiating or discontinuing [methylphenidate](#) therapy[402].

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

3.5.1.IW] [Methysergide](#)

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

2) Summary: Concomitant use of [fluoxetine](#), a weak CYP3A4 inhibitor, and an ergot derivative may result in increased plasma concentrations of the ergot derivative due to inhibition of CYP3A4-mediated ergot

metabolism. Because of the potential for serious toxicity including [vasospasm](#) can occur, use caution with the concurrent use of [fluoxetine](#) and ergot derivatives[189][188].

3J) Severity: moderate

4J) Onset: unspecified

5J) Substantiation: theoretical

6J) Clinical Management: [Fluoxetine](#) may increase the plasma concentrations of ergot derivatives. Use caution when [fluoxetine](#) is coadministered with an ergot derivative, such as [dihydroergotamine](#), [ergotamine](#), or [methylergonovine](#), due to the potential for serious toxicity including [vasospasm](#) that can occur[188][189].

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

3.5.1.IX] [Metoclopramide](#)

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

2J) Summary: Concomitant use of [metoclopramide](#) with antipsychotic agents may increase the risk of extrapyramidal symptoms, such as [tardive dyskinesia](#) or [neuroleptic malignant syndrome](#), and is contraindicated[98]. 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 [99].

3J) Severity: contraindicated

4J) Onset: unspecified

5J) Substantiation: theoretical

6J) Clinical Management: Concomitant use of [metoclopramide](#) with antipsychotic agents is contraindicated[98]. 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 [99].

7J) Probable Mechanism: unknown

3.5.1.IY] [Metoclopramide](#)

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

2J) Summary: Concomitant use of [fluoxetine](#) with [metoclopramide](#) may increase the risk of extrapyramidal symptoms, such as [tardive dyskinesia](#) or [neuroleptic malignant syndrome](#), and is contraindicated[98]. 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 [99].

3J) Severity: contraindicated

4J) Onset: unspecified

5J) Substantiation: theoretical

6J) Clinical Management: Concomitant use of [fluoxetine](#) with [metoclopramide](#) is contraindicated[98]. 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 [99].

7) Probable Mechanism: unknown

3.5.1.IZ] **Metoprolol**

1) Interaction Effect: increased **metoprolol** exposure

2) Summary: The concomitant use of **metoprolol** (a CYP2D6 substrate) with a CYP2D6 inhibitor may increase the exposure of **metoprolol**, thereby decreasing **metoprolol** cardioselectivity[194][195]. If concomitant administration is required, use with caution, consider **metoprolol** dose reduction, and monitor the patient closely.

3) Severity: moderate

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: The concomitant use of **metoprolol** (a CYP2D6 substrate) with a CYP2D6 inhibitor may increase the exposure of **metoprolol**, thereby decreasing **metoprolol** cardioselectivity[194][195]. If concomitant administration is required, use with caution, consider **metoprolol** dose reduction, and monitor the patient closely.

7) Probable Mechanism: inhibition of CYP2D6-mediated metabolism of **metoprolol**

8) Literature Reports

a) For both S- and R-metoprolol, the mean AUC was increased approximately 3-fold and 4-fold (respectively) and the C_{max} was increased by 2- to 3-fold of both tartrate and succinate formulations by **paroxetine** (a strong CYP2D6 inhibitor) in an open-labeled cross-over study of healthy patients with at least 1 active CYP2D6 allele (N=15). **Paroxetine** coadministered with **metoprolol** also lowered exercise heart rate and systolic blood pressure when compared with **metoprolol** administration alone, representing an increase in the magnitude and duration of beta-blockade. Exercise heart rate was significantly lower at the 2-hour time point with **paroxetine** coadministered with **metoprolol** tartrate than with **metoprolol** succinate [196].

3.5.1.JA] **Metronidazole**

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

2) Summary: Concurrent use of **metronidazole** with other QT-prolonging drugs was a probable cause of QT-interval prolongation in one study of cardiac ICU patients. Use caution with coadministration of **metronidazole** with other QT interval-prolonging drugs, as life-threatening additive effects on the QT interval, including **torsades de pointes**, may occur. Consider close **ECG monitoring** at baseline and during concurrent therapy with QT-interval prolonging drugs[72].

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Use caution with coadministration of **metronidazole** with other QT interval-prolonging drugs, as life-threatening additive effects on the QT interval, including **torsades de pointes**, may occur. Consider close **ECG monitoring** at baseline and during concurrent therapy with QT-interval prolonging drugs[72].

7) Probable Mechanism: additive QT-interval prolongation

8) Literature Reports

a) In a retrospective study, 164 of 501 patients admitted in cardiac ICUs (87.7%) developed QT-interval prolongation potentially linked to inhibition of CYP450-mediated metabolism. Out of 1027 total interactions that were potentially associated with QT-interval prolonging effects,

interactions with [metronidazole](#) (n=22) were some of the most common. No patients developed [torsades de pointes](#) during their ICU stays. Close [ECG monitoring](#) at baseline and during concurrent therapy with drugs known to cause QT-interval prolongation is recommended [72].

b)) A 71-year-old woman with antibiotic-induced [pseudomembranous colitis](#) developed ECG QTc interval prolongation and [torsades de pointes](#) with concurrent [amiodarone](#) 450 mg bolus followed by 900 mg/day IV and [metronidazole](#) 1500 mg/day oral administration. Baseline QTc interval was 440 msec. [Amiodarone](#) was added after trial fibrillation developed with 3 days of [amiodarone](#) therapy. Conversion to sinus rhythm occurred 2 days later; however, the follow-up ECG revealed a QTc interval of 625 msec. Symptoms progressed to sustained torsades de pointes-variant [ventricular tachycardia](#) that required emergent [cardioversion/defibrillation](#) to restore normal sinus rhythm. [Amiodarone](#) and [metronidazole](#) were immediately withdrawn, and the QTc interval slowly returned to baseline values without further clinically significant [arrhythmia](#) events [73].

3.5.1.JB] [Midazolam](#)

- 1)) Interaction Effect: potentiation of excessive sedation and cardiorespiratory depression
- 2)) Summary: The concomitant use of intramuscularly administered [olanzapine](#) and parenteral benzodiazepines ([diazepam](#), [lorazepam](#), [midazolam](#)) is not recommended due to the potentiation of excessive sedation and cardiorespiratory depression[68].
- 3)) Severity: major
- 4)) Onset: unspecified
- 5)) Substantiation: theoretical
- 6)) Clinical Management: The concomitant use of intramuscularly administered [olanzapine](#) and parenteral benzodiazepines ([diazepam](#), [lorazepam](#), [midazolam](#)) is not recommended due to additive CNS depression[68].
- 7)) Probable Mechanism: additive CNS depression

3.5.1.JC] [Milnacipran](#)

- 1)) Interaction Effect: increased risk of [serotonin syndrome](#) ([hypertension](#), [hyperthermia](#), myoclonus, mental status changes)
- 2)) Summary: Concomitant use of milnacipran and an antipsychotic may result in [hypertension](#), coronary artery vasoconstriction or [serotonin syndrome](#), which may be life-threatening. When concomitant use of milnacipran and an antipsychotic is required, caution should be used. If symptoms of [serotonin syndrome](#) develop (eg, restlessness, hallucinations, loss of coordination, fast heart beat, rapid changes in blood pressure, increased body temperature, overreactive reflexes, nausea, vomiting, and diarrhea), treatment should be immediately discontinued and the appropriate supportive therapy initiated[133].
- 3)) Severity: major
- 4)) Onset: unspecified
- 5)) Substantiation: theoretical
- 6)) Clinical Management: Coadministration of milnacipran and an antipsychotic may result in [hypertension](#) and coronary artery vasoconstriction through additive serotonergic effects. Therefore, use caution when coadministering these agents. If symptoms of [serotonin syndrome](#) develop, discontinue treatment immediately and institute the appropriate supportive symptomatic treatment[133].
- 7)) Probable Mechanism: additive serotonergic effect

3.5.1.JD] [Milnacipran](#)

- 1) Interaction Effect: increased risk of [serotonin syndrome](#) ([hypertension](#), [hyperthermia](#), myoclonus, mental status changes)
- 2) Summary: Concurrent use of milnacipran and an SSRI or a serotonin [norepinephrine](#) reuptake inhibitor (SNRI) may result in [hypertension](#), coronary artery vasoconstriction or [serotonin syndrome](#), which may be life-threatening. Symptoms of [serotonin syndrome](#) may include restlessness, hallucinations, loss of coordination, fast heart beat, rapid changes in blood pressure, increased body temperature, overreactive reflexes, nausea, vomiting, and diarrhea[398].
- 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[398].
- 7) Probable Mechanism: additive serotonergic effect

3.5.1.JE] [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[395]. 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 [146].
- 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](#)[395].
- 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 [396].

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 [397].

3.5.1.JF] Moclobemide

- 1)) Interaction Effect: an increased risk of [serotonin syndrome](#) ([hypertension](#), [tachycardia](#), [hyperthermia](#), myoclonus, mental status changes)
- 2)) Summary: Concomitant use of [fluoxetine](#) and an MAOI is contraindicated. Concurrent administration or overlapping therapy with [fluoxetine](#) and an MAOI 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 SSRIs and MAOIs. A minimum of 14 days should elapse after discontinuing an MAOI intended to treat psychiatric disorders before initiating therapy with [fluoxetine](#), and a minimum of 5 weeks should elapse after discontinuing [fluoxetine](#) before initiating therapy with an MAOI intended to treat psychiatric disorders[283].
- 3)) Severity: contraindicated
- 4)) Onset: unspecified
- 5)) Substantiation: theoretical
- 6)) Clinical Management: Concurrent use of [fluoxetine](#) and an MAOI is contraindicated. Wait at least 14 days after discontinuing an MAOI intended to treat psychiatric disorders before initiating [fluoxetine](#). Wait at least 5 weeks after discontinuing [fluoxetine](#) before initiating therapy with an MAOI intended to treat psychiatric disorders[283].
- 7)) Probable Mechanism: additive serotonergic effect

3.5.1.JG] Morniflumate

- 1)) Interaction Effect: an increased risk of bleeding
- 2)) Summary: Caution is recommended with the concomitant use of NSAIDs and antidepressants, including SSRIs due to an increased risk of [intracranial hemorrhage](#)[529] and [gastrointestinal bleeding](#) [533][534][530][531]. Bleeding events have included [epistaxis](#), ecchymosis, [hematoma](#), [petechiae](#), and life-threatening hemorrhages [536][535][537][538]. When an SSRI and an NSAID are given concurrently, monitor the patient for signs of increased bleeding.
- 3)) Severity: major
- 4)) Onset: unspecified
- 5)) Substantiation: established
- 6)) Clinical Management: Use caution if NSAIDs and SSRIs are coadministered. Concomitant use of NSAIDs and SSRIs may cause an increased risk of [intracranial hemorrhage](#)[529] and [gastrointestinal bleeding](#) [530][531]. When an SSRI and an NSAID are given concurrently, monitor the patient for signs of increased bleeding.
- 7)) Probable Mechanism: depletion of [platelet](#) serotonin by SSRI; additive effects
- 8)) Literature Reports

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

use alone. There was no significant difference between the antidepressant drug classes and the increased risk; however, there was an increased risk associated with male patients compared with female patients [529].

b)) SSRIs increase the risk of upper gastrointestinal (GI) bleeding, and this effect is potentiated by concurrent use of NSAIDs or low-dose [aspirin](#). Hospitalizations for [upper GI bleeding](#) were searched among 26,005 users of antidepressant medications and compared with the number of hospitalizations in those patients who did not receive prescriptions for antidepressants. The amount of [upper GI bleeding](#) episodes was 3.6 times more than expected. Combined use of an SSRI and NSAIDs or low-dose [aspirin](#) increased the risk to 12.2 and 5.2 times, respectively. The findings of this study demonstrate an increased risk of [upper GI bleeding](#) during the use of SSRIs. Combined use of SSRIs and NSAIDs or low-dose [aspirin](#) increased the risk even further [532].

c)) Two metaanalyses of incidents of upper GI bleed due to SSRIs, NSAIDs, and their combination found that SSRIs increased the risk by 1.73 [533] to 2.36 times [534], NSAIDs by 2.55 times [533], and the combination of SSRIs and NSAIDs by 4.02 [533] to 6.33 times [534].

d)) The release of serotonin by [platelets](#) is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs and NSAIDs have been associated with an increased risk of bleeding [535].

3.5.1.JH] [Morphine](#)

1)) Interaction Effect: increased risk of [paralytic ileus](#); increased risk of CNS depression

2)) Summary: Coadministration of [morphine](#) and this drug may result in additive respiratory and CNS depressant effects. Concomitant use may also cause urinary retention or severe constipation resulting in [paralytic ileus](#). Assess the duration of use and degree of tolerance to CNS depressants prior to concurrent use. If coadministration is clinically necessary, initiate treatment with [morphine](#) at the lowest possible dose (ie, 30 mg every 24 hours or 15 mg every 12 hours) and reduce the dose of 1 or both agents. In addition, monitor patients for sedation, [respiratory depression](#), and signs of urinary retention or reduced gastric motility[79][81][80].

3)) Severity: major

4)) Onset: unspecified

5)) Substantiation: theoretical

6)) Clinical Management: Coadministration of [morphine](#) and this drug may result in additive respiratory and CNS depressant effects. Concomitant use may also cause urinary retention or severe constipation resulting in [paralytic ileus](#). Assess the duration of use and degree of tolerance to CNS depressants prior to concurrent use. If coadministration is clinically necessary, initiate treatment with [morphine](#) at the lowest possible dose (ie, 30 mg every 24 hours or 15 mg every 12 hours) and reduce the dose of 1 or both agents. In addition, monitor patients for sedation, [respiratory depression](#), and signs of urinary retention or reduced gastric motility[79][80][81].

7)) Probable Mechanism: unknown; additive CNS depression

3.5.1.JI] [Morphine Sulfate Liposome](#)

1)) Interaction Effect: increased risk of [paralytic ileus](#); increased risk of CNS depression

2)) Summary: Coadministration of [morphine](#) and this drug may result in additive respiratory and CNS depressant effects. Concomitant use may also cause urinary retention or severe constipation resulting in [paralytic ileus](#). Assess the duration of use and degree of tolerance to CNS depressants prior to concurrent use. If coadministration is clinically necessary, initiate treatment with [morphine](#) at the lowest possible dose (ie, 30 mg every 24 hours or 15 mg every 12 hours) and reduce the dose of 1 or both agents. In addition,

monitor patients for sedation, [respiratory depression](#), and signs of urinary retention or reduced gastric motility[79][81][80].

3J) Severity: major

4J) Onset: unspecified

5J) Substantiation: theoretical

6J) Clinical Management: Coadministration of [morphine](#) and this drug may result in additive respiratory and CNS depressant effects. Concomitant use may also cause urinary retention or severe constipation resulting in [paralytic ileus](#). Assess the duration of use and degree of tolerance to CNS depressants prior to concurrent use. If coadministration is clinically necessary, initiate treatment with [morphine](#) at the lowest possible dose (ie, 30 mg every 24 hours or 15 mg every 12 hours) and reduce the dose of 1 or both agents. In addition, monitor patients for sedation, [respiratory depression](#), and signs of urinary retention or reduced gastric motility[79][80][81].

7J) Probable Mechanism: unknown; additive CNS depression

3.5.1.JJ] [Moxifloxacin](#)

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

2J) Summary: [Moxifloxacin](#) has been associated with QT-interval prolongation. Coadministration with another drug known to prolong the QT-interval should be avoided because of risk for additive effects on the QT-interval that can lead to serious cardiac adverse effects, including [torsade de pointes](#). Elderly patients receiving treatment with IV [moxifloxacin](#) may be at an increased risk for QT prolongation. If concurrent use is not avoidable, do not exceed the recommended dose or infusion rate of [moxifloxacin](#)[53] and monitor for changes in the QT-interval.

3J) Severity: major

4J) Onset: unspecified

5J) Substantiation: theoretical

6J) Clinical Management: [Moxifloxacin](#) has been associated with QT-interval prolongation. Coadministration with another drug known to prolong the QT-interval should be avoided because of risk for additive effects on the QT-interval that can lead to serious cardiac adverse effects, including [torsade de pointes](#). Elderly patients receiving treatment with IV [moxifloxacin](#) may be at an increased risk for QT prolongation. If concurrent use is not avoidable, do not exceed the recommended dose or infusion rate of [moxifloxacin](#)[53] and monitor for changes in the QT-interval.

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

3.5.1.JK] [Nabumetone](#)

1J) Interaction Effect: an increased risk of bleeding

2J) Summary: Caution is recommended with the concomitant use of NSAIDs and antidepressants, including SSRIs due to an increased risk of [intracranial hemorrhage](#)[529] and [gastrointestinal bleeding](#) [533][534][530][531]. Bleeding events have included [epistaxis](#), ecchymosis, [hematoma](#), [petechiae](#), and life-threatening hemorrhages [536][535][537][538]. When an SSRI and an NSAID are given concurrently, monitor the patient for signs of increased bleeding.

3J) Severity: major

4J) Onset: unspecified

5J) Substantiation: established

6J) Clinical Management: Use caution if NSAIDs and SSRIs are coadministered. Concomitant use of NSAIDs and SSRIs may cause an increased risk of [intracranial hemorrhage](#)[529] and [gastrointestinal bleeding](#) [530][531]. When an SSRI and an NSAID are given concurrently, monitor the patient for signs of increased bleeding.

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

8) Literature Reports

a) Concomitant use of NSAIDs and antidepressants, including tricyclic antidepressants, SSRIs, serotonin-norepinephrine reuptake inhibitors, and MAOIs, resulted in a 60% increased risk of **intracranial hemorrhage** within 30 days of concomitant use compared with antidepressant use alone. There was no significant difference between the antidepressant drug classes and the increased risk; however, there was an increased risk associated with male patients compared with female patients [529].

b) SSRIs increase the risk of upper gastrointestinal (GI) bleeding, and this effect is potentiated by concurrent use of NSAIDs or low-dose **aspirin**. Hospitalizations for **upper GI bleeding** were searched among 26,005 users of antidepressant medications and compared with the number of hospitalizations in those patients who did not receive prescriptions for antidepressants. The amount of **upper GI bleeding** episodes was 3.6 times more than expected. Combined use of an SSRI and NSAIDs or low-dose **aspirin** increased the risk to 12.2 and 5.2 times, respectively. The findings of this study demonstrate an increased risk of **upper GI bleeding** during the use of SSRIs. Combined use of SSRIs and NSAIDs or low-dose **aspirin** increased the risk even further [532].

c) Two metaanalyses of incidents of upper GI bleed due to SSRIs, NSAIDs, and their combination found that SSRIs increased the risk by 1.73 [533] to 2.36 times [534], NSAIDs by 2.55 times [533], and the combination of SSRIs and NSAIDs by 4.02 [533] to 6.33 times [534].

d) The release of serotonin by **platelets** is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs and NSAIDs have been associated with an increased risk of bleeding [535].

3.5.1.JL] Nadroparin

1) Interaction Effect: an increased risk of bleeding

2) Summary: The release of serotonin by **platelets** is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs and anticoagulants has been associated with an increased risk of bleeding[458][457]. Bleeding events reported have included **epistaxis**, ecchymosis, **hematoma**, **petechiae**, and life-threatening hemorrhages. Altered anticoagulant effects (including increased bleeding) have been reported with the coadministration of SSRIs with anticoagulants [457].

3) Severity: major

4) Onset: delayed

5) Substantiation: probable

6) Clinical Management: When **fluoxetine** and an anticoagulant are given concurrently, monitor patient for signs of increased bleeding. Patients who are taking an anticoagulant should be monitored closely for altered anticoagulant effects, including increased bleeding, when **fluoxetine** therapy is initiated or discontinued[457].

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

a significant 1.7-fold increased risk for hospitalization for nongastrointestinal bleeding; however, the rate of [gastrointestinal bleeding](#) was not significantly different [458].

3.5.1.JM] [Nafarelin](#)

- 1) Interaction Effect: increased risk of QT-interval prolongation
- 2) Summary: Use caution with coadministration of gonadotropin-releasing hormone (GnRH) agonists with QT-interval prolonging drugs. Androgen deprivation caused by GnRH agonists may prolong the QT interval and cause additive effects when administered with QT-interval prolonging drugs[141][142][143]. If concurrent therapy is necessary, monitor patients closely for signs and symptoms of [cardiac toxicity](#), including changes in the ECG.
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Use caution with coadministration of gonadotropin-releasing hormone (GnRH) agonists with QT-interval prolonging drugs, as additive effects on the QT interval may occur[141][142][143].
- 7) Probable Mechanism: additive effects on the QT interval

3.5.1.JN] [Naproxen](#)

- 1) Interaction Effect: an increased risk of bleeding
- 2) Summary: Caution is recommended with the concomitant use of NSAIDs and antidepressants, including SSRIs due to an increased risk of [intracranial hemorrhage](#)[529] and [gastrointestinal bleeding](#) [533][534][530][531]. Bleeding events have included [epistaxis](#), ecchymosis, [hematoma](#), [petechiae](#), and life-threatening hemorrhages [536][535][537][538]. When an SSRI and an NSAID are given concurrently, monitor the patient for signs of increased bleeding.
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: established
- 6) Clinical Management: Use caution if NSAIDs and SSRIs are coadministered. Concomitant use of NSAIDs and SSRIs may cause an increased risk of [intracranial hemorrhage](#)[529] and [gastrointestinal bleeding](#) [530][531]. When an SSRI and an NSAID are given concurrently, monitor the patient for signs of increased bleeding.
- 7) Probable Mechanism: depletion of [platelet](#) serotonin by SSRI; additive effects
- 8) Literature Reports

a) Concomitant use of NSAIDs and antidepressants, including tricyclic antidepressants, SSRIs, serotonin-norepinephrine reuptake inhibitors, and MAOIs, resulted in a 60% increased risk of [intracranial hemorrhage](#) within 30 days of concomitant use compared with antidepressant use alone. There was no significant difference between the antidepressant drug classes and the increased risk; however, there was an increased risk associated with male patients compared with female patients [529].

b) SSRIs increase the risk of upper gastrointestinal (GI) bleeding, and this effect is potentiated by concurrent use of NSAIDs or low-dose [aspirin](#). Hospitalizations for [upper GI bleeding](#) were searched among 26,005 users of antidepressant medications and compared with the number of hospitalizations in those patients who did not receive prescriptions for antidepressants. The amount of [upper GI bleeding](#) episodes was 3.6 times more than expected. Combined use of an SSRI and NSAIDs or low-dose [aspirin](#) increased the risk to 12.2 and 5.2 times, respectively. The

findings of this study demonstrate an increased risk of [upper GI bleeding](#) during the use of SSRIs. Combined use of SSRIs and NSAIDs or low-dose [aspirin](#) increased the risk even further [532].

c) Two metaanalyses of incidents of upper GI bleed due to SSRIs, NSAIDs, and their combination found that SSRIs increased the risk by 1.73 [533] to 2.36 times [534], NSAIDs by 2.55 times [533], and the combination of SSRIs and NSAIDs by 4.02 [533] to 6.33 times [534].

d) The release of serotonin by [platelets](#) is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs and NSAIDs have been associated with an increased risk of bleeding [535].

3.5.1.JO] [Naratriptan](#)

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

2) Summary: Rare incidences of weakness, hyperreflexia, and incoordination have been reported with the concurrent use of a selective serotonin reuptake inhibitor (SSRI) and a 5-hydroxytryptamine-1 (5HT-1) agonist[321]. Concurrent use of a triptan and an SSRI may result in [serotonin syndrome](#) which may be life-threatening. Symptoms of [serotonin syndrome](#) may include restlessness, hallucinations, loss of coordination, fast heart beat, rapid changes in blood pressure, increased body temperature, overreactive reflexes, nausea, vomiting, and diarrhea. Clinicians should be aware that triptans may be commonly used intermittently and that either the triptan or the SSRI may be prescribed by a different physician. Discuss the risks of [serotonin syndrome](#) with patients who are prescribed this combination and monitor them closely for symptoms of [serotonin syndrome](#) [199].

3) Severity: major

4) Onset: delayed

5) Substantiation: probable

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

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

3.5.1.JP] [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[315] as it may increase plasma concentrations of nebivolol [315][316]. If coadministration is required, patients should be closely monitored, and dose adjustment may be required [316].

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Concomitant use of nebivolol and a CYP2D6 inhibitor should be avoided[315] as it may increase plasma concentrations of nebivolol[315][316]. If coadministration is required, patients should be closely monitored, and dose adjustment may be required [316].

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) [317].

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) [315].

3.5.1.JQ] Nefazodone

1) Interaction Effect: increased risk of serotonin syndrome

2) Summary: Serotonin syndrome may be the result from concomitant use of fluoxetine and serotonergic agents, such as triptans or other antidepressants. Monitor patients for symptoms of serotonin syndrome, including neuromuscular abnormalities, autonomic instability, and mental status changes, especially during treatment initiation and dose increases. Serotonin syndrome can be life-threatening. If serotonin syndrome develops, discontinue fluoxetine and any concomitant serotonergic agent and initiate supportive care[173].

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Exercise caution with coadministration of fluoxetine and serotonergic agents, such as triptans or other antidepressants, because it may result in a life-threatening condition called serotonin syndrome. If these agents are used together, discuss the risks of serotonin syndrome with the patient and monitor closely for symptoms of serotonin syndrome (mental status changes, autonomic instability, neuromuscular symptoms, seizures, and gastrointestinal symptoms), especially during treatment initiation and dose increases. If serotonin syndrome develops, discontinue fluoxetine and any concomitant serotonergic agent and initiate supportive care[173]

7) Probable Mechanism: additive serotonergic effect

3.5.1.JR] Nepafenac

1) Interaction Effect: an increased risk of bleeding

2) Summary: Caution is recommended with the concomitant use of NSAIDs and antidepressants, including SSRIs due to an increased risk of intracranial hemorrhage[529] and gastrointestinal bleeding [533][534][530][531]. Bleeding events have included epistaxis, ecchymosis, hematoma, petechiae, and life-threatening hemorrhages [536][535][537][538]. When an SSRI and an NSAID are given concurrently, monitor the patient for signs of increased bleeding.

3) Severity: major

4) Onset: unspecified

5) Substantiation: established

6) Clinical Management: Use caution if NSAIDs and SSRIs are coadministered. Concomitant use of NSAIDs and SSRIs may cause an increased risk of intracranial hemorrhage[529] and gastrointestinal bleeding [530][531]. When an SSRI and an NSAID are given concurrently, monitor the patient for signs of increased bleeding.

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

8) Literature Reports

a) Concomitant use of NSAIDs and antidepressants, including tricyclic antidepressants, SSRIs, serotonin-norepinephrine reuptake inhibitors, and MAOIs, resulted in a 60% increased risk of intracranial hemorrhage within 30 days of concomitant use compared with antidepressant use alone. There was no significant difference between the antidepressant drug classes and the

increased risk; however, there was an increased risk associated with male patients compared with female patients [529].

b) SSRIs increase the risk of upper gastrointestinal (GI) bleeding, and this effect is potentiated by concurrent use of NSAIDs or low-dose [aspirin](#). Hospitalizations for [upper GI bleeding](#) were searched among 26,005 users of antidepressant medications and compared with the number of hospitalizations in those patients who did not receive prescriptions for antidepressants. The amount of [upper GI bleeding](#) episodes was 3.6 times more than expected. Combined use of an SSRI and NSAIDs or low-dose [aspirin](#) increased the risk to 12.2 and 5.2 times, respectively. The findings of this study demonstrate an increased risk of [upper GI bleeding](#) during the use of SSRIs. Combined use of SSRIs and NSAIDs or low-dose [aspirin](#) increased the risk even further [532].

c) Two metaanalyses of incidents of upper GI bleed due to SSRIs, NSAIDs, and their combination found that SSRIs increased the risk by 1.73 [533] to 2.36 times [534], NSAIDs by 2.55 times [533], and the combination of SSRIs and NSAIDs by 4.02 [533] to 6.33 times [534].

d) The release of serotonin by [platelets](#) is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs and NSAIDs have been associated with an increased risk of bleeding [535].

3.5.1.JS] Nialamide

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

2) Summary: Concurrent administration or overlapping therapy with [fluoxetine](#) and a monoamine oxidase (MAO) inhibitor may result in CNS toxicity or [serotonin syndrome](#), a hyperserotonergic state characterized by symptoms such as restlessness, myoclonus, changes in mental status, hyperreflexia, diaphoresis, shivering, and tremor. Serious, even fatal, reactions have been reported[263][264][265][266][267][268]. Concomitant use is contraindicated.

3) Severity: contraindicated

4) Onset: rapid

5) Substantiation: probable

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

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

8) Literature Reports

a) Concomitant use of serotonin specific reuptake inhibitors and monoamine oxidase inhibitors can produce a toxic reaction known as [serotonin syndrome](#) [258]. [Serotonin syndrome](#) is a condition of serotonergic hyperstimulation and manifests as restlessness, myoclonus, changes in mental status, hyperreflexia, diaphoresis, shivering, and tremor [258]. If the syndrome is not recognized and correctly treated, death can result.

b) It has been suggested that [fluoxetine](#) therapy be discontinued for at least five weeks before beginning therapy with a monoamine oxidase inhibitor. A 28-year old woman discontinued [fluoxetine](#) for six weeks before starting therapy with [tranylcypromine](#). Over the next few days the patient developed fever, paresthesias, confusion, abdominal cramping, and various other CNS symptoms. Upon discontinuation of [tranylcypromine](#), the patient's symptoms began to resolve. Blood samples taken three days after discontinuation of [tranylcypromine](#) revealed no presence of [fluoxetine](#); however, the norfluoxetine level was 84 ng/mL (284 nanomol/L) [259].

c) Adverse reactions reported when [fluoxetine](#) was given concomitantly with [phenelzine](#) (n=9) or [tranylcypromine](#) (n=4) include tremor (50%), agitation or restlessness (42%), mental status changes (42%), myoclonus (33%), diarrhea (33%), and blood pressure changes (25%) [260]. All but one of the patients were taking other medications (ie, benzodiazepines, neuroleptics, anticonvulsants, antidepressants) that may have contributed to the adverse reactions.

d) Ten hours after her last dose of [fluoxetine](#), a 45-year-old woman began [tranylcypromine](#) therapy [261]. Headache, muscle contractions, insomnia, and unsteady gait were reported on the second day. [Thioridazine](#) and tryptophan were added to her therapy. The patient experienced fever, rigidity of the arms and legs, and hyperreflexia. She died in the intensive care unit of a hospital 44 hours later.

e) Two cases reports suggested a possible interaction between [fluoxetine](#) and [selegiline](#) [262]. One case involved a first episode of mania being observed approximately one month after adding [selegiline](#) to [fluoxetine](#) therapy. The patient improved two months after both drugs were discontinued, and no further details were provided. The second case involved diaphoresis, vasoconstriction, and cyanosis of the hands which occurred in close temporal relationship to adding [fluoxetine](#) and [selegiline](#). Both drugs were discontinued, with relatively quick resolution of symptoms. Rechallenge with [fluoxetine](#) alone occurred without incident.

3.5.1.JT] [Nifedipine](#)

- 1) Interaction Effect: increased [NIFEdipine](#) exposure
- 2) Summary: [Fluoxetine](#) is an inhibitor of the CYP3A4 isoenzyme and may inhibit the metabolism of [NIFEdipine](#). [NIFEdipine](#) plasma concentrations may be increased by the presence of [fluoxetine](#). Clinical monitoring for [NIFEdipine](#) toxicity and possible dose reduction is recommended[372].
- 3) Severity: moderate
- 4) Onset: delayed
- 5) Substantiation: theoretical
- 6) Clinical Management: Concomitant administration of [NIFEdipine](#) and [fluoxetine](#) may increase exposure to [NIFEdipine](#). Monitor for clinical signs of [NIFEdipine](#) toxicity, including hypotension, peripheral edema, and bradycardia. Consider a dose reduction of [NIFEdipine](#)[372].
- 7) Probable Mechanism: inhibition of CYP3A-mediated [NIFEdipine](#) metabolism

3.5.1.JU] [Niflumic Acid](#)

- 1) Interaction Effect: an increased risk of bleeding
- 2) Summary: Caution is recommended with the concomitant use of NSAIDs and antidepressants, including SSRIs due to an increased risk of [intracranial hemorrhage](#)[529] and [gastrointestinal bleeding](#) [533][534][530][531]. Bleeding events have included [epistaxis](#), ecchymosis, [hematoma](#), [petechiae](#), and life-threatening hemorrhages [536][535][537][538]. When an SSRI and an NSAID are given concurrently, monitor the patient for signs of increased bleeding.
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: established
- 6) Clinical Management: Use caution if NSAIDs and SSRIs are coadministered. Concomitant use of NSAIDs and SSRIs may cause an increased risk of [intracranial hemorrhage](#)[529] and [gastrointestinal bleeding](#) [530][531]. When an SSRI and an NSAID are given concurrently, monitor the patient for signs of increased bleeding.
- 7) Probable Mechanism: depletion of [platelet](#) serotonin by SSRI; additive effects

8j) Literature Reports

aj) Concomitant use of NSAIDs and antidepressants, including tricyclic antidepressants, SSRIs, serotonin-norepinephrine reuptake inhibitors, and MAOIs, resulted in a 60% increased risk of [intracranial hemorrhage](#) within 30 days of concomitant use compared with antidepressant use alone. There was no significant difference between the antidepressant drug classes and the increased risk; however, there was an increased risk associated with male patients compared with female patients [529].

bj) SSRIs increase the risk of upper gastrointestinal (GI) bleeding, and this effect is potentiated by concurrent use of NSAIDs or low-dose [aspirin](#). Hospitalizations for [upper GI bleeding](#) were searched among 26,005 users of antidepressant medications and compared with the number of hospitalizations in those patients who did not receive prescriptions for antidepressants. The amount of [upper GI bleeding](#) episodes was 3.6 times more than expected. Combined use of an SSRI and NSAIDs or low-dose [aspirin](#) increased the risk to 12.2 and 5.2 times, respectively. The findings of this study demonstrate an increased risk of [upper GI bleeding](#) during the use of SSRIs. Combined use of SSRIs and NSAIDs or low-dose [aspirin](#) increased the risk even further [532].

cj) Two metaanalyses of incidents of upper GI bleed due to SSRIs, NSAIDs, and their combination found that SSRIs increased the risk by 1.73 [533] to 2.36 times [534], NSAIDs by 2.55 times [533], and the combination of SSRIs and NSAIDs by 4.02 [533] to 6.33 times [534].

dj) The release of serotonin by [platelets](#) is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs and NSAIDs have been associated with an increased risk of bleeding [535].

3.5.1.JV) Nimesulide

1j) Interaction Effect: an increased risk of bleeding

2j) Summary: Caution is recommended with the concomitant use of NSAIDs and antidepressants, including SSRIs due to an increased risk of [intracranial hemorrhage](#)[529] and [gastrointestinal bleeding](#) [533][534][530][531]. Bleeding events have included [epistaxis](#), ecchymosis, [hematoma](#), [petechiae](#), and life-threatening hemorrhages [536][535][537][538]. When an SSRI and an NSAID are given concurrently, monitor the patient for signs of increased bleeding.

3j) Severity: major

4j) Onset: unspecified

5j) Substantiation: established

6j) Clinical Management: Use caution if NSAIDs and SSRIs are coadministered. Concomitant use of NSAIDs and SSRIs may cause an increased risk of [intracranial hemorrhage](#)[529] and [gastrointestinal bleeding](#) [530][531]. When an SSRI and an NSAID are given concurrently, monitor the patient for signs of increased bleeding.

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

8j) Literature Reports

aj) Concomitant use of NSAIDs and antidepressants, including tricyclic antidepressants, SSRIs, serotonin-norepinephrine reuptake inhibitors, and MAOIs, resulted in a 60% increased risk of [intracranial hemorrhage](#) within 30 days of concomitant use compared with antidepressant use alone. There was no significant difference between the antidepressant drug classes and the increased risk; however, there was an increased risk associated with male patients compared with female patients [529].

b) SSRIs increase the risk of upper gastrointestinal (GI) bleeding, and this effect is potentiated by concurrent use of NSAIDs or low-dose [aspirin](#). Hospitalizations for [upper GI bleeding](#) were searched among 26,005 users of antidepressant medications and compared with the number of hospitalizations in those patients who did not receive prescriptions for antidepressants. The amount of [upper GI bleeding](#) episodes was 3.6 times more than expected. Combined use of an SSRI and NSAIDs or low-dose [aspirin](#) increased the risk to 12.2 and 5.2 times, respectively. The findings of this study demonstrate an increased risk of [upper GI bleeding](#) during the use of SSRIs. Combined use of SSRIs and NSAIDs or low-dose [aspirin](#) increased the risk even further [532].

c) Two metaanalyses of incidents of upper GI bleed due to SSRIs, NSAIDs, and their combination found that SSRIs increased the risk by 1.73 [533] to 2.36 times [534], NSAIDs by 2.55 times [533], and the combination of SSRIs and NSAIDs by 4.02 [533] to 6.33 times [534].

d) The release of serotonin by [platelets](#) is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs and NSAIDs have been associated with an increased risk of bleeding [535].

3.5.1.JW] Nimesulide Beta Cyclodextrin

1) Interaction Effect: an increased risk of bleeding

2) Summary: Caution is recommended with the concomitant use of NSAIDs and antidepressants, including SSRIs due to an increased risk of [intracranial hemorrhage](#)[529] and [gastrointestinal bleeding](#) [533][534][530][531]. Bleeding events have included [epistaxis](#), ecchymosis, [hematoma](#), [petechiae](#), and life-threatening hemorrhages [536][535][537][538]. When an SSRI and an NSAID are given concurrently, monitor the patient for signs of increased bleeding.

3) Severity: major

4) Onset: unspecified

5) Substantiation: established

6) Clinical Management: Use caution if NSAIDs and SSRIs are coadministered. Concomitant use of NSAIDs and SSRIs may cause an increased risk of [intracranial hemorrhage](#)[529] and [gastrointestinal bleeding](#) [530][531]. When an SSRI and an NSAID are given concurrently, monitor the patient for signs of increased bleeding.

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

8) Literature Reports

a) Concomitant use of NSAIDs and antidepressants, including tricyclic antidepressants, SSRIs, serotonin-norepinephrine reuptake inhibitors, and MAOIs, resulted in a 60% increased risk of [intracranial hemorrhage](#) within 30 days of concomitant use compared with antidepressant use alone. There was no significant difference between the antidepressant drug classes and the increased risk; however, there was an increased risk associated with male patients compared with female patients [529].

b) SSRIs increase the risk of upper gastrointestinal (GI) bleeding, and this effect is potentiated by concurrent use of NSAIDs or low-dose [aspirin](#). Hospitalizations for [upper GI bleeding](#) were searched among 26,005 users of antidepressant medications and compared with the number of hospitalizations in those patients who did not receive prescriptions for antidepressants. The amount of [upper GI bleeding](#) episodes was 3.6 times more than expected. Combined use of an SSRI and NSAIDs or low-dose [aspirin](#) increased the risk to 12.2 and 5.2 times, respectively. The findings of this study demonstrate an increased risk of [upper GI bleeding](#) during the use of SSRIs. Combined use of SSRIs and NSAIDs or low-dose [aspirin](#) increased the risk even further [532].

c) Two metaanalyses of incidents of upper GI bleed due to SSRIs, NSAIDs, and their combination found that SSRIs increased the risk by 1.73 [533] to 2.36 times [534], NSAIDs by 2.55 times [533], and the combination of SSRIs and NSAIDs by 4.02 [533] to 6.33 times [534].

d) The release of serotonin by [platelets](#) is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs and NSAIDs have been associated with an increased risk of bleeding [535].

3.5.1.JX] [Nortriptyline](#)

1) Interaction Effect: increased risk of tricyclic antidepressant toxicity, QT prolongation and [serotonin syndrome](#)

2) Summary: [Fluoxetine](#), a potent CYP2D6 inhibitor, is associated with an increased risk of [serotonin syndrome](#), QT prolongation, and [ventricular arrhythmias](#) (including [torsade de pointes](#)). Concomitant therapy with CYP2D6-metabolized tricyclic antidepressants (TCAs) may potentiate these risks and introduce TCA toxicity[173]; concurrent use of [fluoxetine](#) and [desipramine](#), [nortriptyline](#), and [imipramine](#) has resulted in significant increases in TCA concentrations [517][523][524][525][526][527]. Use caution with concurrent administration of [fluoxetine](#) and TCAs. If [fluoxetine](#) is added to an existing TCA regimen, consider TCA dose reduction. If [fluoxetine](#) and a TCA are coadministered or [fluoxetine](#) has been recently discontinued, consider plasma TCA monitoring. If [serotonin syndrome](#) occurs, immediately discontinue [fluoxetine](#) and TCA. If [ventricular arrhythmias](#) develop, consider [fluoxetine](#) discontinuation and cardiac evaluation [173].

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Use caution with concurrent administration of [fluoxetine](#) and TCAs, as elevated TCA plasma concentrations may occur. If [fluoxetine](#) is added to an existing TCA regimen, consider TCA dose reduction. If [fluoxetine](#) and a TCA are coadministered or [fluoxetine](#) has been recently discontinued, consider plasma TCA monitoring. If [serotonin syndrome](#) occurs, immediately discontinue [fluoxetine](#) and TCA. If [ventricular arrhythmias](#) develop, consider [fluoxetine](#) discontinuation and cardiac evaluation[173]

7) Probable Mechanism: decreased CYP2D6-mediated metabolism of tricyclic antidepressants by [fluoxetine](#); additive effects on QT prolongation; additive serotonergic effects

8) Literature Reports

a) Previously stable plasma levels of [imipramine](#) and [desipramine](#) rose more than 2- to 10-fold with [fluoxetine](#) coadministration in 2 clinical studies. This effect may persist for 3 weeks or more after [fluoxetine](#) discontinuation. Dose reduction and temporary monitoring of tricyclic antidepressant plasma concentrations may be indicated with concurrent [fluoxetine](#) treatment or recent [fluoxetine](#) discontinuation [173].

b) [Fluoxetine](#) statistically and clinically significantly increased [desipramine](#) concentrations in 18 healthy subjects. When [fluoxetine](#) (20 mg daily) was added to [desipramine](#) (50 mg daily), the mean maximum concentration of [desipramine](#) increased by 278% and the AUC increased by 342%. [Desipramine](#) trough concentrations continued to be 198% above baseline 3 weeks after [fluoxetine](#) was discontinued. The same study compared pharmacokinetics of [desipramine](#) when combined with [sertraline](#). The impact of [sertraline](#) was modest, resulting in small and short-term increases in [desipramine](#) plasma concentrations [517].

c) Concomitant administration of fluoxetine and desipramine was reported to result in an increased desipramine level and new onset of delirium in a 69-year-old male within 10 days of the addition of fluoxetine to the patient's regimen [518].

d) Fluoxetine increased the level of tricyclic antidepressants (nortriptyline, imipramine, desipramine) in 4 patients. After the addition of fluoxetine, the ratio of antidepressant level to dose increased by 109% to 486% in the patients. Three patients developed clinical symptoms (anticholinergic effects, constipation, urinary hesitancy, sedation, unstable gait) as a result of the increased levels [519].

e) A 39-year-old female experienced symptomatic increases in her desipramine levels with concomitant fluoxetine therapy. Prior to fluoxetine therapy, the patient's measured levels of desipramine had ranged from 148 to 160 nanograms/milliliter (ng/mL; 556 to 601 nanomol/L) on a regimen of 300 mg daily. Five weeks after the addition of fluoxetine 20 mg daily, she reported anticholinergic symptoms, sedation, and confusion with a desipramine level of 527 ng/mL (1978 nanomol/L). The desipramine dose was lowered to 200 mg/day; 11 days later, the level was 244 ng/mL (916 nanomol/L); the patient reported decreased energy, impaired short-term memory, and some "garbled" speech, as well as an episode of nausea, dizziness, and syncope. The desipramine dose was reduced to 50 mg/day, and the adverse effects resolved in 6 days. Eight days later, the desipramine level was 122 ng/mL (458 nanomol/L) [520].

f) A 33-year-old depressed male developed adverse effects of dry mouth, tinnitus, and difficulties with alertness and memory while receiving fluoxetine 40 mg daily and desipramine 150 mg daily for 5 weeks; fluoxetine was discontinued and the blood levels of desipramine decreased from 938 to 48 nanograms/mL (3521 to 180 nanomol/L) with resolution of clinical symptoms [521].

g) A 75-year-old female experienced symptomatic increases in her desipramine serum concentrations when fluoxetine was added. Desipramine serum levels ranged from 109 to 150 ng/mL (409 to 563 nanomol/L) with oral doses of 300 mg at bedtime prior to fluoxetine therapy. Following the addition of oral fluoxetine 20 mg daily to the regimen, the desipramine serum level increased to 212 ng/mL (796 nanomol/L) within five days. The fluoxetine dose was increased to 40 mg/day three days later, and the desipramine serum level was 419 ng/mL (1573 nanomol/L) after four days. A worsening of depression and severe fatigue coincided with the increases in desipramine serum levels. Withdrawal of fluoxetine and reduction in the desipramine dose to 200 mg daily reduced the desipramine serum level to 231 ng/mL (867 nanomol/L) within two weeks [522].

3.5.1.JY| Octreotide

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

2) Summary: Octreotide and fluoxetine have been shown to prolong the QTc interval at the recommended therapeutic dose[244][245]. Even though no formal drug interaction studies have been done, the coadministration of drugs known to prolong the QTc interval is not recommended.

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

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

7) Probable Mechanism: additive effects on QT prolongation

3.5.1.JZ| Ondansetron

- 1) Interaction Effect: an increased risk of QT interval prolongation
- 2) Summary: **Ondansetron** prolongs the QT interval in a dose-dependent manner and postmarketing cases of **torsade de pointes** have been reported. Concomitant use of **ondansetron** with other QT-prolonging drugs may result in additive prolongation of the QT interval. If coadministration is necessary, **ECG monitoring** is recommended[104][105].
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: **Ondansetron** prolongs the QT interval in a dose-dependent manner. Use caution with concomitant use of **ondansetron** and drugs known to prolong the QT interval. If coadministration is necessary, **ECG monitoring** is recommended[104][105].
- 7) Probable Mechanism: additive effects on QT interval prolongation

3.5.1.KA| Ondansetron

- 1) Interaction Effect: increased plasma concentrations of **ondansetron** and increased risk of QT prolongation
- 2) Summary: The concomitant use of **fluoxetine** with drugs known to prolong the QT interval, such as **ondansetron**, should be avoided. **Fluoxetine** is a potent inhibitor of CYP2D6 and **ondansetron** is a CYP2D6 substrate. Coadministration with **fluoxetine** may increase the plasma concentration of **ondansetron** via the inhibition of CYP2D6-mediated metabolism pathway, increasing the risk of QT interval prolongation effects. If **fluoxetine** is added to a preexisting **ondansetron** regimen, consider a baseline ECG, on-treatment monitoring, and decreasing the dose of **ondansetron**[173][105].
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Avoid the concomitant use of **fluoxetine** with drugs known to prolong the QT interval, such as **ondansetron** because the coadministration may increase the plasma concentration of **ondansetron**, increasing the risk of QT interval prolongation effects. If **fluoxetine** is added to a preexisting **ondansetron** regimen, consider a baseline ECG, on-treatment monitoring, and decreasing the dose of **ondansetron**[173][105].
- 7) Probable Mechanism: additive QT interval prolongation; inhibition of CYP2D6-mediated metabolism of **ondansetron** by **fluoxetine**

3.5.1.KB| Opipramol

- 1) Interaction Effect: increased risk of tricyclic antidepressant toxicity, QT prolongation and **serotonin syndrome**
- 2) Summary: **Fluoxetine**, a potent CYP2D6 inhibitor, is associated with an increased risk of **serotonin syndrome**, QT prolongation, and **ventricular arrhythmias** (including **torsade de pointes**). Concomitant therapy with CYP2D6-metabolized tricyclic antidepressants (TCAs) may potentiate these risks and introduce TCA toxicity[173]; concurrent use of **fluoxetine** and **desipramine**, **nortriptyline**, and **imipramine** has resulted in significant increases in TCA concentrations [517][523][524][525][526][527]. Use caution with concurrent administration of **fluoxetine** and TCAs. If **fluoxetine** is added to an existing TCA regimen, consider TCA dose reduction. If **fluoxetine** and a TCA are coadministered or **fluoxetine** has been recently discontinued, consider plasma TCA monitoring. If **serotonin syndrome** occurs, immediately discontinue **fluoxetine** and TCA. If **ventricular arrhythmias** develop, consider **fluoxetine** discontinuation and cardiac evaluation [173].

- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Use caution with concurrent administration of [fluoxetine](#) and TCAs, as elevated TCA plasma concentrations may occur. If [fluoxetine](#) is added to an existing TCA regimen, consider TCA dose reduction. If [fluoxetine](#) and a TCA are coadministered or [fluoxetine](#) has been recently discontinued, consider plasma TCA monitoring. If [serotonin syndrome](#) occurs, immediately discontinue [fluoxetine](#) and TCA. If [ventricular arrhythmias](#) develop, consider [fluoxetine](#) discontinuation and cardiac evaluation[173]
- 7) Probable Mechanism: decreased CYP2D6-mediated metabolism of tricyclic antidepressants by [fluoxetine](#); additive effects on QT prolongation; additive serotonergic effects
- 8) Literature Reports

a) Previously stable plasma levels of [imipramine](#) and [desipramine](#) rose more than 2- to 10-fold with [fluoxetine](#) coadministration in 2 clinical studies. This effect may persist for 3 weeks or more after [fluoxetine](#) discontinuation. Dose reduction and temporary monitoring of tricyclic antidepressant plasma concentrations may be indicated with concurrent [fluoxetine](#) treatment or recent [fluoxetine](#) discontinuation [173].

b) [Fluoxetine](#) statistically and clinically significantly increased [desipramine](#) concentrations in 18 healthy subjects. When [fluoxetine](#) (20 mg daily) was added to [desipramine](#) (50 mg daily), the mean maximum concentration of [desipramine](#) increased by 278% and the AUC increased by 342%. [Desipramine](#) trough concentrations continued to be 198% above baseline 3 weeks after [fluoxetine](#) was discontinued. The same study compared pharmacokinetics of [desipramine](#) when combined with [sertraline](#). The impact of [sertraline](#) was modest, resulting in small and short-term increases in [desipramine](#) plasma concentrations [517].

c) Concomitant administration of [fluoxetine](#) and [desipramine](#) was reported to result in an increased [desipramine](#) level and new onset of [delirium](#) in a 69-year-old male within 10 days of the addition of [fluoxetine](#) to the patient's regimen [518].

d) [Fluoxetine](#) increased the level of tricyclic antidepressants ([nortriptyline](#), [imipramine](#), [desipramine](#)) in 4 patients. After the addition of [fluoxetine](#), the ratio of antidepressant level to dose increased by 109% to 486% in the patients. Three patients developed clinical symptoms (anticholinergic effects, constipation, urinary hesitancy, sedation, unstable gait) as a result of the increased levels [519].

e) A 39-year-old female experienced symptomatic increases in her [desipramine](#) levels with concomitant [fluoxetine](#) therapy. Prior to [fluoxetine](#) therapy, the patient's measured levels of [desipramine](#) had ranged from 148 to 160 nanograms/milliliter (ng/mL; 556 to 601 nanomol/L) on a regimen of 300 mg daily. Five weeks after the addition of [fluoxetine](#) 20 mg daily, she reported anticholinergic symptoms, sedation, and confusion with a [desipramine](#) level of 527 ng/mL (1978 nanomol/L). The [desipramine](#) dose was lowered to 200 mg/day; 11 days later, the level was 244 ng/mL (916 nanomol/L); the patient reported decreased energy, impaired short-term memory, and some "garbled" speech, as well as an episode of nausea, dizziness, and syncope. The [desipramine](#) dose was reduced to 50 mg/day, and the adverse effects resolved in 6 days. Eight days later, the [desipramine](#) level was 122 ng/mL (458 nanomol/L) [520].

f) A 33-year-old depressed male developed adverse effects of dry mouth, tinnitus, and difficulties with alertness and memory while receiving [fluoxetine](#) 40 mg daily and [desipramine](#) 150 mg daily for 5 weeks; [fluoxetine](#) was discontinued and the blood levels of [desipramine](#) decreased from 938 to 48 nanograms/mL (3521 to 180 nanomol/L) with resolution of clinical symptoms [521].

g) A 75-year-old female experienced symptomatic increases in her [desipramine](#) serum concentrations when [fluoxetine](#) was added. [Desipramine](#) serum levels ranged from 109 to 150 ng/mL (409 to 563 nanomol/L) with oral doses of 300 mg at bedtime prior to [fluoxetine](#) therapy. Following the addition of oral [fluoxetine](#) 20 mg daily to the regimen, the [desipramine](#) serum level increased to 212 ng/mL (796 nanomol/L) within five days. The [fluoxetine](#) dose was increased to 40 mg/day three days later, and the [desipramine](#) serum level was 419 ng/mL (1573 nanomol/L) after four days. A worsening of depression and severe fatigue coincided with the increases in [desipramine](#) serum levels. Withdrawal of [fluoxetine](#) and reduction in the [desipramine](#) dose to 200 mg daily reduced the [desipramine](#) serum level to 231 ng/mL (867 nanomol/L) within two weeks [522].

3.5.1.KC| [Oxaprozin](#)

1) Interaction Effect: an increased risk of bleeding

2) Summary: Caution is recommended with the concomitant use of NSAIDs and antidepressants, including SSRIs due to an increased risk of [intracranial hemorrhage](#)[529] and [gastrointestinal bleeding](#) [533][534][530][531]. Bleeding events have included [epistaxis](#), ecchymosis, [hematoma](#), [petechiae](#), and life-threatening hemorrhages [536][535][537][538]. When an SSRI and an NSAID are given concurrently, monitor the patient for signs of increased bleeding.

3) Severity: major

4) Onset: unspecified

5) Substantiation: established

6) Clinical Management: Use caution if NSAIDs and SSRIs are coadministered. Concomitant use of NSAIDs and SSRIs may cause an increased risk of [intracranial hemorrhage](#)[529] and [gastrointestinal bleeding](#) [530][531]. When an SSRI and an NSAID are given concurrently, monitor the patient for signs of increased bleeding.

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

8) Literature Reports

a) Concomitant use of NSAIDs and antidepressants, including tricyclic antidepressants, SSRIs, serotonin-norepinephrine reuptake inhibitors, and MAOIs, resulted in a 60% increased risk of [intracranial hemorrhage](#) within 30 days of concomitant use compared with antidepressant use alone. There was no significant difference between the antidepressant drug classes and the increased risk; however, there was an increased risk associated with male patients compared with female patients [529].

b) SSRIs increase the risk of upper gastrointestinal (GI) bleeding, and this effect is potentiated by concurrent use of NSAIDs or low-dose [aspirin](#). Hospitalizations for [upper GI bleeding](#) were searched among 26,005 users of antidepressant medications and compared with the number of hospitalizations in those patients who did not receive prescriptions for antidepressants. The amount of [upper GI bleeding](#) episodes was 3.6 times more than expected. Combined use of an SSRI and NSAIDs or low-dose [aspirin](#) increased the risk to 12.2 and 5.2 times, respectively. The findings of this study demonstrate an increased risk of [upper GI bleeding](#) during the use of SSRIs. Combined use of SSRIs and NSAIDs or low-dose [aspirin](#) increased the risk even further [532].

c) Two metaanalyses of incidents of upper GI bleed due to SSRIs, NSAIDs, and their combination found that SSRIs increased the risk by 1.73 [533] to 2.36 times [534], NSAIDs by 2.55 times [533], and the combination of SSRIs and NSAIDs by 4.02 [533] to 6.33 times [534].

d)) The release of serotonin by [platelets](#) is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs and NSAIDs have been associated with an increased risk of bleeding [535].

3.5.1.KD] [Oxycodone](#)

1)) Interaction Effect: increased risk of CNS depression

2)) Summary: Use caution with concomitant use of the CNS depressant [oxycodone](#) with another CNS depressant, as additive CNS depressant effects, such as [respiratory depression](#), hypotension, and profound sedation, can progress to coma or death. Assess the duration of use and degree of tolerance to CNS depressants (including alcohol and illicit drugs) before concurrent use. If coadministration is clinically necessary, monitor the patient and decrease the dose of 1 or both drugs[123]. Initiate [oxycodone](#) controlled-release formulations at one-third to one-half of the usual dosage [124][125].

3)) Severity: major

4)) Onset: unspecified

5)) Substantiation: theoretical

6)) Clinical Management: Use caution with concomitant use of [oxycodone](#) with another CNS depressant, as additive CNS depressant effects, such as [respiratory depression](#), hypotension, and profound sedation, can progress to coma or death. Assess the duration of use and degree of tolerance to CNS depressants (including alcohol and illicit drugs) before concurrent use. If coadministration is clinically necessary, monitor the patient and decrease the dose of 1 or both drugs[123]. Initiate [oxycodone](#) controlled-release formulations at one-third to one-half of the usual dosage [124][125].

7)) Probable Mechanism: additive CNS depression effects

3.5.1.KE] [Oxycodone](#)

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

2)) Summary: Coadministration of [fluoxetine](#), a CYP2D6 inhibitor, and [oxycodone](#) may result in prolonged or increased opioid effects. These effects may be more pronounced when [fluoxetine](#) is added after stable dose of [oxycodone](#) is achieved. Because both [fluoxetine](#) and [oxycodone](#) both affect the serotonergic neurotransmitter system, coadministration may also result in [serotonin syndrome](#). If concomitant use of [oxycodone](#) and [fluoxetine](#) is clinically required, monitor patients frequently for signs of sedation, [respiratory depression](#), and [serotonin syndrome](#), especially during treatment initiation and dosage adjustment. Consider dosage reduction of [oxycodone](#) until stable plasma concentrations are achieved. Discontinue [oxycodone](#) if [serotonin syndrome](#) is suspected. If [fluoxetine](#) is discontinued, monitor for signs of [opioid withdrawal](#) and consider increasing the [oxycodone](#) dosage until stable drug effects are achieved[123].

3)) Severity: major

4)) Onset: unspecified

5)) Substantiation: theoretical

6)) Clinical Management: Coadministration of [fluoxetine](#), a CYP2D6 inhibitor, and [oxycodone](#) may result in prolonged or increased opioid effects. These effects may be more pronounced when [fluoxetine](#) is added after stable dose of [oxycodone](#) is achieved. Because both [fluoxetine](#) and [oxycodone](#) both affect the serotonergic neurotransmitter system, coadministration may also result in [serotonin syndrome](#). If concomitant use of [oxycodone](#) and [fluoxetine](#) is clinically required, monitor patients frequently for signs of sedation, [respiratory depression](#), and [serotonin syndrome](#), especially during treatment initiation and dosage adjustment. Consider dosage reduction of [oxycodone](#) until stable plasma concentrations are achieved. Discontinue [oxycodone](#) if [serotonin syndrome](#) is suspected. If [fluoxetine](#) is discontinued, monitor for signs of [opioid withdrawal](#) and consider increasing the [oxycodone](#) dosage until stable drug effects are achieved[123].

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

3.5.1.KF] [Oxymorphone](#)

- 1J) Interaction Effect: increased risk of [paralytic ileus](#); increased risk of respiratory and CNS depression
- 2J) Summary: Coadministration of [oxymorphone](#) and an anticholinergic agent may result in additive respiratory and CNS depressant effects. Concomitant use may also cause urinary retention or severe constipation resulting in [paralytic ileus](#). If coadministration is clinically necessary, monitor for respiratory or CNS depression[127]. Dose reductions of one or both agents may be warranted.
- 3J) Severity: major
- 4J) Onset: unspecified
- 5J) Substantiation: probable
- 6J) Clinical Management: Coadministration of [oxymorphone](#) and an anticholinergic agent may result in additive respiratory and CNS depressant effects. Concomitant use may also cause urinary retention or severe constipation resulting in [paralytic ileus](#). If coadministration is clinically necessary, monitor for respiratory or CNS depression[127]. Dose reductions of one or both agents may be warranted.
- 7J) Probable Mechanism: unknown; additive respiratory and CNS depressant effects

3.5.1.KG] [Oxyphenbutazone](#)

- 1J) Interaction Effect: an increased risk of bleeding
- 2J) Summary: Caution is recommended with the concomitant use of NSAIDs and antidepressants, including SSRIs due to an increased risk of [intracranial hemorrhage](#)[529] and [gastrointestinal bleeding](#) [533][534][530][531]. Bleeding events have included [epistaxis](#), ecchymosis, [hematoma](#), [petechiae](#), and life-threatening hemorrhages [536][535][537][538]. When an SSRI and an NSAID are given concurrently, monitor the patient for signs of increased bleeding.
- 3J) Severity: major
- 4J) Onset: unspecified
- 5J) Substantiation: established
- 6J) Clinical Management: Use caution if NSAIDs and SSRIs are coadministered. Concomitant use of NSAIDs and SSRIs may cause an increased risk of [intracranial hemorrhage](#)[529] and [gastrointestinal bleeding](#) [530][531]. When an SSRI and an NSAID are given concurrently, monitor the patient for signs of increased bleeding.
- 7J) Probable Mechanism: depletion of [platelet](#) serotonin by SSRI; additive effects
- 8J) Literature Reports

aJ) Concomitant use of NSAIDs and antidepressants, including tricyclic antidepressants, SSRIs, serotonin-norepinephrine reuptake inhibitors, and MAOIs, resulted in a 60% increased risk of [intracranial hemorrhage](#) within 30 days of concomitant use compared with antidepressant use alone. There was no significant difference between the antidepressant drug classes and the increased risk; however, there was an increased risk associated with male patients compared with female patients [529].

bJ) SSRIs increase the risk of upper gastrointestinal (GI) bleeding, and this effect is potentiated by concurrent use of NSAIDs or low-dose [aspirin](#). Hospitalizations for [upper GI bleeding](#) were searched among 26,005 users of antidepressant medications and compared with the number of hospitalizations in those patients who did not receive prescriptions for antidepressants. The amount of [upper GI bleeding](#) episodes was 3.6 times more than expected. Combined use of an SSRI and NSAIDs or low-dose [aspirin](#) increased the risk to 12.2 and 5.2 times, respectively. The

findings of this study demonstrate an increased risk of [upper GI bleeding](#) during the use of SSRIs. Combined use of SSRIs and NSAIDs or low-dose [aspirin](#) increased the risk even further [532].

c) Two metaanalyses of incidents of upper GI bleed due to SSRIs, NSAIDs, and their combination found that SSRIs increased the risk by 1.73 [533] to 2.36 times [534], NSAIDs by 2.55 times [533], and the combination of SSRIs and NSAIDs by 4.02 [533] to 6.33 times [534].

d) The release of serotonin by [platelets](#) is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs and NSAIDs have been associated with an increased risk of bleeding [535].

3.5.1.KH] [Palonosetron](#)

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

2) Summary: Concomitant use of [mirtazapine](#) with other serotonergic agents may increase the risk of [serotonin syndrome](#). Monitor for the emergence of [serotonin syndrome](#); symptoms include mental status changes (eg, agitation, hallucinations, [delirium](#), coma), autonomic instability (eg, [tachycardia](#), labile blood pressure, dizziness, diaphoresis, flushing, [hyperthermia](#)), neuromuscular abnormalities (eg, tremor, rigidity, myoclonus, hyperreflexia, incoordination), seizures, with or without, gastrointestinal symptoms (eg, nausea, vomiting, diarrhea). Discontinue use of [palonosetron](#) and begin supportive treatment if the patient exhibits signs and symptoms of [serotonin syndrome](#)[474].

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: If concomitant use with other serotonergic drugs is clinically warranted, monitor for the emergence of [serotonin syndrome](#). Discontinue use of [palonosetron](#) and begin supportive treatment if the patient exhibits signs and symptoms of [serotonin syndrome](#)[474].

7) Probable Mechanism: unknown

3.5.1.KI] [Panobinostat](#)

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

2) Summary: Concurrent use of panobinostat with QT-prolonging drugs is not recommended, as additive effects on the QT interval may develop. Conduct frequent [ECG monitoring](#) if concurrent use with antiemetics known to prolong the QT interval is warranted. Interrupt treatment if the Fridericia-corrected QT interval increases to 480 msec or more. Discontinue panobinostat if QT-interval prolongation does not resolve after any electrolyte abnormalities are corrected[147].

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Concurrent use of panobinostat with QT-prolonging drugs is not recommended, as additive effects on the QT interval may develop. Conduct frequent [ECG monitoring](#) if concurrent use with antiemetics known to prolong the QT interval is warranted. Interrupt treatment if the Fridericia-corrected QT interval increases to 480 msec or more. Discontinue panobinostat if QT-interval prolongation does not resolve after any electrolyte abnormalities are corrected[147].

7) Probable Mechanism: additive QT effects

3.5.1.KJ] [Parecoxib](#)

1) Interaction Effect: an increased risk of bleeding

2j) Summary: Caution is recommended with the concomitant use of NSAIDs and antidepressants, including SSRIs due to an increased risk of [intracranial hemorrhage](#)[529] and [gastrointestinal bleeding](#) [533][534][530][531]. Bleeding events have included [epistaxis](#), ecchymosis, [hematoma](#), [petechiae](#), and life-threatening hemorrhages [536][535][537][538]. When an SSRI and an NSAID are given concurrently, monitor the patient for signs of increased bleeding.

3j) Severity: major

4j) Onset: unspecified

5j) Substantiation: established

6j) Clinical Management: Use caution if NSAIDs and SSRIs are coadministered. Concomitant use of NSAIDs and SSRIs may cause an increased risk of [intracranial hemorrhage](#)[529] and [gastrointestinal bleeding](#) [530][531]. When an SSRI and an NSAID are given concurrently, monitor the patient for signs of increased bleeding.

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

8j) Literature Reports

aj) Concomitant use of NSAIDs and antidepressants, including tricyclic antidepressants, SSRIs, serotonin-norepinephrine reuptake inhibitors, and MAOIs, resulted in a 60% increased risk of [intracranial hemorrhage](#) within 30 days of concomitant use compared with antidepressant use alone. There was no significant difference between the antidepressant drug classes and the increased risk; however, there was an increased risk associated with male patients compared with female patients [529].

bj) SSRIs increase the risk of upper gastrointestinal (GI) bleeding, and this effect is potentiated by concurrent use of NSAIDs or low-dose [aspirin](#). Hospitalizations for [upper GI bleeding](#) were searched among 26,005 users of antidepressant medications and compared with the number of hospitalizations in those patients who did not receive prescriptions for antidepressants. The amount of [upper GI bleeding](#) episodes was 3.6 times more than expected. Combined use of an SSRI and NSAIDs or low-dose [aspirin](#) increased the risk to 12.2 and 5.2 times, respectively. The findings of this study demonstrate an increased risk of [upper GI bleeding](#) during the use of SSRIs. Combined use of SSRIs and NSAIDs or low-dose [aspirin](#) increased the risk even further [532].

cj) Two metaanalyses of incidents of upper GI bleed due to SSRIs, NSAIDs, and their combination found that SSRIs increased the risk by 1.73 [533] to 2.36 times [534], NSAIDs by 2.55 times [533], and the combination of SSRIs and NSAIDs by 4.02 [533] to 6.33 times [534].

dj) The release of serotonin by [platelets](#) is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs and NSAIDs have been associated with an increased risk of bleeding [535].

3.5.1.KK] Pargyline

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

2j) Summary: Concomitant use of [fluoxetine](#) and an MAOI is contraindicated. Concurrent administration or overlapping therapy with [fluoxetine](#) and an MAOI 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 SSRIs and MAOIs. A minimum of 14 days should elapse after discontinuing an MAOI intended to treat psychiatric disorders before initiating therapy with [fluoxetine](#), and a minimum of 5 weeks should elapse after discontinuing [fluoxetine](#) before initiating therapy with an MAOI intended to treat psychiatric disorders[283].

- 3J) Severity: contraindicated
- 4J) Onset: unspecified
- 5J) Substantiation: theoretical
- 6J) Clinical Management: Concurrent use of [fluoxetine](#) and an MAOI is contraindicated. Wait at least 14 days after discontinuing an MAOI intended to treat psychiatric disorders before initiating [fluoxetine](#). Wait at least 5 weeks after discontinuing [fluoxetine](#) before initiating therapy with an MAOI intended to treat psychiatric disorders[283].
- 7J) Probable Mechanism: additive serotonergic effect

3.5.1.KLJ Parnaparin

- 1J) Interaction Effect: an increased risk of bleeding
- 2J) Summary: The release of serotonin by [platelets](#) is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs and anticoagulants has been associated with an increased risk of bleeding[458][457]. Bleeding events reported have included [epistaxis](#), ecchymosis, [hematoma](#), [petechiae](#), and life-threatening hemorrhages. Altered anticoagulant effects (including increased bleeding) have been reported with the coadministration of SSRIs with anticoagulants [457].
- 3J) Severity: major
- 4J) Onset: delayed
- 5J) Substantiation: probable
- 6J) Clinical Management: When [fluoxetine](#) and an anticoagulant are given concurrently, monitor patient for signs of increased bleeding. Patients who are taking an anticoagulant should be monitored closely for altered anticoagulant effects, including increased bleeding, when [fluoxetine](#) therapy is initiated or discontinued[457].
- 7J) Probable Mechanism: unknown
- 8J) Literature Reports

aJ) 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 a significant 1.7-fold increased risk for hospitalization for nongastrointestinal bleeding; however, the rate of [gastrointestinal bleeding](#) was not significantly different [458].

3.5.1.KMJ Paroxetine

- 1J) Interaction Effect: increased exposure of [fluoxetine](#), [paroxetine](#), or both; increased risk of [serotonin syndrome](#); increased risk of QT-interval prolongation
- 2J) Summary: [Fluoxetine](#) is an SSRI and a potent CYP2D6 inhibitor, predominantly metabolized by CYP2D6[173]. [Paroxetine](#) is also an SSRI, a CYP2D6 substrate, and a strong CYP2D6 inhibitor [346]. Concomitant use may result in additive effects on the QT-interval or additive serotonergic effects and should be avoided. If coadministration of [fluoxetine](#) and [paroxetine](#) is necessary, consider periodic [ECG monitoring](#) and monitor patients for symptoms of [serotonin syndrome](#), including neuromuscular abnormalities, autonomic instability, gastrointestinal symptoms, and mental status changes, especially during treatment initiation and dose increases. [Serotonin syndrome](#) can be life-threatening. If [serotonin syndrome](#) develops or symptoms of [ventricular arrhythmia](#) occur, discontinue [fluoxetine](#) and [paroxetine](#) and initiate supportive care [173].
- 3J) Severity: major
- 4J) Onset: unspecified

5J) Substantiation: theoretical

6J) Clinical Management: Coadministration of [fluoxetine](#) and [paroxetine](#) should be avoided, because it may result in additive effects on the QT-interval or a life-threatening condition called [serotonin syndrome](#). If concomitant use is necessary, consider periodic [ECG monitoring](#) and discuss the risks of [serotonin syndrome](#) with the patient. Monitor closely for symptoms of [serotonin syndrome](#) (mental status changes, autonomic instability, neuromuscular symptoms, seizures, and gastrointestinal symptoms), especially during treatment initiation and dose increases. If [serotonin syndrome](#) develops or symptoms of [ventricular arrhythmia](#) occur, discontinue [fluoxetine](#) and [paroxetine](#) and initiate supportive care[173].

7J) Probable Mechanism: inhibition of CYP2D6-mediated metabolism by both [fluoxetine](#) and [paroxetine](#); additive serotonergic effects; additive QT-interval prolongation effects

3.5.1.KN] Pasireotide

1J) Interaction Effect: increased risk of QT prolongation

2J) Summary: Pasireotide is associated with QT-interval prolongation. In 2 studies, QT prolongation occurred at both therapeutic and supratherapeutic doses of pasireotide. Concomitant administration of pasireotide with other drugs that prolong the QT interval, including antiarrhythmic medications, may have additive prolonging effects on the QT interval. ECGs at baseline and at 21 days after treatment initiation are recommended when pasireotide is coadministered with other QT-prolonging agents[67].

3J) Severity: major

4J) Onset: unspecified

5J) Substantiation: theoretical

6J) Clinical Management: Concomitant administration of pasireotide and QT-prolonging drugs, including antiarrhythmic medications, may result in additive prolongation of the QT interval. ECGs at baseline and 21 days after treatment initiation are recommended when pasireotide is coadministered with other QT-prolonging agents[67].

7J) Probable Mechanism: additive QT-interval prolongation

3.5.1.KO] Pazopanib

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

2J) Summary: Due to the potential for additive effects on QT-interval prolongation and increased risk of [torsade de pointes](#), coadministration of pazopanib with drugs that prolong the QT interval should be done cautiously. Baseline and periodic [monitoring of ECG](#) and electrolyte maintenance (eg, [calcium](#), magnesium, potassium) within the normal range is recommended[70].

3J) Severity: major

4J) Onset: unspecified

5J) Substantiation: theoretical

6J) Clinical Management: Coadministration of pazopanib with this drugs that prolong the QT interval should be done cautiously due to the potential for additive effects on the QT interval and increased risk of [torsade de pointes](#). Baseline and periodic [monitoring of ECG](#) and electrolyte maintenance (eg, [calcium](#), magnesium, potassium) within the normal range is recommended[70].

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

3.5.1.KP] [Pentamidine](#)

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

2J) Summary: [Pentamidine](#) and [fluoxetine](#) have been shown to prolong the QTc interval at the recommended therapeutic dose[347][348]. Even though no formal drug interaction studies have been done, the coadministration of drugs known to prolong the QTc interval is not recommended.

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

3.5.1.KQ] [Pentazocine](#)

- 1) Interaction Effect: increased risk of CNS depression (ie, [respiratory depression](#), profound sedation, coma)
- 2) Summary: The concomitant use of [pentazocine](#) with other CNS depressants may result in profound sedation, [respiratory depression](#), coma, and/or death. Reserve concomitant use to clinical settings where alternative treatment options are inadequate. If combination therapy is required, reduce the initial dose of the newly prescribed medication and titrate to clinical response while monitoring for [respiratory depression](#) and sedation[78].
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Reserve concomitant use of [pentazocine](#) with other CNS depressants to clinical settings where alternative treatment options are inadequate. If combination therapy is required, reduce the initial dose of the newly prescribed medication and titrate to clinical response while monitoring for [respiratory depression](#) and sedation[78].
- 7) Probable Mechanism: additive CNS depression

3.5.1.KR] [Pentazocine](#)

- 1) Interaction Effect: increased risk of [serotonin syndrome](#)
- 2) Summary: [Serotonin syndrome](#) may the result from concomitant use of [fluoxetine](#) and serotonergic agents, such as a triptans or other antidepressants. Monitor patients for symptoms of [serotonin syndrome](#), including neuromuscular abnormalities, autonomic instability, and mental status changes, especially during treatment initiation and dose increases. [Serotonin syndrome](#) can be life-threatening. If [serotonin syndrome](#) develops, discontinue [fluoxetine](#) and any concomitant serotonergic agent and initiate supportive care[173].
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Exercise caution with coadministration of [fluoxetine](#) and serotonergic agents, such as a triptans or other antidepressants, because it may result in a life-threatening condition called [serotonin syndrome](#). If these agents are used together, discuss the risks of [serotonin syndrome](#) with the patient and monitor closely for symptoms of [serotonin syndrome](#) (mental status changes, autonomic instability, neuromuscular symptoms, seizures, and gastrointestinal symptoms), especially during treatment initiation and dose increases. If [serotonin syndrome](#) develops, discontinue [fluoxetine](#) and any concomitant serotonergic agent and initiate supportive care[173]
- 7) Probable Mechanism: additive serotonergic effect

3.5.1.KS] [Pentosan Polysulfate Sodium](#)

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

with an increased risk of bleeding[458][457]. Bleeding events reported have included [epistaxis](#), ecchymosis, [hematoma](#), [petechiae](#), and life-threatening hemorrhages. Altered anticoagulant effects (including increased bleeding) have been reported with the coadministration of SSRIs with anticoagulants [457].

3) Severity: major

4) Onset: delayed

5) Substantiation: probable

6) Clinical Management: When [fluoxetine](#) and an anticoagulant are given concurrently, monitor patient for signs of increased bleeding. Patients who are taking an anticoagulant should be monitored closely for altered anticoagulant effects, including increased bleeding, when [fluoxetine](#) therapy is initiated or discontinued[457].

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 a significant 1.7-fold increased risk for hospitalization for nongastrointestinal bleeding; however, the rate of [gastrointestinal bleeding](#) was not significantly different [458].

3.5.1.KT] Periciazine

1) Interaction Effect: risk of enhanced CNS depression

2) Summary: Concomitant use of periciazine with other phenothiazine derivatives or CNS depressants may enhance the CNS depressive effects of both agents. If coadministered, reduce the dose of the phenothiazine derivative or CNS depressant by at least 50% while periciazine is being gradually initiated[44][45].

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Concomitant use of periciazine with other phenothiazine derivatives or CNS depressants may enhance the CNS depressive effects of both agents. If coadministered, reduce the dose of the phenothiazine derivative or CNS depressant by at least 50% while periciazine is being gradually initiated[44][45].

7) Probable Mechanism: additive CNS depression

3.5.1.KU] Phenelzine

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

2) Summary: Concomitant use of [fluoxetine](#) and an MAOI is contraindicated. Concurrent administration or overlapping therapy with [fluoxetine](#) and an MAOI 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 SSRIs and MAOIs. A minimum of 14 days should elapse after discontinuing an MAOI intended to treat psychiatric disorders before initiating therapy with [fluoxetine](#), and a minimum of 5 weeks should elapse after discontinuing [fluoxetine](#) before initiating therapy with an MAOI intended to treat psychiatric disorders[283].

3) Severity: contraindicated

- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Concurrent use of [fluoxetine](#) and an MAOI is contraindicated. Wait at least 14 days after discontinuing an MAOI intended to treat psychiatric disorders before initiating [fluoxetine](#). Wait at least 5 weeks after discontinuing [fluoxetine](#) before initiating therapy with an MAOI intended to treat psychiatric disorders[283].
- 7) Probable Mechanism: additive serotonergic effect

3.5.1.KV] Phenindione

- 1) Interaction Effect: an increased risk of bleeding
- 2) Summary: The release of serotonin by [platelets](#) is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs and anticoagulants has been associated with an increased risk of bleeding[458][457]. Bleeding events reported have included [epistaxis](#), ecchymosis, [hematoma](#), [petechiae](#), and life-threatening hemorrhages. Altered anticoagulant effects (including increased bleeding) have been reported with the coadministration of SSRIs with anticoagulants [457].
- 3) Severity: major
- 4) Onset: delayed
- 5) Substantiation: probable
- 6) Clinical Management: When [fluoxetine](#) and an anticoagulant are given concurrently, monitor patient for signs of increased bleeding. Patients who are taking an anticoagulant should be monitored closely for altered anticoagulant effects, including increased bleeding, when [fluoxetine](#) therapy is initiated or discontinued[457].
- 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 a significant 1.7-fold increased risk for hospitalization for nongastrointestinal bleeding; however, the rate of [gastrointestinal bleeding](#) was not significantly different [458].

3.5.1.KW] Phenprocoumon

- 1) Interaction Effect: an increased risk of bleeding
- 2) Summary: The release of serotonin by [platelets](#) is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs and anticoagulants has been associated with an increased risk of bleeding[458][457]. Bleeding events reported have included [epistaxis](#), ecchymosis, [hematoma](#), [petechiae](#), and life-threatening hemorrhages. Altered anticoagulant effects (including increased bleeding) have been reported with the coadministration of SSRIs with anticoagulants [457].
- 3) Severity: major
- 4) Onset: delayed
- 5) Substantiation: probable
- 6) Clinical Management: When [fluoxetine](#) and an anticoagulant are given concurrently, monitor patient for signs of increased bleeding. Patients who are taking an anticoagulant should be monitored closely for altered anticoagulant effects, including increased bleeding, when [fluoxetine](#) therapy is initiated or discontinued[457].
- 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 a significant 1.7-fold increased risk for hospitalization for nongastrointestinal bleeding; however, the rate of [gastrointestinal bleeding](#) was not significantly different [458].

3.5.1.KX] [Phenylalanine](#)

1) Interaction Effect: increased incidence of [tardive dyskinesia](#)

2) Summary: Taking [phenylalanine](#) concomitantly with certain neuroleptic drugs may exacerbate [tardive dyskinesia](#)[66]. Abnormal [phenylalanine](#) metabolism in certain patients may lead to [phenylalanine](#) accumulation in the brain and in turn, reduced brain availability of other large neutral amino acids. This may interfere with the synthesis of catecholamines [66].

3) Severity: moderate

4) Onset: rapid

5) Substantiation: theoretical

6) Clinical Management: Caution is advised if [phenylalanine](#) is administered with a neuroleptic agent. Monitor the patient closely for signs of [tardive dyskinesia](#).

7) Probable Mechanism: reduced brain availability of other large neutral amino acids and interference with catecholamine synthesis

8) Literature Reports

a) [Phenylalanine](#) tended to increase the incidence of [tardive dyskinesia](#) in patients taking neuroleptics in an open study. Three groups of patients were studied: (1) patients with [unipolar depression](#) with [tardive dyskinesia](#) (n=11), (2) patients with no [tardive dyskinesia](#) with current or past exposure to greater than or equal to 100 milligrams (mg) of a [chlorpromazine](#) equivalent for at least 3 months (n=10), and (3) patients with no [tardive dyskinesia](#) not previously exposed to a neuroleptic drug (n=10). Neuroleptic agents were taken during the study by 6 patients in group 1, and 5 patients in group 2. Patients received powdered [phenylalanine](#) 100 mg/kilogram dissolved in orange juice after an overnight fast. Blood samples were obtained just prior to [phenylalanine](#) administration and 2 hours after administration. Three patients in group 1 (with [tardive dyskinesia](#)) had the highest postloading [phenylalanine](#) plasma levels, this group as a whole had higher (though nonsignificant) mean [phenylalanine](#) levels than the other groups. [Tardive dyskinesia](#) score (measured using the [Abnormal Involuntary Movements Scale \(AIMS\)](#)) nonsignificantly increased in group 1. Postloading [phenylalanine](#) level and postloading AIMS scores were significantly positively correlated in group 1 (rs=0.347, p less than 0.05; Spearman correlation coefficient 0.543, p less than 0.05). Postloading [phenylalanine](#) level and baseline AIMS scores demonstrated a trend toward correlation (rs=0.246, p=0.092; Spearman correlation coefficient 0.679, p less than 0.05). In all patients, [phenylalanine](#) loading increased plasma [phenylalanine](#) levels approximately eight-fold, and plasma tyrosine increased 2.5 times as a result of conversion of [phenylalanine](#) to tyrosine. Plasma levels of competing large neutral amino acids such as tryptophan decreased slightly [65].

3.5.1.KY] [Phenylbutazone](#)

1) Interaction Effect: an increased risk of bleeding

2j) Summary: Caution is recommended with the concomitant use of NSAIDs and antidepressants, including SSRIs due to an increased risk of [intracranial hemorrhage](#)[529] and [gastrointestinal bleeding](#) [533][534][530][531]. Bleeding events have included [epistaxis](#), ecchymosis, [hematoma](#), [petechiae](#), and life-threatening hemorrhages [536][535][537][538]. When an SSRI and an NSAID are given concurrently, monitor the patient for signs of increased bleeding.

3j) Severity: major

4j) Onset: unspecified

5j) Substantiation: established

6j) Clinical Management: Use caution if NSAIDs and SSRIs are coadministered. Concomitant use of NSAIDs and SSRIs may cause an increased risk of [intracranial hemorrhage](#)[529] and [gastrointestinal bleeding](#) [530][531]. When an SSRI and an NSAID are given concurrently, monitor the patient for signs of increased bleeding.

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

8j) Literature Reports

aj) Concomitant use of NSAIDs and antidepressants, including tricyclic antidepressants, SSRIs, serotonin-norepinephrine reuptake inhibitors, and MAOIs, resulted in a 60% increased risk of [intracranial hemorrhage](#) within 30 days of concomitant use compared with antidepressant use alone. There was no significant difference between the antidepressant drug classes and the increased risk; however, there was an increased risk associated with male patients compared with female patients [529].

bj) SSRIs increase the risk of upper gastrointestinal (GI) bleeding, and this effect is potentiated by concurrent use of NSAIDs or low-dose [aspirin](#). Hospitalizations for [upper GI bleeding](#) were searched among 26,005 users of antidepressant medications and compared with the number of hospitalizations in those patients who did not receive prescriptions for antidepressants. The amount of [upper GI bleeding](#) episodes was 3.6 times more than expected. Combined use of an SSRI and NSAIDs or low-dose [aspirin](#) increased the risk to 12.2 and 5.2 times, respectively. The findings of this study demonstrate an increased risk of [upper GI bleeding](#) during the use of SSRIs. Combined use of SSRIs and NSAIDs or low-dose [aspirin](#) increased the risk even further [532].

cj) Two metaanalyses of incidents of upper GI bleed due to SSRIs, NSAIDs, and their combination found that SSRIs increased the risk by 1.73 [533] to 2.36 times [534], NSAIDs by 2.55 times [533], and the combination of SSRIs and NSAIDs by 4.02 [533] to 6.33 times [534].

dj) The release of serotonin by [platelets](#) is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs and NSAIDs have been associated with an increased risk of bleeding [535].

3.5.1.KZ| [Phenytoin](#)

1j) Interaction Effect: increased risk of [phenytoin](#) toxicity (ataxia, hyperreflexia, [nystagmus](#), tremor)

2j) Summary: Patients receiving stable doses of [phenytoin](#) have developed elevated [phenytoin](#) plasma concentrations and clinical toxicity following initiation of concomitant [fluoxetine](#)[173]; alternatively, patients stabilized on [fluoxetine](#) and [phenytoin](#) therapy may experience subtherapeutic concentrations of [phenytoin](#) and loss of seizure control when concurrent [fluoxetine](#) is discontinued [449]. During concurrent use, measure baseline [phenytoin](#) serum levels and monitor periodically to assure stability; lower [phenytoin](#) dosage may be required during coadministration. Serum levels of [phenytoin](#) should also be monitored following the discontinuation of [fluoxetine](#); however, because of the long half-life of [fluoxetine](#), decreases in [phenytoin](#) levels may not be clinically significant for a few weeks.

3j) Severity: moderate

4) Onset: delayed

5) Substantiation: probable

6) Clinical Management: Patients receiving stable doses of [phenytoin](#) have developed elevated [phenytoin](#) plasma concentrations and clinical toxicity following initiation of concomitant [fluoxetine](#)[173], and alternatively, patients stabilized on [fluoxetine](#) and [phenytoin](#) therapy may experience subtherapeutic concentrations of [phenytoin](#) and loss of seizure control when concurrent [fluoxetine](#) is discontinued [449]. During concurrent use, measure baseline [phenytoin](#) serum levels and monitor periodically to assure stability; lower [phenytoin](#) dosage may be required during coadministration. Serum levels of [phenytoin](#) should also be monitored following the discontinuation of [fluoxetine](#); however, because of the long half-life of [fluoxetine](#), decreases in [phenytoin](#) levels may not be clinically significant for a few weeks.

7) Probable Mechanism: decreased [phenytoin](#) metabolism

8) Literature Reports

a) A 42-year-old man receiving [phenytoin](#) 200 mg daily and [carbamazepine](#) 600 mg daily for grand mal seizures remained symptomatic with a [phenytoin](#) level of 2 nanograms/milliliter (ng/mL; 7.9 nanomol/L). [Phenytoin](#) was subsequently increased to 400 mg daily, [fluoxetine](#) 20 mg daily was added for aggression, and the patient experienced resolution of his behavioral problems and a cessation of his seizure activity. The [phenytoin](#) level ranged between 10.9 ng/mL and 15.7 ng/mL (43.21 nanomol/L and 62.23 nanomol/L) during [fluoxetine](#) therapy. However, the patient discontinued [fluoxetine](#) on his own and after a month experienced a recurrence of problems. [Phenytoin](#) concentration was measured at 6.6 ng/mL (26.2 nanomol/L) 6 weeks after the discontinuation of [fluoxetine](#), despite no change in his [phenytoin](#) dose. This case report illustrates the need for close monitoring of [phenytoin](#) levels when [fluoxetine](#) is initiated and discontinued, since subtherapeutic levels of [phenytoin](#) may result if doses of [phenytoin](#) are not readjusted following the cessation of [fluoxetine](#) [449].

b) During an in vitro study, the inhibitory effects of [fluoxetine](#) on CYP2C9 were evaluated using p-hydroxylation of [phenytoin](#) as an established index reaction reflecting CYP2C9 activity. In vivo, p-hydroxylation of [phenytoin](#) depends on the formation of 5-(p-hydroxy-phenyl)-5-phenylhydantoin (HPPH). [Fluoxetine](#), specifically the R-enantiomer, impaired the formation of HPPH, which can lead to an increase in steady-state [phenytoin](#) levels [450].

c) Twenty-three reported cases of fluoxetine-phenytoin interactions have resulted in large increases in serum [phenytoin](#) levels and/or symptoms of [phenytoin](#) toxicity. On the average, the adverse effects began within 2 weeks after [fluoxetine](#) was added to existing [phenytoin](#) therapy. The average increase in plasma levels in 9 evaluable cases was 161% (range 75 to 309%) and the maximum [phenytoin](#) serum concentration in 16 evaluable cases ranged from 22 to 53.5 mcg/mL (87.21 to 212.07 mcg/L; therapeutic level, 10 to 20 mcg/mL [39.6 to 79.3 mcg/L]) [451].

d) An 84-year-old woman experienced [phenytoin](#) toxicity within 5 days of adding [fluoxetine](#) to stabilized [phenytoin](#) therapy. After 2 months of [phenytoin](#) 300 mg/day, [fluoxetine](#) 20 mg daily was added and increased to 40 mg daily after 10 days. Within five days of starting [fluoxetine](#), she developed vertigo, gait ataxia, [diplopia](#), and altered mental status; her [phenytoin](#) serum level had increased from 15 to 35 mcg/mL (59.5 to 138.7 mcg/L). Both [phenytoin](#) and [fluoxetine](#) were gradually reduced and the signs and symptoms of toxicity abated. Four weeks later she was rechallenged with the same dose of [fluoxetine](#) without a return of toxicity [452].

e) A 57-year-old woman experienced [phenytoin](#) toxicity within 10 days of adding [fluoxetine](#) to stabilized [phenytoin](#) therapy. After [phenytoin](#) 400 mg daily for a year (serum level, 11.5 mcg/mL [45.59 mcg/L]), [fluoxetine](#) 20 mg daily was added. Ten days later she developed vomiting, vertigo, trunk ataxia, limb dysmetria, and [multidirectional nystagmus](#), and the [phenytoin](#) serum

level was 47 mcg/mL (186.3 mmol/L). [Fluoxetine](#) was discontinued and all signs and symptoms of toxicity disappeared over a 3-week period. At 4 weeks post-fluoxetine, the [phenytoin](#) serum level was 20 mcg/mL (79.3 mmol/L) [452].

3.5.1.LA] [Piketoprofen](#)

- 1) Interaction Effect: an increased risk of bleeding
- 2) Summary: Caution is recommended with the concomitant use of NSAIDs and antidepressants, including SSRIs due to an increased risk of [intracranial hemorrhage](#)[529] and [gastrointestinal bleeding](#) [533][534][530][531]. Bleeding events have included [epistaxis](#), ecchymosis, [hematoma](#), [petechiae](#), and life-threatening hemorrhages [536][535][537][538]. When an SSRI and an NSAID are given concurrently, monitor the patient for signs of increased bleeding.
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: established
- 6) Clinical Management: Use caution if NSAIDs and SSRIs are coadministered. Concomitant use of NSAIDs and SSRIs may cause an increased risk of [intracranial hemorrhage](#)[529] and [gastrointestinal bleeding](#) [530][531]. When an SSRI and an NSAID are given concurrently, monitor the patient for signs of increased bleeding.
- 7) Probable Mechanism: depletion of [platelet](#) serotonin by SSRI; additive effects
- 8) Literature Reports

a) Concomitant use of NSAIDs and antidepressants, including tricyclic antidepressants, SSRIs, serotonin-norepinephrine reuptake inhibitors, and MAOIs, resulted in a 60% increased risk of [intracranial hemorrhage](#) within 30 days of concomitant use compared with antidepressant use alone. There was no significant difference between the antidepressant drug classes and the increased risk; however, there was an increased risk associated with male patients compared with female patients [529].

b) SSRIs increase the risk of upper gastrointestinal (GI) bleeding, and this effect is potentiated by concurrent use of NSAIDs or low-dose [aspirin](#). Hospitalizations for [upper GI bleeding](#) were searched among 26,005 users of antidepressant medications and compared with the number of hospitalizations in those patients who did not receive prescriptions for antidepressants. The amount of [upper GI bleeding](#) episodes was 3.6 times more than expected. Combined use of an SSRI and NSAIDs or low-dose [aspirin](#) increased the risk to 12.2 and 5.2 times, respectively. The findings of this study demonstrate an increased risk of [upper GI bleeding](#) during the use of SSRIs. Combined use of SSRIs and NSAIDs or low-dose [aspirin](#) increased the risk even further [532].

c) Two metaanalyses of incidents of upper GI bleed due to SSRIs, NSAIDs, and their combination found that SSRIs increased the risk by 1.73 [533] to 2.36 times [534], NSAIDs by 2.55 times [533], and the combination of SSRIs and NSAIDs by 4.02 [533] to 6.33 times [534].

d) The release of serotonin by [platelets](#) is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs and NSAIDs have been associated with an increased risk of bleeding [535].

3.5.1.LB] [Pimavanserin](#)

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

- 2)) Summary: Clinically significant QT-interval prolongation has occurred at the usual pimavanserin dosage. Avoid concomitant use of pimavanserin with other agents that prolong the QT interval due to the potential for additive effects on the QT interval and an increased risk of [cardiac arrhythmia](#)[43].
- 3)) Severity: major
- 4)) Onset: unspecified
- 5)) Substantiation: theoretical
- 6)) Clinical Management: Concomitant use of pimavanserin with other agents that prolong the QT interval should be avoided due to the potential for additive effects on the QT interval and an increased risk of [cardiac arrhythmia](#)[43].
- 7)) Probable Mechanism: additive effects on the QT interval

3.5.1.LC] [Pimozide](#)

- 1)) Interaction Effect: increased risk of QT-interval prolongation
- 2)) Summary: The concomitant use of [pimozide](#) with drugs that cause QT-interval prolongation is contraindicated, as coadministration may increase the risk of QT prolongation and serious [ventricular arrhythmias](#)[93].
- 3)) Severity: contraindicated
- 4)) Onset: unspecified
- 5)) Substantiation: theoretical
- 6)) Clinical Management: The concomitant use of [pimozide](#) with drugs that cause QT-interval prolongation is contraindicated, as coadministration may increase the risk of QT prolongation and serious [ventricular arrhythmias](#)[93].
- 7)) Probable Mechanism: additive QT-interval prolongation

3.5.1.LD] [Pimozide](#)

- 1)) Interaction Effect: increased [pimozide](#) levels and increased risk of QT-interval prolongation and [ventricular arrhythmia](#)
- 2)) Summary: The concomitant use of [fluoxetine](#) and [pimozide](#) may result in elevated [pimozide](#) levels and an increased risk of additive QT-interval prolongation via inhibition of CYP2D6-mediated metabolism of [pimozide](#) by [fluoxetine](#), a strong CYP2D6 inhibitor[173]. One case of bradycardia and somnolence resulting from concomitant [fluoxetine](#) and [pimozide](#) therapy has been reported [336]. The concurrent use of [fluoxetine](#) and [pimozide](#) is contraindicated [173].
- 3)) Severity: contraindicated
- 4)) Onset: unspecified
- 5)) Substantiation: probable
- 6)) Clinical Management: Due to the possibility of increased [pimozide](#) levels and additive effects of QT-interval prolongation, the concurrent administration of [fluoxetine](#) and [pimozide](#) is contraindicated[173].
- 7)) Probable Mechanism: inhibition of CYP2D6-mediated metabolism of [pimozide](#) by [fluoxetine](#); additive effects on QT-interval prolongation
- 8)) Literature Reports

- a)) One case has been reported in which concurrent use of [pimozide](#) 5 mg daily and [fluoxetine](#) 20 mg daily in an elderly patient resulted in severe bradycardia and somnolence. The pulse rate gradually returned to normal after discontinuation of [pimozide](#); rechallenge with a lower [pimozide](#) dose and a higher [fluoxetine](#) dose also resulted in bradycardia [336].

3.5.1.LE] [Piperaquine](#)

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

2)) Summary: Concomitant administration of piperazine (a QT-interval prolonging drug) with other drugs that cause QT-interval prolongation, including antiarrhythmic medications, is contraindicated. Additionally, recent use of QT-interval prolonging drugs, that may still be circulating (based on the half-life) at the time of piperazine administration, is contraindicated[60].

3)) Severity: contraindicated

4)) Onset: unspecified

5)) Substantiation: theoretical

6)) Clinical Management: Concomitant administration of piperazine (a QT-interval prolonging drug) with other drugs that cause QT-interval prolongation, including antiarrhythmic medications, is contraindicated. Additionally, recent use of QT-interval prolonging drugs, that may still be circulating (based on the half-life) at the time of piperazine administration, is contraindicated[60].

7)) Probable Mechanism: additive QT-interval prolongation

3.5.1.LF] Piperazine

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

2)) Summary: Concomitant administration of piperazine and QT-interval prolonging drugs may result in additive prolongation effects on the QT interval and is contraindicated. Recent use of QT-interval prolonging drugs, that may still be circulating at the time of piperazine administration, is contraindicated. Additionally, the concomitant use of piperazine (a CYP3A4 substrate) with a CYP3A4 inhibitor may increase the exposure of piperazine and further increase the risk for QT-interval prolongation. Due to the long half-life of piperazine, caution is advised when administering CYP3A4 inhibitors for up to 3 months after discontinuation of piperazine therapy[60].

3)) Severity: contraindicated

4)) Onset: unspecified

5)) Substantiation: theoretical

6)) Clinical Management: Concomitant administration of piperazine and QT-interval prolonging drugs may result in additive prolongation effects on the QT interval and is contraindicated. Recent use of QT-interval prolonging drugs, that may still be circulating at the time of piperazine administration, is contraindicated. Additionally, the concomitant use of piperazine (a CYP3A4 substrate) with a CYP3A4 inhibitor may increase the exposure of piperazine and further increase the risk for QT-interval prolongation. Due to the long half-life of piperazine, caution is advised when administering CYP3A4 inhibitors for up to 3 months after discontinuation of piperazine therapy[60].

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

3.5.1.LG] Pirfenidone

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

2)) Summary: Even though no formal drug interaction studies have been done, the coadministration of Class Ia antiarrhythmics and other drugs known to prolong the QTc interval is not recommended[343]. [Fluoxetine](#) has demonstrated QT prolongation at therapeutic doses [344].

3)) Severity: major

4)) Onset: unspecified

5)) Substantiation: theoretical

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

7)) Probable Mechanism: additive effects on QT prolongation

3.5.1.LH] Piroxicam

- 1) Interaction Effect: an increased risk of bleeding
- 2) Summary: Caution is recommended with the concomitant use of NSAIDs and antidepressants, including SSRIs due to an increased risk of [intracranial hemorrhage](#)[529] and [gastrointestinal bleeding](#) [533][534][530][531]. Bleeding events have included [epistaxis](#), ecchymosis, [hematoma](#), [petechiae](#), and life-threatening hemorrhages [536][535][537][538]. When an SSRI and an NSAID are given concurrently, monitor the patient for signs of increased bleeding.
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: established
- 6) Clinical Management: Use caution if NSAIDs and SSRIs are coadministered. Concomitant use of NSAIDs and SSRIs may cause an increased risk of [intracranial hemorrhage](#)[529] and [gastrointestinal bleeding](#) [530][531]. When an SSRI and an NSAID are given concurrently, monitor the patient for signs of increased bleeding.
- 7) Probable Mechanism: depletion of [platelet](#) serotonin by SSRI; additive effects
- 8) Literature Reports

a) Concomitant use of NSAIDs and antidepressants, including tricyclic antidepressants, SSRIs, serotonin-norepinephrine reuptake inhibitors, and MAOIs, resulted in a 60% increased risk of [intracranial hemorrhage](#) within 30 days of concomitant use compared with antidepressant use alone. There was no significant difference between the antidepressant drug classes and the increased risk; however, there was an increased risk associated with male patients compared with female patients [529].

b) SSRIs increase the risk of upper gastrointestinal (GI) bleeding, and this effect is potentiated by concurrent use of NSAIDs or low-dose [aspirin](#). Hospitalizations for [upper GI bleeding](#) were searched among 26,005 users of antidepressant medications and compared with the number of hospitalizations in those patients who did not receive prescriptions for antidepressants. The amount of [upper GI bleeding](#) episodes was 3.6 times more than expected. Combined use of an SSRI and NSAIDs or low-dose [aspirin](#) increased the risk to 12.2 and 5.2 times, respectively. The findings of this study demonstrate an increased risk of [upper GI bleeding](#) during the use of SSRIs. Combined use of SSRIs and NSAIDs or low-dose [aspirin](#) increased the risk even further [532].

c) Two metaanalyses of incidents of upper GI bleed due to SSRIs, NSAIDs, and their combination found that SSRIs increased the risk by 1.73 [533] to 2.36 times [534], NSAIDs by 2.55 times [533], and the combination of SSRIs and NSAIDs by 4.02 [533] to 6.33 times [534].

d) The release of serotonin by [platelets](#) is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs and NSAIDs have been associated with an increased risk of bleeding [535].

3.5.1.LI] Pitolisant

- 1) Interaction Effect: increased risk of QT-interval prolongation
- 2) Summary: The concomitant administration of pitolisant and another drug that prolongs the QT interval should be done with careful monitoring[85].
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical

- 6) Clinical Management: The concomitant administration of pitolisant and another drug that prolongs the QT interval should be done with careful monitoring[85].
- 7) Probable Mechanism: additive QT prolongation

3.5.1.LJ] 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[35].
- 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[35].
- 7) Probable Mechanism: inhibition of CYP1A2-mediated metabolism by pixantrone

3.5.1.LK] Prajmaline

- 1) Interaction Effect: an increased risk of [cardiotoxicity](#) (QT prolongation, [torsades de pointes](#), [cardiac arrest](#))
- 2) Summary: Even though no formal drug interaction studies have been done, the coadministration of Class Ia antiarrhythmics and other drugs known to prolong the QTc interval is not recommended[343]. [Fluoxetine](#) has demonstrated QT prolongation at therapeutic doses [344].
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: The concurrent administration of class Ia antiarrhythmic agents and agents that prolong the QT interval, such as [fluoxetine](#), is not recommended.
- 7) Probable Mechanism: additive effects on QT prolongation

3.5.1.LL] Pramlintide

- 1) Interaction Effect: increased risk of [hypoglycemia](#)
- 2) Summary: Use caution when coadministering [fluoxetine](#) and [insulins](#) or [pramlintide](#), as this may increase the risk of [hypoglycemia](#). Monitor glucose levels more frequently and adjust the dose of [insulin](#) if necessary[355][356][357].
- 3) Severity: moderate
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Use caution when coadministering [fluoxetine](#) and [insulins](#) or [pramlintide](#), as this may increase the risk of [hypoglycemia](#). Monitor glucose levels more frequently and adjust the dose of [insulin](#) if necessary[355][356][357].
- 7) Probable Mechanism: unknown

3.5.1.LM] Pranoprofen

- 1) Interaction Effect: an increased risk of bleeding
- 2) Summary: Caution is recommended with the concomitant use of NSAIDs and antidepressants, including SSRIs due to an increased risk of [intracranial hemorrhage](#)[529] and [gastrointestinal bleeding](#)

[533][534][530][531]. Bleeding events have included [epistaxis](#), ecchymosis, [hematoma](#), [petechiae](#), and life-threatening hemorrhages [536][535][537][538]. When an SSRI and an NSAID are given concurrently, monitor the patient for signs of increased bleeding.

3) Severity: major

4) Onset: unspecified

5) Substantiation: established

6) Clinical Management: Use caution if NSAIDs and SSRIs are coadministered. Concomitant use of NSAIDs and SSRIs may cause an increased risk of [intracranial hemorrhage](#)[529] and [gastrointestinal bleeding](#) [530][531]. When an SSRI and an NSAID are given concurrently, monitor the patient for signs of increased bleeding.

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

8) Literature Reports

a) Concomitant use of NSAIDs and antidepressants, including tricyclic antidepressants, SSRIs, serotonin-norepinephrine reuptake inhibitors, and MAOIs, resulted in a 60% increased risk of [intracranial hemorrhage](#) within 30 days of concomitant use compared with antidepressant use alone. There was no significant difference between the antidepressant drug classes and the increased risk; however, there was an increased risk associated with male patients compared with female patients [529].

b) SSRIs increase the risk of upper gastrointestinal (GI) bleeding, and this effect is potentiated by concurrent use of NSAIDs or low-dose [aspirin](#). Hospitalizations for [upper GI bleeding](#) were searched among 26,005 users of antidepressant medications and compared with the number of hospitalizations in those patients who did not receive prescriptions for antidepressants. The amount of [upper GI bleeding](#) episodes was 3.6 times more than expected. Combined use of an SSRI and NSAIDs or low-dose [aspirin](#) increased the risk to 12.2 and 5.2 times, respectively. The findings of this study demonstrate an increased risk of [upper GI bleeding](#) during the use of SSRIs. Combined use of SSRIs and NSAIDs or low-dose [aspirin](#) increased the risk even further [532].

c) Two metaanalyses of incidents of upper GI bleed due to SSRIs, NSAIDs, and their combination found that SSRIs increased the risk by 1.73 [533] to 2.36 times [534], NSAIDs by 2.55 times [533], and the combination of SSRIs and NSAIDs by 4.02 [533] to 6.33 times [534].

d) The release of serotonin by [platelets](#) is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs and NSAIDs have been associated with an increased risk of bleeding [535].

3.5.1.LN] Prasugrel

1) Interaction Effect: increased risk of bleeding

2) Summary: Exercise caution when coadministering a SSRI and an antiplatelet agent or anticoagulant as this may increase the risk of bleeding events[272][173][385].

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Use caution with concomitant use of [fluoxetine](#) with anticoagulants or antiplatelet agents, as coadministration may increase bleeding risk[272][173][385].

7) Probable Mechanism: altered anticoagulant effects

8) Literature Reports

a)) In a retrospective study of patients over 50 years of age with the diagnosis of acute [myocardial infarction](#) (N=27,058), SSRI use with any antiplatelet therapy significantly increased the risk of bleeding by 1.42-fold compared with [aspirin](#) use alone. Therapy with [aspirin](#), [clopidogrel](#), and an SSRI significantly increased risk by 2.35-fold compared with [aspirin](#) use alone and by 1.57-fold compared with [clopidogrel](#) and [aspirin](#) combination therapy [385].

b)) In a systematic review and meta-analysis of 22 observational studies, SSRI use was associated with a significant 1.55 fold increase in risk of [upper gastrointestinal bleeding](#) (UGIB). Concomitant use of SSRIs and antiplatelet drugs was associated with a 2.48-fold increase in risk of UGIB (3 studies) [272].

3.5.1.LO] [Probuco](#)

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

2)) Summary: [Fluoxetine](#) and [probuco](#) have been shown to prolong the QTc interval at the recommended therapeutic dose[286][287][288]. Even though no formal drug interaction studies have been done, the coadministration of drugs known to prolong the QTc interval is not recommended.

3)) Severity: major

4)) Onset: unspecified

5)) Substantiation: theoretical

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

7)) Probable Mechanism: additive effects on QT prolongation

3.5.1.LP] [Procainamide](#)

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

2)) Summary: Even though no formal drug interaction studies have been done, the coadministration of Class Ia antiarrhythmics and other drugs known to prolong the QTc interval is not recommended[343]. [Fluoxetine](#) has demonstrated QT prolongation at therapeutic doses [344].

3)) Severity: major

4)) Onset: unspecified

5)) Substantiation: theoretical

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

7)) Probable Mechanism: additive effects on QT prolongation

3.5.1.LQ] [Procarbazine](#)

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

2)) Summary: Concomitant use of [fluoxetine](#) and an MAOI is contraindicated. Concurrent administration or overlapping therapy with [fluoxetine](#) and an MAOI 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 SSRIs and MAOIs. A minimum of 14 days should elapse after discontinuing an MAOI intended to treat psychiatric disorders before initiating therapy with [fluoxetine](#), and a minimum of 5 weeks should elapse after discontinuing [fluoxetine](#) before initiating therapy with an MAOI intended to treat psychiatric disorders[283].

- 3) Severity: contraindicated
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Concurrent use of [fluoxetine](#) and an MAOI is contraindicated. Wait at least 14 days after discontinuing an MAOI intended to treat psychiatric disorders before initiating [fluoxetine](#). Wait at least 5 weeks after discontinuing [fluoxetine](#) before initiating therapy with an MAOI intended to treat psychiatric disorders[283].
- 7) Probable Mechanism: additive serotonergic effect

3.5.1.LR] [Prochlorperazine](#)

- 1) Interaction Effect: an increased risk of [cardiotoxicity](#) (QT prolongation, [torsades de pointes](#), [cardiac arrest](#))
- 2) Summary: Although citing no data, the manufacturers of some phenothiazines state that concomitant use with other drugs which prolong the QT interval is not recommended. Q and T wave distortions have been observed in patients taking phenothiazines[311][312][313]. Other phenothiazines may have similar effects, though no reports are available. [Fluoxetine](#) has been shown to prolong the QTc interval at the recommended therapeutic dose [314].
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: The concurrent administration of [fluoxetine](#) and a phenothiazine is not recommended.
- 7) Probable Mechanism: additive effects on QT prolongation

3.5.1.LS] [Proglumetacin](#)

- 1) Interaction Effect: an increased risk of bleeding
- 2) Summary: Caution is recommended with the concomitant use of NSAIDs and antidepressants, including SSRIs due to an increased risk of [intracranial hemorrhage](#)[529] and [gastrointestinal bleeding](#) [533][534][530][531]. Bleeding events have included [epistaxis](#), ecchymosis, [hematoma](#), [petechiae](#), and life-threatening hemorrhages [536][535][537][538]. When an SSRI and an NSAID are given concurrently, monitor the patient for signs of increased bleeding.
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: established
- 6) Clinical Management: Use caution if NSAIDs and SSRIs are coadministered. Concomitant use of NSAIDs and SSRIs may cause an increased risk of [intracranial hemorrhage](#)[529] and [gastrointestinal bleeding](#) [530][531]. When an SSRI and an NSAID are given concurrently, monitor the patient for signs of increased bleeding.
- 7) Probable Mechanism: depletion of [platelet](#) serotonin by SSRI; additive effects
- 8) Literature Reports

a) Concomitant use of NSAIDs and antidepressants, including tricyclic antidepressants, SSRIs, serotonin-norepinephrine reuptake inhibitors, and MAOIs, resulted in a 60% increased risk of [intracranial hemorrhage](#) within 30 days of concomitant use compared with antidepressant use alone. There was no significant difference between the antidepressant drug classes and the increased risk; however, there was an increased risk associated with male patients compared with female patients [529].

b)) SSRIs increase the risk of upper gastrointestinal (GI) bleeding, and this effect is potentiated by concurrent use of NSAIDs or low-dose [aspirin](#). Hospitalizations for [upper GI bleeding](#) were searched among 26,005 users of antidepressant medications and compared with the number of hospitalizations in those patients who did not receive prescriptions for antidepressants. The amount of [upper GI bleeding](#) episodes was 3.6 times more than expected. Combined use of an SSRI and NSAIDs or low-dose [aspirin](#) increased the risk to 12.2 and 5.2 times, respectively. The findings of this study demonstrate an increased risk of [upper GI bleeding](#) during the use of SSRIs. Combined use of SSRIs and NSAIDs or low-dose [aspirin](#) increased the risk even further [532].

c)) Two metaanalyses of incidents of upper GI bleed due to SSRIs, NSAIDs, and their combination found that SSRIs increased the risk by 1.73 [533] to 2.36 times [534], NSAIDs by 2.55 times [533], and the combination of SSRIs and NSAIDs by 4.02 [533] to 6.33 times [534].

d)) The release of serotonin by [platelets](#) is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs and NSAIDs have been associated with an increased risk of bleeding [535].

3.5.1.LT] [Propafenone](#)

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

2)) Summary: [Propafenone](#) has been shown to prolong the QTc interval[222]. [Fluoxetine](#) has been shown to prolong the QTc interval at the recommended therapeutic dose [223]. Even though no formal drug interaction studies have been done, caution is advised if drugs known to prolong the QT interval are used concomitantly. In addition, [fluoxetine](#) may inhibit cytochrome P450 2D6 (CYP2D6) and impair the metabolism of [propafenone](#) [224].

3)) Severity: major

4)) Onset: rapid

5)) Substantiation: probable

6)) Clinical Management: Caution is advised if [fluoxetine](#) and [propafenone](#) are used concomitantly.

7)) Probable Mechanism: inhibition of cytochrome P450 2D6-mediated [propafenone](#) metabolism; theoretical additive effects on QT prolongation

8)) Literature Reports

a)) The metabolism of [propafenone](#) enantiomers was altered after [fluoxetine](#) treatment in 9 healthy Chinese subjects. All subjects were extensive CYP2D6 metabolizers. Subjects received a single oral dose of [propafenone](#) 400 mg both before and after [fluoxetine](#) 20 mg daily for ten days. The oral clearance of both S- and P- enantiomers of [propafenone](#) decreased from approximately 75 L/hr to 50 L/hr and 107 L/hr to 70 L/hr, respectively. Compared to baseline, the elimination half life, peak concentration, and area under the curve for both enantiomers after [fluoxetine](#) therapy were significantly increased [221].

3.5.1.LU] [Propionic Acid](#)

1)) Interaction Effect: an increased risk of bleeding

2)) Summary: Caution is recommended with the concomitant use of NSAIDs and antidepressants, including SSRIs due to an increased risk of [intracranial hemorrhage](#)[529] and [gastrointestinal bleeding](#) [533][534][530][531]. Bleeding events have included [epistaxis](#), ecchymosis, [hematoma](#), [petechiae](#), and life-threatening hemorrhages [536][535][537][538]. When an SSRI and an NSAID are given concurrently, monitor the patient for signs of increased bleeding.

- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: established
- 6) Clinical Management: Use caution if NSAIDs and SSRIs are coadministered. Concomitant use of NSAIDs and SSRIs may cause an increased risk of [intracranial hemorrhage](#)[529] and [gastrointestinal bleeding](#) [530][531]. When an SSRI and an NSAID are given concurrently, monitor the patient for signs of increased bleeding.
- 7) Probable Mechanism: depletion of [platelet](#) serotonin by SSRI; additive effects
- 8) Literature Reports

a) Concomitant use of NSAIDs and antidepressants, including tricyclic antidepressants, SSRIs, serotonin-norepinephrine reuptake inhibitors, and MAOIs, resulted in a 60% increased risk of [intracranial hemorrhage](#) within 30 days of concomitant use compared with antidepressant use alone. There was no significant difference between the antidepressant drug classes and the increased risk; however, there was an increased risk associated with male patients compared with female patients [529].

b) SSRIs increase the risk of upper gastrointestinal (GI) bleeding, and this effect is potentiated by concurrent use of NSAIDs or low-dose [aspirin](#). Hospitalizations for [upper GI bleeding](#) were searched among 26,005 users of antidepressant medications and compared with the number of hospitalizations in those patients who did not receive prescriptions for antidepressants. The amount of [upper GI bleeding](#) episodes was 3.6 times more than expected. Combined use of an SSRI and NSAIDs or low-dose [aspirin](#) increased the risk to 12.2 and 5.2 times, respectively. The findings of this study demonstrate an increased risk of [upper GI bleeding](#) during the use of SSRIs. Combined use of SSRIs and NSAIDs or low-dose [aspirin](#) increased the risk even further [532].

c) Two metaanalyses of incidents of upper GI bleed due to SSRIs, NSAIDs, and their combination found that SSRIs increased the risk by 1.73 [533] to 2.36 times [534], NSAIDs by 2.55 times [533], and the combination of SSRIs and NSAIDs by 4.02 [533] to 6.33 times [534].

d) The release of serotonin by [platelets](#) is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs and NSAIDs have been associated with an increased risk of bleeding [535].

3.5.1.LV] [Propranolol](#)

- 1) Interaction Effect: increased risk of [propranolol](#) toxicity, including [complete heart block](#)
- 2) Summary: [Fluoxetine](#) (a potent CYP2D6 inhibitor) may increase the exposure of antiarrhythmic drugs that are metabolized by CYP2D6, including [propranolol](#)[173]. Increased [propranolol](#) exposure may increase the risk of [propranolol](#) toxicity, including [complete heart block](#). One case report described a man who developed [complete heart block](#) 2 weeks after [fluoxetine](#) was added to [propranolol](#) therapy [280]. Use caution when coadministering [fluoxetine](#) with [propranolol](#) [173].
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: probable
- 6) Clinical Management: Use caution when coadministering [fluoxetine](#) with [propranolol](#), as coadministration may increase [propranolol](#) exposure[173] and increase the risk of [propranolol](#) toxicity, including [complete heart block](#) [279].
- 7) Probable Mechanism: inhibition of CYP2D6-mediated metabolism of [propranolol](#) by [fluoxetine](#)
- 8) Literature Reports

a) A 53-year-old man experienced a loss of consciousness 2 weeks after fluoxetine 20 mg daily was prescribed for depression. Other medications included propranolol 40 mg twice daily for anxiety. He had no previous cardiac history. An ECG revealed a complete heart block, and fluoxetine and propranolol were both discontinued. Two days later, the patient reverted to sinus rhythm with a heart rate of 60 beats per minute. The heart block was attributed to the fluoxetine-propranolol combination, since sinus rhythm returned 2 days after the discontinuation of fluoxetine, and the patient had no previous complications from propranolol therapy. Because 5-hydroxytryptamine (5-HT) receptors are located in the atrium of the heart, fluoxetine may have potentiated the action of 5-HT, causing impaired atrioventricular conduction [279].

3.5.1.LW] Propyphenazone

1) Interaction Effect: an increased risk of bleeding

2) Summary: Caution is recommended with the concomitant use of NSAIDs and antidepressants, including SSRIs due to an increased risk of intracranial hemorrhage[529] and gastrointestinal bleeding [533][534][530][531]. Bleeding events have included epistaxis, ecchymosis, hematoma, petechiae, and life-threatening hemorrhages [536][535][537][538]. When an SSRI and an NSAID are given concurrently, monitor the patient for signs of increased bleeding.

3) Severity: major

4) Onset: unspecified

5) Substantiation: established

6) Clinical Management: Use caution if NSAIDs and SSRIs are coadministered. Concomitant use of NSAIDs and SSRIs may cause an increased risk of intracranial hemorrhage[529] and gastrointestinal bleeding [530][531]. When an SSRI and an NSAID are given concurrently, monitor the patient for signs of increased bleeding.

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

8) Literature Reports

a) Concomitant use of NSAIDs and antidepressants, including tricyclic antidepressants, SSRIs, serotonin-norepinephrine reuptake inhibitors, and MAOIs, resulted in a 60% increased risk of intracranial hemorrhage within 30 days of concomitant use compared with antidepressant use alone. There was no significant difference between the antidepressant drug classes and the increased risk; however, there was an increased risk associated with male patients compared with female patients [529].

b) SSRIs increase the risk of upper gastrointestinal (GI) bleeding, and this effect is potentiated by concurrent use of NSAIDs or low-dose aspirin. Hospitalizations for upper GI bleeding were searched among 26,005 users of antidepressant medications and compared with the number of hospitalizations in those patients who did not receive prescriptions for antidepressants. The amount of upper GI bleeding episodes was 3.6 times more than expected. Combined use of an SSRI and NSAIDs or low-dose aspirin increased the risk to 12.2 and 5.2 times, respectively. The findings of this study demonstrate an increased risk of upper GI bleeding during the use of SSRIs. Combined use of SSRIs and NSAIDs or low-dose aspirin increased the risk even further [532].

c) Two metaanalyses of incidents of upper GI bleed due to SSRIs, NSAIDs, and their combination found that SSRIs increased the risk by 1.73 [533] to 2.36 times [534], NSAIDs by 2.55 times [533], and the combination of SSRIs and NSAIDs by 4.02 [533] to 6.33 times [534].

d)) The release of serotonin by [platelets](#) is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs and NSAIDs have been associated with an increased risk of bleeding [535].

3.5.1.LX] Proquazone

1)) Interaction Effect: an increased risk of bleeding

2)) Summary: Caution is recommended with the concomitant use of NSAIDs and antidepressants, including SSRIs due to an increased risk of [intracranial hemorrhage](#)[529] and [gastrointestinal bleeding](#) [533][534][530][531]. Bleeding events have included [epistaxis](#), ecchymosis, [hematoma](#), [petechiae](#), and life-threatening hemorrhages [536][535][537][538]. When an SSRI and an NSAID are given concurrently, monitor the patient for signs of increased bleeding.

3)) Severity: major

4)) Onset: unspecified

5)) Substantiation: established

6)) Clinical Management: Use caution if NSAIDs and SSRIs are coadministered. Concomitant use of NSAIDs and SSRIs may cause an increased risk of [intracranial hemorrhage](#)[529] and [gastrointestinal bleeding](#) [530][531]. When an SSRI and an NSAID are given concurrently, monitor the patient for signs of increased bleeding.

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

8)) Literature Reports

a)) Concomitant use of NSAIDs and antidepressants, including tricyclic antidepressants, SSRIs, serotonin-norepinephrine reuptake inhibitors, and MAOIs, resulted in a 60% increased risk of [intracranial hemorrhage](#) within 30 days of concomitant use compared with antidepressant use alone. There was no significant difference between the antidepressant drug classes and the increased risk; however, there was an increased risk associated with male patients compared with female patients [529].

b)) SSRIs increase the risk of upper gastrointestinal (GI) bleeding, and this effect is potentiated by concurrent use of NSAIDs or low-dose [aspirin](#). Hospitalizations for [upper GI bleeding](#) were searched among 26,005 users of antidepressant medications and compared with the number of hospitalizations in those patients who did not receive prescriptions for antidepressants. The amount of [upper GI bleeding](#) episodes was 3.6 times more than expected. Combined use of an SSRI and NSAIDs or low-dose [aspirin](#) increased the risk to 12.2 and 5.2 times, respectively. The findings of this study demonstrate an increased risk of [upper GI bleeding](#) during the use of SSRIs. Combined use of SSRIs and NSAIDs or low-dose [aspirin](#) increased the risk even further [532].

c)) Two metaanalyses of incidents of upper GI bleed due to SSRIs, NSAIDs, and their combination found that SSRIs increased the risk by 1.73 [533] to 2.36 times [534], NSAIDs by 2.55 times [533], and the combination of SSRIs and NSAIDs by 4.02 [533] to 6.33 times [534].

d)) The release of serotonin by [platelets](#) is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs and NSAIDs have been associated with an increased risk of bleeding [535].

3.5.1.LY] Protein C

1)) Interaction Effect: increased risk of bleeding

2)) Summary: Exercise caution when coadministering a SSRI and an antiplatelet agent or anticoagulant as this may increase the risk of bleeding events[272][173][385].

- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Use caution with concomitant use of [fluoxetine](#) with anticoagulants or antiplatelet agents, as coadministration may increase bleeding risk[272][173][385].
- 7) Probable Mechanism: altered anticoagulant effects
- 8) Literature Reports

a) In a retrospective study of patients over 50 years of age with the diagnosis of acute [myocardial infarction](#) (N=27,058), SSRI use with any antiplatelet therapy significantly increased the risk of bleeding by 1.42-fold compared with [aspirin](#) use alone. Therapy with [aspirin](#), [clopidogrel](#), and an SSRI significantly increased risk by 2.35-fold compared with [aspirin](#) use alone and by 1.57-fold compared with [clopidogrel](#) and [aspirin](#) combination therapy [385].

b) In a systematic review and meta-analysis of 22 observational studies, SSRI use was associated with a significant 1.55 fold increase in risk of [upper gastrointestinal bleeding](#) (UGIB). Concomitant use of SSRIs and antiplatelet drugs was associated with a 2.48-fold increase in risk of UGIB (3 studies) [272].

3.5.1.LZ] [Protriptyline](#)

- 1) Interaction Effect: increased risk of tricyclic antidepressant toxicity, QT prolongation and [serotonin syndrome](#)

2) Summary: [Fluoxetine](#), a potent CYP2D6 inhibitor, is associated with an increased risk of [serotonin syndrome](#), QT prolongation, and [ventricular arrhythmias](#) (including [torsade de pointes](#)). Concomitant therapy with CYP2D6-metabolized tricyclic antidepressants (TCAs) may potentiate these risks and introduce TCA toxicity[173]; concurrent use of [fluoxetine](#) and [desipramine](#), [nortriptyline](#), and [imipramine](#) has resulted in significant increases in TCA concentrations [517][523][524][525][526][527]. Use caution with concurrent administration of [fluoxetine](#) and TCAs. If [fluoxetine](#) is added to an existing TCA regimen, consider TCA dose reduction. If [fluoxetine](#) and a TCA are coadministered or [fluoxetine](#) has been recently discontinued, consider plasma TCA monitoring. If [serotonin syndrome](#) occurs, immediately discontinue [fluoxetine](#) and TCA. If [ventricular arrhythmias](#) develop, consider [fluoxetine](#) discontinuation and cardiac evaluation [173].

- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Use caution with concurrent administration of [fluoxetine](#) and TCAs, as elevated TCA plasma concentrations may occur. If [fluoxetine](#) is added to an existing TCA regimen, consider TCA dose reduction. If [fluoxetine](#) and a TCA are coadministered or [fluoxetine](#) has been recently discontinued, consider plasma TCA monitoring. If [serotonin syndrome](#) occurs, immediately discontinue [fluoxetine](#) and TCA. If [ventricular arrhythmias](#) develop, consider [fluoxetine](#) discontinuation and cardiac evaluation[173]
- 7) Probable Mechanism: decreased CYP2D6-mediated metabolism of tricyclic antidepressants by [fluoxetine](#); additive effects on QT prolongation; additive serotonergic effects
- 8) Literature Reports

a) Previously stable plasma levels of [imipramine](#) and [desipramine](#) rose more than 2- to 10-fold with [fluoxetine](#) coadministration in 2 clinical studies. This effect may persist for 3 weeks or more after [fluoxetine](#) discontinuation. Dose reduction and temporary monitoring of tricyclic antidepressant plasma concentrations may be indicated with concurrent [fluoxetine](#) treatment or recent [fluoxetine](#) discontinuation [173].

b) **Fluoxetine** statistically and clinically significantly increased **desipramine** concentrations in 18 healthy subjects. When **fluoxetine** (20 mg daily) was added to **desipramine** (50 mg daily), the mean maximum concentration of **desipramine** increased by 278% and the AUC increased by 342%. **Desipramine** trough concentrations continued to be 198% above baseline 3 weeks after **fluoxetine** was discontinued. The same study compared pharmacokinetics of **desipramine** when combined with **sertraline**. The impact of **sertraline** was modest, resulting in small and short-term increases in **desipramine** plasma concentrations [517].

c) Concomitant administration of **fluoxetine** and **desipramine** was reported to result in an increased **desipramine** level and new onset of **delirium** in a 69-year-old male within 10 days of the addition of **fluoxetine** to the patient's regimen [518].

d) **Fluoxetine** increased the level of tricyclic antidepressants (**nortriptyline**, **imipramine**, **desipramine**) in 4 patients. After the addition of **fluoxetine**, the ratio of antidepressant level to dose increased by 109% to 486% in the patients. Three patients developed clinical symptoms (anticholinergic effects, constipation, urinary hesitancy, sedation, unstable gait) as a result of the increased levels [519].

e) A 39-year-old female experienced symptomatic increases in her **desipramine** levels with concomitant **fluoxetine** therapy. Prior to **fluoxetine** therapy, the patient's measured levels of **desipramine** had ranged from 148 to 160 nanograms/milliliter (ng/mL; 556 to 601 nanomol/L) on a regimen of 300 mg daily. Five weeks after the addition of **fluoxetine** 20 mg daily, she reported anticholinergic symptoms, sedation, and confusion with a **desipramine** level of 527 ng/mL (1978 nanomol/L). The **desipramine** dose was lowered to 200 mg/day; 11 days later, the level was 244 ng/mL (916 nanomol/L); the patient reported decreased energy, impaired short-term memory, and some "garbled" speech, as well as an episode of nausea, dizziness, and syncope. The **desipramine** dose was reduced to 50 mg/day, and the adverse effects resolved in 6 days. Eight days later, the **desipramine** level was 122 ng/mL (458 nanomol/L) [520].

f) A 33-year-old depressed male developed adverse effects of dry mouth, tinnitus, and difficulties with alertness and memory while receiving **fluoxetine** 40 mg daily and **desipramine** 150 mg daily for 5 weeks; **fluoxetine** was discontinued and the blood levels of **desipramine** decreased from 938 to 48 nanograms/mL (3521 to 180 nanomol/L) with resolution of clinical symptoms [521].

g) A 75-year-old female experienced symptomatic increases in her **desipramine** serum concentrations when **fluoxetine** was added. **Desipramine** serum levels ranged from 109 to 150 ng/mL (409 to 563 nanomol/L) with oral doses of 300 mg at bedtime prior to **fluoxetine** therapy. Following the addition of oral **fluoxetine** 20 mg daily to the regimen, the **desipramine** serum level increased to 212 ng/mL (796 nanomol/L) within five days. The **fluoxetine** dose was increased to 40 mg/day three days later, and the **desipramine** serum level was 419 ng/mL (1573 nanomol/L) after four days. A worsening of depression and severe fatigue coincided with the increases in **desipramine** serum levels. Withdrawal of **fluoxetine** and reduction in the **desipramine** dose to 200 mg daily reduced the **desipramine** serum level to 231 ng/mL (867 nanomol/L) within two weeks [522].

3.5.1.MA] **Quetiapine**

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

2)) Summary: The concomitant use of [quetiapine](#) and a QT-prolonging drug should be avoided. [Quetiapine](#) is known to increase the QT interval and concurrent use with another drug known to prolong the QT interval may lead to an increased risk of serious cardiac adverse events[102].

3)) Severity: major

4)) Onset: unspecified

5)) Substantiation: theoretical

6)) Clinical Management: The coadministration of [quetiapine](#) and a drug known to prolong the QT interval should be avoided, as concurrent use of such agents may lead to an increased risk of serious cardiac adverse events[102].

7)) Probable Mechanism: additive effects on QT interval

3.5.1.MB| [Quinidine](#)

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

2)) Summary: Even though no formal drug interaction studies have been done, the coadministration of Class IA antiarrhythmics such as [quinidine](#) and other drugs known to prolong the QTc interval is not recommended[494]. [Fluoxetine](#) has demonstrated QT prolongation at therapeutic doses [495]. In addition, [quinidine](#) inhibits CYP2D6 which may reduce [fluoxetine](#) metabolism [496] and [fluoxetine](#) inhibits CYP3A4, which may reduce [quinidine](#) metabolism [497].

3)) Severity: moderate

4)) Onset: delayed

5)) Substantiation: theoretical

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

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

8)) Literature Reports

a)) In vitro studies found that [quinidine](#), a potent inhibitor of CYP2D6, inhibited [fluoxetine](#) N-demethylation by 20% [493]. While indicating that [fluoxetine](#) is, in part, metabolized by CYP2D6, this study showed that much of [fluoxetine](#) metabolism may occur via alternate pathways.

3.5.1.MC| [Rasagiline](#)

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

2)) Summary: Concomitant use of [fluoxetine](#) and an MAOI is contraindicated. Concurrent administration or overlapping therapy with [fluoxetine](#) and an MAOI 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 SSRIs and MAOIs. A minimum of 14 days should elapse after discontinuing an MAOI intended to treat psychiatric disorders before initiating therapy with [fluoxetine](#), and a minimum of 5 weeks should elapse after discontinuing [fluoxetine](#) before initiating therapy with an MAOI intended to treat psychiatric disorders[283].

3)) Severity: contraindicated

4)) Onset: unspecified

5)) Substantiation: theoretical

6)) Clinical Management: Concurrent use of [fluoxetine](#) and an MAOI is contraindicated. Wait at least 14 days after discontinuing an MAOI intended to treat psychiatric disorders before initiating [fluoxetine](#). Wait at least 5 weeks after discontinuing [fluoxetine](#) before initiating therapy with an MAOI intended to treat psychiatric disorders[283].

7J) Probable Mechanism: additive serotonergic effect

3.5.1.MD] **Remifentanyl**

1J) Interaction Effect: increased risk of CNS depression (ie, **respiratory depression**, profound sedation, coma)

2J) Summary: The concomitant use of **remifentanyl** with other CNS depressants may result in profound sedation, **respiratory depression**, coma, and/or death. Reserve concomitant use to clinical settings where alternative treatment options are inadequate. If combination therapy is required, reduce the initial dose of the newly prescribed medication and titrate to clinical response while monitoring for **respiratory depression** and sedation[78].

3J) Severity: major

4J) Onset: unspecified

5J) Substantiation: theoretical

6J) Clinical Management: Reserve concomitant use of **remifentanyl** with other CNS depressants to clinical settings where alternative treatment options are inadequate. If combination therapy is required, reduce the initial dose of the newly prescribed medication and titrate to clinical response while monitoring for **respiratory depression** and sedation[78].

7J) Probable Mechanism: additive CNS depression

3.5.1.ME] **Reviparin**

1J) Interaction Effect: an increased risk of bleeding

2J) Summary: The release of serotonin by **platelets** is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs and anticoagulants has been associated with an increased risk of bleeding[458][457]. Bleeding events reported have included **epistaxis**, ecchymosis, **hematoma**, **petechiae**, and life-threatening hemorrhages. Altered anticoagulant effects (including increased bleeding) have been reported with the coadministration of SSRIs with anticoagulants [457].

3J) Severity: major

4J) Onset: delayed

5J) Substantiation: probable

6J) Clinical Management: When **fluoxetine** and an anticoagulant are given concurrently, monitor patient for signs of increased bleeding. Patients who are taking an anticoagulant should be monitored closely for altered anticoagulant effects, including increased bleeding, when **fluoxetine** therapy is initiated or discontinued[457].

7J) Probable Mechanism: unknown

8J) Literature Reports

aJ) 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 a significant 1.7-fold increased risk for hospitalization for nongastrointestinal bleeding; however, the rate of **gastrointestinal bleeding** was not significantly different [458].

3.5.1.MF] **Risperidone**

1J) Interaction Effect: increased plasma concentrations of **risperiDONE**; increased risk of QT-interval prolongation

2j) Summary: Concomitant use of [fluoxetine](#), a CYP2D6 inhibitor and QT prolonging drug, and [risperiDONE](#), a CYP2D6 substrate and QT prolonging drug, should be avoided as this may result in increased [risperiDONE](#) exposure. Additionally, concomitant administration of [fluoxetine](#) and [risperiDONE](#) may result in additive effects on the QT interval[173]. Carefully monitor patients for [risperiDONE](#) toxicity [469] and periodic [ECG monitoring](#) should be considered [173]. If coadministration of [fluoxetine](#) and intramuscular [risperiDONE](#) is necessary, consider a lower [risperiDONE](#) dose 2 to 4 weeks prior to [fluoxetine](#) initiation. Patients receiving the standard [risperiDONE](#) injection dose of 25 mg may continue that dose when [fluoxetine](#) is initiated, unless clinical judgement necessitates the initiation of a lower [risperiDONE](#) dose of 12.5 mg. When [risperiDONE](#) injection is initiated in patients already on [fluoxetine](#), a reduced starting dose of 12.5 mg may be utilized; however, the efficacy of 12.5 mg dose has not been proven in clinical trials [470].

3j) Severity: major

4j) Onset: unspecified

5j) Substantiation: probable

6j) Clinical Management: Concomitant use of [fluoxetine](#) and [risperiDONE](#) may result in increased [risperiDONE](#) exposure, as well as additive effects on the QT-interval, and should be avoided[173]. Carefully monitor patients for [risperiDONE](#) toxicity [469] and consider ECG testing during coadministration [173]. If coadministration of [fluoxetine](#) and IM [risperiDONE](#) is necessary, consider a lower [risperiDONE](#) dose 2 to 4 weeks prior to [fluoxetine](#) initiation. Patients receiving [risperiDONE](#) 25 mg IM may continue that dose when [fluoxetine](#) is initiated, unless clinical judgement necessitates the initiation of a lower [risperiDONE](#) dose of 12.5 mg. When [risperiDONE](#) IM is initiated in patients already on [fluoxetine](#), a starting dose of 12.5 mg may be used; however, the efficacy of 12.5 mg has not been proven in clinical trials [470].

7j) Probable Mechanism: inhibition of CYP2D6-mediated metabolism of [risperiDONE](#); additive QT-interval prolongation effects

8j) Literature Reports

a) [Fluoxetine](#) (a CYP2D6 inhibitor) 20 mg/day has been shown to increase the plasma concentration of [risperiDONE](#) (a CYP2D6 substrate) 2.5- to 2.8-fold. [Fluoxetine](#) did not affect the concentration of 9-hydroxyrisperidone. The dosage of [risperiDONE](#) should be reevaluated when [fluoxetine](#) is initiated or discontinued [471].

b) [Fluoxetine](#), an inhibitor of cytochrome CYP2D6, may impair the elimination of [risperiDONE](#), primarily by inhibiting CYP2D6-mediated alpha-hydroxylation and, to a lesser extent, by simultaneously affecting the further metabolism of 9-hydroxyrisperidone (9-OH-[risperiDONE](#)) or other pathways of [risperiDONE](#) biotransformation. In an open, 4-week, [pharmacokinetic study](#) including 9 patients with [schizophrenia](#) or [schizoaffective disorder](#), depressive type, [risperiDONE](#) concentrations increased when [fluoxetine](#) was coadministered with [risperiDONE](#). Patients were stabilized on a fixed dose of [risperiDONE](#) 4 to 6 mg/day for at least four weeks and received adjunctive [fluoxetine](#) therapy 20 mg/day for the management of concomitant depression. Mean plasma [risperiDONE](#) concentrations increased from 12 ng/mL (29 nanomol/L) at baseline to 49 nanograms (ng)/mL (119 nanomol/L; p less than 0.01) at week 2, and 56 ng/mL (136 nanomol/L; p less than 0.01) at week 4. Plasma concentrations of 9-hydroxyrisperidone (9-OH-[risperiDONE](#)) showed no significant increase at 4 weeks compared with baseline. After 4 weeks of concurrent therapy, the active moiety ([risperiDONE](#) plus 9-OH-[risperiDONE](#)) was increased by 75% (range: 9% to 204%, p less than 0.01) compared with baseline. The mean plasma [risperiDONE](#) to 9-OH-[risperiDONE](#) ratio also increased significantly. Two patients experienced Parkinsonian symptoms during week 2 of concomitant therapy and were treated with anticholinergic medication. The authors suggest that monitoring plasma [risperiDONE](#) levels may be warranted in patients receiving concomitant [fluoxetine](#) and [risperiDONE](#) treatment [469].

3.5.1.MG| Ritonavir

- 1) Interaction Effect: reduced olanzapine exposure
- 2) Summary: Coadministration of olanzapine (CYP1A2 and UGT substrate) and ritonavir (CYP1A2 and UGT inducer) may result in decreased olanzapine exposure[54][55]. Increasing the olanzapine dose by 50% (from 10 to 15 mg/day) when coadministered with fosamprenavir/ritonavir compensated for the induction of CYP1A2- and UGT-mediated olanzapine metabolism and resulted in olanzapine exposure that was comparable to when olanzapine was administered alone in a randomized trial in 20 healthy volunteers [54].
- 3) Severity: moderate
- 4) Onset: unspecified
- 5) Substantiation: established
- 6) Clinical Management: Coadministration of olanzapine (CYP1A2 and UGT substrate) and ritonavir (CYP1A2 and UGT inducer) may result in decreased olanzapine exposure[54][55]. Increasing the olanzapine dose by 50% (from 10 to 15 mg/day) when coadministered with fosamprenavir/ritonavir compensated for the induction of CYP1A2- and UGT-mediated olanzapine metabolism and resulted in olanzapine exposure that was comparable to when olanzapine was administered alone in a randomized trial in 20 healthy volunteers [54].
- 7) Probable Mechanism: induction of CYP1A2- and glucuronosyl transferase-mediated metabolism of olanzapine by ritonavir
- 8) Literature Reports

a) Increasing the olanzapine dose by 50% when coadministered with fosamprenavir/ritonavir compensated for the induction of CYP1A2- and UGT-mediated olanzapine metabolism and resulted in olanzapine exposure that was comparable to when olanzapine was administered alone in a randomized, crossover trial in 20 healthy volunteers. Fosamprenavir 700 mg/ritonavir 100 mg twice daily (for 16 days) was given with a single olanzapine 15 mg (on day 13), and when compared with olanzapine 10 mg alone resulted in similar AUC (438.3 vs 436.9 mcg x hr/L), increased Cmax by 32% (17.4 vs 13.2 mcg/L or 55.7 vs 42.2 nanomol/L), and decreased the t(1/2) by 32% (22.7 vs 33.4 hours). A higher Cmax is due to induction by fosamprenavir/ritonavir having no effect on the absorption phase and was not associated with a higher incidence of olanzapine-associated adverse events in the combination group [54].

b) An open-label study involving 14 healthy volunteers revealed a significant alteration in pharmacokinetic parameters and a reduction in systemic exposure of olanzapine when administered in the presence of ritonavir. Each volunteer received a single dose of olanzapine 10 mg. After a 14-day washout period, subjects received ritonavir 300 mg BID for 3 days, then 400 mg BID for 4 days, then 500 mg BID for 4 days. Significant reductions were seen in the mean olanzapine AUC by 53% (501 to 235 nanograms x hr/mL), t(1/2) by 50% (from 32 to 16 hours), and Cmax by 40% (from 15 to 9 nanogram/mL (48 to 29 nanomol/L). The oral clearance of olanzapine increased by 115% (from 20 to 43 L/hr) [55].

3.5.1.MH| Ritonavir

- 1) Interaction Effect: increased fluoxetine exposure; increased risk of QT-interval prolongation
- 2) Summary: Avoid the concurrent administration of fluoxetine, a selective serotonin reuptake inhibitor with metabolism involving the CYP2D6 system[173], and ritonavir, a CYP2D6 inhibitor and QT prolonging drug, as this may result in increased systemic exposure to fluoxetine [472][473]. Additionally, concomitant administration of fluoxetine and ritonavir may result in additive effects on the QT interval. If concomitant use is required, consider periodic ECG monitoring [173].
- 3) Severity: major

- 4) Onset: unspecified
- 5) Substantiation: established
- 6) Clinical Management: Concomitant administration of [fluoxetine](#), a CYP2D6 substrate and QT prolonging drug, and [ritonavir](#), a CYP2D6 inhibitor and QT prolonging drug, should be avoided as this may result in increased [fluoxetine](#) exposure. Additionally, concomitant administration of [fluoxetine](#) and [ritonavir](#) may result in additive effects on the QT interval. If concomitant use is required, consider periodic [ECG monitoring](#)[173][472][473].
- 7) Probable Mechanism: inhibition of CYP2D6-mediated [fluoxetine](#) metabolism; additive QT-interval prolongation effects
- 8) Literature Reports

a) Coadministration of [fluoxetine](#) 30 mg twice daily for 8 days and [ritonavir](#) 600 mg as a single dose in 16 patients resulted in a 19% increase in [ritonavir](#) AUC, although no changes in the [ritonavir](#) Cmax were noted. During postmarketing experience, cardiac and neurologic events have been reported following coadministration of [fluoxetine](#) and [ritonavir](#) [472][473].

3.5.1.MI] Rivaroxaban

- 1) Interaction Effect: increased risk of bleeding
- 2) Summary: Exercise caution when coadministering a SSRI and an antiplatelet agent or anticoagulant as this may increase the risk of bleeding events[272][173][385].
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Use caution with concomitant use of [fluoxetine](#) with anticoagulants or antiplatelet agents, as coadministration may increase bleeding risk[272][173][385].
- 7) Probable Mechanism: altered anticoagulant effects
- 8) Literature Reports

a) In a retrospective study of patients over 50 years of age with the diagnosis of acute [myocardial infarction](#) (N=27,058), SSRI use with any antiplatelet therapy significantly increased the risk of bleeding by 1.42-fold compared with [aspirin](#) use alone. Therapy with [aspirin](#), [clopidogrel](#), and an SSRI significantly increased risk by 2.35-fold compared with [aspirin](#) use alone and by 1.57-fold compared with [clopidogrel](#) and [aspirin](#) combination therapy [385].

b) In a systematic review and meta-analysis of 22 observational studies, SSRI use was associated with a significant 1.55 fold increase in risk of [upper gastrointestinal bleeding](#) (UGIB). Concomitant use of SSRIs and antiplatelet drugs was associated with a 2.48-fold increase in risk of UGIB (3 studies) [272].

3.5.1.MJ] Rizatriptan

- 1) Interaction Effect: an increased risk of [serotonin syndrome](#)
- 2) Summary: There have been case reports of weakness, hyperreflexia, and incoordination following concomitant use of [sumatriptan](#), a 5-hydroxytryptamine-1 (5HT-1) agonist, and a serotonin specific reuptake inhibitor (SSRI)[338]. Because [rizatriptan](#) is a 5HT 1B/1D receptor agonist, a similar interaction between SSRIs and [rizatriptan](#) may occur [339]. Concurrent use of a triptan and an SSRI may result in [serotonin syndrome](#) which may be life-threatening. Symptoms of [serotonin syndrome](#) may include restlessness, hallucinations, loss of coordination, fast heart beat, rapid changes in blood pressure, increased body temperature, overreactive reflexes, nausea, vomiting, and diarrhea. Clinicians should be aware that triptans may be commonly used intermittently and that either the triptan or the SSRI may be prescribed

by a different physician. Discuss the risks of [serotonin syndrome](#) with patients who are prescribed this combination and monitor them closely for symptoms of [serotonin syndrome](#) [199].

3) Severity: major

4) Onset: delayed

5) Substantiation: probable

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

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

8) Literature Reports

a) Twelve healthy volunteers received [paroxetine](#) 20 mg daily for two weeks and a single dose of [rizatriptan](#) 10 mg. Plasma concentrations of [rizatriptan](#) were not altered by the administration of [paroxetine](#) [337].

3.5.1.MK] [Rofecoxib](#)

1) Interaction Effect: an increased risk of bleeding

2) Summary: Caution is recommended with the concomitant use of NSAIDs and antidepressants, including SSRIs due to an increased risk of [intracranial hemorrhage](#)[529] and [gastrointestinal bleeding](#) [533][534][530][531]. Bleeding events have included [epistaxis](#), ecchymosis, [hematoma](#), [petechiae](#), and life-threatening hemorrhages [536][535][537][538]. When an SSRI and an NSAID are given concurrently, monitor the patient for signs of increased bleeding.

3) Severity: major

4) Onset: unspecified

5) Substantiation: established

6) Clinical Management: Use caution if NSAIDs and SSRIs are coadministered. Concomitant use of NSAIDs and SSRIs may cause an increased risk of [intracranial hemorrhage](#)[529] and [gastrointestinal bleeding](#) [530][531]. When an SSRI and an NSAID are given concurrently, monitor the patient for signs of increased bleeding.

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

8) Literature Reports

a) Concomitant use of NSAIDs and antidepressants, including tricyclic antidepressants, SSRIs, serotonin-norepinephrine reuptake inhibitors, and MAOIs, resulted in a 60% increased risk of [intracranial hemorrhage](#) within 30 days of concomitant use compared with antidepressant use alone. There was no significant difference between the antidepressant drug classes and the increased risk; however, there was an increased risk associated with male patients compared with female patients [529].

b) SSRIs increase the risk of upper gastrointestinal (GI) bleeding, and this effect is potentiated by concurrent use of NSAIDs or low-dose [aspirin](#). Hospitalizations for [upper GI bleeding](#) were searched among 26,005 users of antidepressant medications and compared with the number of hospitalizations in those patients who did not receive prescriptions for antidepressants. The amount of [upper GI bleeding](#) episodes was 3.6 times more than expected. Combined use of an SSRI and NSAIDs or low-dose [aspirin](#) increased the risk to 12.2 and 5.2 times, respectively. The findings of this study demonstrate an increased risk of [upper GI bleeding](#) during the use of SSRIs. Combined use of SSRIs and NSAIDs or low-dose [aspirin](#) increased the risk even further [532].

c) Two metaanalyses of incidents of upper GI bleed due to SSRIs, NSAIDs, and their combination found that SSRIs increased the risk by 1.73 [533] to 2.36 times [534], NSAIDs by 2.55 times [533], and the combination of SSRIs and NSAIDs by 4.02 [533] to 6.33 times [534].

d) The release of serotonin by [platelets](#) is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs and NSAIDs have been associated with an increased risk of bleeding [535].

3.5.1.ML] Sildenafil

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

2) Summary: Concomitant use of serotonergic agents with sildenafil (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[322].

3) Severity: contraindicated

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Concomitant use of serotonergic agents with sildenafil (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[322].

7) Probable Mechanism: Additive serotonergic effects

3.5.1.MM] Salicylic Acid

1) Interaction Effect: an increased risk of bleeding

2) Summary: Caution is recommended with the concomitant use of NSAIDs and antidepressants, including SSRIs due to an increased risk of [intracranial hemorrhage](#)[529] and [gastrointestinal bleeding](#) [533][534][530][531]. Bleeding events have included [epistaxis](#), ecchymosis, [hematoma](#), [petechiae](#), and life-threatening hemorrhages [536][535][537][538]. When an SSRI and an NSAID are given concurrently, monitor the patient for signs of increased bleeding.

3) Severity: major

4) Onset: unspecified

5) Substantiation: established

6) Clinical Management: Use caution if NSAIDs and SSRIs are coadministered. Concomitant use of NSAIDs and SSRIs may cause an increased risk of [intracranial hemorrhage](#)[529] and [gastrointestinal bleeding](#) [530][531]. When an SSRI and an NSAID are given concurrently, monitor the patient for signs of increased bleeding.

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

8) Literature Reports

a) Concomitant use of NSAIDs and antidepressants, including tricyclic antidepressants, SSRIs, serotonin-norepinephrine reuptake inhibitors, and MAOIs, resulted in a 60% increased risk of [intracranial hemorrhage](#) within 30 days of concomitant use compared with antidepressant use alone. There was no significant difference between the antidepressant drug classes and the increased risk; however, there was an increased risk associated with male patients compared with female patients [529].

b) SSRIs increase the risk of upper gastrointestinal (GI) bleeding, and this effect is potentiated by concurrent use of NSAIDs or low-dose [aspirin](#). Hospitalizations for [upper GI bleeding](#) were searched among 26,005 users of antidepressant medications and compared with the number

of hospitalizations in those patients who did not receive prescriptions for antidepressants. The amount of [upper GI bleeding](#) episodes was 3.6 times more than expected. Combined use of an SSRI and NSAIDs or low-dose [aspirin](#) increased the risk to 12.2 and 5.2 times, respectively. The findings of this study demonstrate an increased risk of [upper GI bleeding](#) during the use of SSRIs. Combined use of SSRIs and NSAIDs or low-dose [aspirin](#) increased the risk even further [532].

c) Two metaanalyses of incidents of upper GI bleed due to SSRIs, NSAIDs, and their combination found that SSRIs increased the risk by 1.73 [533] to 2.36 times [534], NSAIDs by 2.55 times [533], and the combination of SSRIs and NSAIDs by 4.02 [533] to 6.33 times [534].

d) The release of serotonin by [platelets](#) is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs and NSAIDs have been associated with an increased risk of bleeding [535].

3.5.1.MN] [Salsalate](#)

1) Interaction Effect: an increased risk of bleeding

2) Summary: Caution is recommended with the concomitant use of NSAIDs and antidepressants, including SSRIs due to an increased risk of [intracranial hemorrhage](#)[529] and [gastrointestinal bleeding](#) [533][534][530][531]. Bleeding events have included [epistaxis](#), ecchymosis, [hematoma](#), [petechiae](#), and life-threatening hemorrhages [536][535][537][538]. When an SSRI and an NSAID are given concurrently, monitor the patient for signs of increased bleeding.

3) Severity: major

4) Onset: unspecified

5) Substantiation: established

6) Clinical Management: Use caution if NSAIDs and SSRIs are coadministered. Concomitant use of NSAIDs and SSRIs may cause an increased risk of [intracranial hemorrhage](#)[529] and [gastrointestinal bleeding](#) [530][531]. When an SSRI and an NSAID are given concurrently, monitor the patient for signs of increased bleeding.

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

8) Literature Reports

a) Concomitant use of NSAIDs and antidepressants, including tricyclic antidepressants, SSRIs, serotonin-norepinephrine reuptake inhibitors, and MAOIs, resulted in a 60% increased risk of [intracranial hemorrhage](#) within 30 days of concomitant use compared with antidepressant use alone. There was no significant difference between the antidepressant drug classes and the increased risk; however, there was an increased risk associated with male patients compared with female patients [529].

b) SSRIs increase the risk of upper gastrointestinal (GI) bleeding, and this effect is potentiated by concurrent use of NSAIDs or low-dose [aspirin](#). Hospitalizations for [upper GI bleeding](#) were searched among 26,005 users of antidepressant medications and compared with the number of hospitalizations in those patients who did not receive prescriptions for antidepressants. The amount of [upper GI bleeding](#) episodes was 3.6 times more than expected. Combined use of an SSRI and NSAIDs or low-dose [aspirin](#) increased the risk to 12.2 and 5.2 times, respectively. The findings of this study demonstrate an increased risk of [upper GI bleeding](#) during the use of SSRIs. Combined use of SSRIs and NSAIDs or low-dose [aspirin](#) increased the risk even further [532].

c) Two metaanalyses of incidents of upper GI bleed due to SSRIs, NSAIDs, and their combination found that SSRIs increased the risk by 1.73 [533] to 2.36 times [534], NSAIDs by 2.55 times [533], and the combination of SSRIs and NSAIDs by 4.02 [533] to 6.33 times [534].

d)) The release of serotonin by [platelets](#) is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs and NSAIDs have been associated with an increased risk of bleeding [535].

3.5.1.MO] [Saquinavir](#)

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

2)) Summary: Both ritonavir-boosted [saquinavir](#) and this drug prolong the QT interval. The concomitant use of ritonavir-boosted [saquinavir](#) is contraindicated with drugs that are CYP3A4 substrates that can have life-threatening reactions with increased plasma levels, drugs that cause QT-interval prolongation, and with drugs that both increase [saquinavir](#) plasma concentrations and cause QT-interval prolongation. If concurrent use of ritonavir-boosted [saquinavir](#) and a QT-prolonging drug is required, perform a baseline ECG. Do not initiate coadministration if QT interval exceeds 450 msec. Perform an on-treatment ECG after 3 to 4 days of concurrent use; if the QT interval exceeds 480 msec or has increased more than 20 msec from baseline, discontinue one or both therapies[175].

3)) Severity: contraindicated

4)) Onset: unspecified

5)) Substantiation: theoretical

6)) Clinical Management: Both ritonavir-boosted [saquinavir](#) and this drug prolong the QT interval. The concomitant use of ritonavir-boosted [saquinavir](#) is contraindicated with drugs that are CYP3A4 substrates that can have life-threatening reactions with increased plasma levels, drugs that cause QT-interval prolongation, and with drugs that both increase [saquinavir](#) plasma concentrations and cause QT-interval prolongation. If concurrent use of ritonavir-boosted [saquinavir](#) and a QT-prolonging drug is required, perform a baseline ECG. Do not initiate coadministration if QT interval exceeds 450 msec. Perform an on-treatment ECG after 3 to 4 days of concurrent use; if the QT interval exceeds 480 msec or has increased more than 20 msec from baseline, discontinue one or both therapies[175].

7)) Probable Mechanism: additive QT interval effects

3.5.1.MP] [Selegiline](#)

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

2)) Summary: Concomitant use of [fluoxetine](#) and an MAOI is contraindicated. Concurrent administration or overlapping therapy with [fluoxetine](#) and an MAOI 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 SSRIs and MAOIs. A minimum of 14 days should elapse after discontinuing an MAOI intended to treat psychiatric disorders before initiating therapy with [fluoxetine](#), and a minimum of 5 weeks should elapse after discontinuing [fluoxetine](#) before initiating therapy with an MAOI intended to treat psychiatric disorders[283].

3)) Severity: contraindicated

4)) Onset: unspecified

5)) Substantiation: theoretical

6)) Clinical Management: Concurrent use of [fluoxetine](#) and an MAOI is contraindicated. Wait at least 14 days after discontinuing an MAOI intended to treat psychiatric disorders before initiating [fluoxetine](#). Wait at least 5 weeks after discontinuing [fluoxetine](#) before initiating therapy with an MAOI intended to treat psychiatric disorders[283].

7)) Probable Mechanism: additive serotonergic effect

3.5.1.MQ] Selexipag

- 1) Interaction Effect: increased risk of bleeding
- 2) Summary: Exercise caution when coadministering a SSRI and an antiplatelet agent or anticoagulant as this may increase the risk of bleeding events[272][173][385].
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Use caution with concomitant use of [fluoxetine](#) with anticoagulants or antiplatelet agents, as coadministration may increase bleeding risk[272][173][385].
- 7) Probable Mechanism: altered anticoagulant effects
- 8) Literature Reports

a) In a retrospective study of patients over 50 years of age with the diagnosis of acute [myocardial infarction](#) (N=27,058), SSRI use with any antiplatelet therapy significantly increased the risk of bleeding by 1.42-fold compared with [aspirin](#) use alone. Therapy with [aspirin](#), [clopidogrel](#), and an SSRI significantly increased risk by 2.35-fold compared with [aspirin](#) use alone and by 1.57-fold compared with [clopidogrel](#) and [aspirin](#) combination therapy [385].

b) In a systematic review and meta-analysis of 22 observational studies, SSRI use was associated with a significant 1.55 fold increase in risk of [upper gastrointestinal bleeding](#) (UGIB). Concomitant use of SSRIs and antiplatelet drugs was associated with a 2.48-fold increase in risk of UGIB (3 studies) [272].

3.5.1.MR] Sematilide

- 1) Interaction Effect: an increased risk of [cardiotoxicity](#) (QT prolongation, [torsades de pointes](#), [cardiac arrest](#))
- 2) Summary: Even though no formal drug interaction studies have been done, the coadministration of Class III antiarrhythmics and other drugs known to prolong the QTc interval is not recommended[300][301][302]. [Fluoxetine](#) has been shown to prolong the QTc interval at the recommended therapeutic dose [303].
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: The concurrent administration of class III antiarrhythmic agents and agents that prolong the QT interval, such as [fluoxetine](#), is not recommended.
- 7) Probable Mechanism: additive effects on QT prolongation

3.5.1.MS] Sertindole

- 1) Interaction Effect: an increased risk of [cardiotoxicity](#) (QT prolongation, [torsade de pointes](#), [cardiac arrest](#))
- 2) Summary: [Fluoxetine](#) has been shown to prolong the QTc interval at the recommended therapeutic dose[304]. Even though no formal drug interaction studies have been done, the coadministration of antipsychotics and other drugs known to prolong the QTc interval, including [fluoxetine](#), is not recommended. Several antipsychotic agents have demonstrated QT prolongation including sertindole [305], sultopride [306], and zotepine [307].
- 3) Severity: major
- 4) Onset: unspecified

- 5) Substantiation: theoretical
- 6) Clinical Management: The concurrent administration of [fluoxetine](#) and antipsychotics is not recommended.
- 7) Probable Mechanism: additive effects on QT prolongation

3.5.1.MT] [Sertraline](#)

- 1) Interaction Effect: increased exposure of CYP2D6 substrate and risk of [serotonin syndrome](#)
- 2) Summary: Caution is advised with concomitant administration of [sertraline](#) and drugs that are CYP2D6 substrates and serotonergic agents. [Sertraline](#) is a CYP2D6 inhibitor and has been associated with [serotonin syndrome](#) during monotherapy. Risk of this event is increased when [sertraline](#) is coadministered with other serotonergic agents. If coadministration is necessary, monitor for symptoms of [serotonin syndrome](#), especially with treatment initiation and dose increases. If [serotonin syndrome](#) is suspected, immediately discontinue [sertraline](#) and other serotonergic agents and provide supportive treatment[427].
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Use caution with concomitant administration of [sertraline](#) and drugs that are CYP2D6 substrates and serotonergic agents. [Sertraline](#) is a CYP2D6 inhibitor and has been associated with [serotonin syndrome](#) during monotherapy. Risk of this event is increased when [sertraline](#) is coadministered with other serotonergic agents. If coadministration is necessary, monitor for symptoms of [serotonin syndrome](#), especially with treatment initiation and dose increases. If [serotonin syndrome](#) is suspected, immediately discontinue [sertraline](#) and other serotonergic agents and provide supportive treatment[427].
- 7) Probable Mechanism: inhibition of CYP2D6-mediated metabolism; additive serotonergic effects

3.5.1.MU] [Sevoflurane](#)

- 1) Interaction Effect: increased risk of QT-interval prolongation
- 2) Summary: [Sevoflurane](#) is a QT-interval-prolonging drug. Use caution with concurrent use of other QT-interval-prolonging agents, due to increased risk of additive QT-interval prolongation and [torsade de pointes](#)[83].
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: [Sevoflurane](#) is a QT-interval-prolonging drug. Use caution with concurrent use of other QT-interval-prolonging agents, due to increased risk of additive QT-interval prolongation and [torsade de pointes](#)[83].
- 7) Probable Mechanism: additive effects on QT interval

3.5.1.MV] [Sibutramine](#)

- 1) Interaction Effect: an increased risk of [serotonin syndrome](#) ([hypertension](#), [hyperthermia](#), myoclonus, mental status changes)
- 2) Summary: [Sibutramine](#) inhibits the reuptake of [norepinephrine](#), [dopamine](#), and serotonin. In addition, the two major metabolites of [sibutramine](#), M1 and M2, also inhibit the reuptake of these neurotransmitters. A hyperserotonergic state, termed [serotonin syndrome](#), may result if [sibutramine](#) is given concurrently with a selective serotonin reuptake inhibitor. Coadministration of [sibutramine](#) and selective serotonin reuptake inhibitors is not recommended[462].
- 3) Severity: major

- 4) Onset: rapid
- 5) Substantiation: probable
- 6) Clinical Management: [Sibutramine](#) should not be administered with serotonergic agents, including selective serotonin reuptake inhibitors, because of the increased risk of [serotonin syndrome](#).
- 7) Probable Mechanism: additive pharmacologic effects resulting in excessive serotonergic stimulation
- 8) Literature Reports

a) [Serotonin syndrome](#) is a condition of serotonergic hyperstimulation and manifests as restlessness, myoclonus, changes in mental status, hyperreflexia, diaphoresis, shivering, and tremor. If the syndrome is not recognized and correctly treated, death can result [461].

3.5.1.MW] [Sodium Salicylate](#)

- 1) Interaction Effect: an increased risk of bleeding
- 2) Summary: Caution is recommended with the concomitant use of NSAIDs and antidepressants, including SSRIs due to an increased risk of [intracranial hemorrhage](#)[529] and [gastrointestinal bleeding](#) [533][534][530][531]. Bleeding events have included [epistaxis](#), ecchymosis, [hematoma](#), [petechiae](#), and life-threatening hemorrhages [536][535][537][538]. When an SSRI and an NSAID are given concurrently, monitor the patient for signs of increased bleeding.
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: established
- 6) Clinical Management: Use caution if NSAIDs and SSRIs are coadministered. Concomitant use of NSAIDs and SSRIs may cause an increased risk of [intracranial hemorrhage](#)[529] and [gastrointestinal bleeding](#) [530][531]. When an SSRI and an NSAID are given concurrently, monitor the patient for signs of increased bleeding.
- 7) Probable Mechanism: depletion of [platelet](#) serotonin by SSRI; additive effects
- 8) Literature Reports

a) Concomitant use of NSAIDs and antidepressants, including tricyclic antidepressants, SSRIs, serotonin-norepinephrine reuptake inhibitors, and MAOIs, resulted in a 60% increased risk of [intracranial hemorrhage](#) within 30 days of concomitant use compared with antidepressant use alone. There was no significant difference between the antidepressant drug classes and the increased risk; however, there was an increased risk associated with male patients compared with female patients [529].

b) SSRIs increase the risk of upper gastrointestinal (GI) bleeding, and this effect is potentiated by concurrent use of NSAIDs or low-dose [aspirin](#). Hospitalizations for [upper GI bleeding](#) were searched among 26,005 users of antidepressant medications and compared with the number of hospitalizations in those patients who did not receive prescriptions for antidepressants. The amount of [upper GI bleeding](#) episodes was 3.6 times more than expected. Combined use of an SSRI and NSAIDs or low-dose [aspirin](#) increased the risk to 12.2 and 5.2 times, respectively. The findings of this study demonstrate an increased risk of [upper GI bleeding](#) during the use of SSRIs. Combined use of SSRIs and NSAIDs or low-dose [aspirin](#) increased the risk even further [532].

c) Two metaanalyses of incidents of upper GI bleed due to SSRIs, NSAIDs, and their combination found that SSRIs increased the risk by 1.73 [533] to 2.36 times [534], NSAIDs by 2.55 times [533], and the combination of SSRIs and NSAIDs by 4.02 [533] to 6.33 times [534].

d)) The release of serotonin by [platelets](#) is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs and NSAIDs have been associated with an increased risk of bleeding [535].

3.5.1.MX] [Sotalol](#)

1)) Interaction Effect: increased risk for [torsade de pointes](#)

2)) Summary: Avoid use of [sotalol](#) with agents that prolong the QT interval. If use is unavoidable, monitor the ECG for excessive increases in the QT interval[86][87]. There have been isolated reports of QTc prolongation and [torsade de pointes](#) temporally related to the concomitant administration of [ciprofloxacin](#) and [sotalol](#) [89][88].

3)) Severity: major

4)) Onset: rapid

5)) Substantiation: theoretical

6)) Clinical Management: Avoid use of [sotalol](#) with agents that prolong the QT interval. If use is unavoidable, monitor the ECG for excessive increases in the QT interval[86][87].

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

8)) Literature Reports

a)) A 70-year-old female receiving [sotalol](#) therapy experienced [torsade de pointes](#) following coadministration of [ciprofloxacin](#). The patient was admitted with new onset [atrial fibrillation](#) with rapid ventricular response and was given IV [amiodarone](#) (loading dose, 450 mg; followed by 24-hour infusion, 650 mg) and [digoxin](#) (0.25 mg/day). The patient converted to sinus rhythm within 48 hours of admission. Both [amiodarone](#) and [digoxin](#) were discontinued and [sotalol](#) (40 mg twice daily) was initiated. The next day the patient presented with [jaundice](#), fever, and [cholecystitis](#), and was treated with IV [ciprofloxacin](#) 400 mg twice daily. Within 12 hours of [ciprofloxacin](#) administration, the patient developed syncope with documented [torsade de pointes](#) that necessitated [defibrillation](#). Her QTc interval, which was 0.38 seconds prior to [ciprofloxacin](#) initiation, was significantly (0.62 seconds) increased following resuscitation. Within 3 days of [ciprofloxacin](#) and [sotalol](#) discontinuation, the QTc interval decreased to 0.42 seconds [88].

b)) [Torsade de pointes](#) temporally related to [ciprofloxacin](#) administration was reported in a 44-year-old female who was stable on [sotalol](#) 160 mg twice a day for the treatment of [supraventricular arrhythmia](#). [Pyelonephritis](#) was treated with [ciprofloxacin](#) 1 g in the emergency room (ER). At that time, the QTc interval measured 405 milliseconds. The patient was discharged on [ciprofloxacin](#) 500 mg twice a day. Within hours of discharge, she experienced several presyncopal and syncopal episodes and returned to the ER. Torsade-induced syncope was diagnosed and [defibrillation](#) was required. The QTc interval following resuscitation was 590 milliseconds which was compared with previous normal or slightly increased intervals (maximum, 460 milliseconds) during [sotalol](#) maintenance therapy. Upon discontinuation of both medications, the QTc interval normalized within 2 days [89].

3.5.1.MY] [Sotalol](#)

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

2)) Summary: Even though no formal drug interaction studies have been done, the coadministration of Class III antiarrhythmics and other drugs known to prolong the QTc interval is not recommended[300] [301][302]. [Fluoxetine](#) has been shown to prolong the QTc interval at the recommended therapeutic dose [303].

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

3.5.1.MZ] [Sparfloxacin](#)

- 1) Interaction Effect: increased risk of QT-interval prolongation
- 2) Summary: The concomitant use of [sparfloxacin](#) with drugs that cause QT-interval prolongation is contraindicated, as coadministration may increase the risk of QT prolongation and serious [ventricular arrhythmias](#)[176].
- 3) Severity: contraindicated
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: The concomitant use of [sparfloxacin](#) with drugs that cause QT-interval prolongation is contraindicated, as coadministration may increase the risk of QT prolongation and serious [ventricular arrhythmias](#)[176].
- 7) Probable Mechanism: additive QT interval effects

3.5.1.NA] [Spiramycin](#)

- 1) Interaction Effect: an increased risk of [cardiotoxicity](#) (QT prolongation, [torsades de pointes](#), [cardiac arrest](#))
- 2) Summary: Spiramycin and [fluoxetine](#) have been shown to prolong the QTc interval at the recommended therapeutic dose[284][285]. Even though no formal drug interaction studies have been done, the coadministration of drugs known to prolong the QTc interval is not recommended.
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: The concurrent administration of spiramycin and [fluoxetine](#) is not recommended.
- 7) Probable Mechanism: additive effects on QT prolongation

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

- 1) Interaction Effect: reduced [olanzapine](#) efficacy
- 2) Summary: This interaction is based on in vitro information that St. John's Wort induced CYP1A2 enzymes, and a case report of a patient experiencing reduced blood [theophylline](#) concentrations and loss of efficacy[140]. Since [olanzapine](#) is metabolized by CYP1A2 enzymes, like [theophylline](#), [olanzapine](#) may be similarly affected. If St. John's Wort and [olanzapine](#) are taken together, their dosages should be consistently administered, recognizing that increased dosages of [olanzapine](#) may be required. Discontinuation of St. John's Wort should be done carefully as side effects of [olanzapine](#) may increase and dose reduction may be required.
- 3) Severity: moderate
- 4) Onset: delayed
- 5) Substantiation: theoretical
- 6) Clinical Management: Avoid concomitant use of [olanzapine](#) with St. John's Wort. If patients elect to remain on St. John's Wort, they should maintain consistent dosing. [Olanzapine](#) dosage may need to be increased. Patients should not discontinue St. John's Wort without first consulting their clinician, as

downward adjustments in [olanzapine](#) dose may be necessary as well as monitoring for increased side effects of [olanzapine](#) (e.g. somnolence, nausea, constipation, dry mouth, asthenia).

7J) Probable Mechanism: induction of cytochrome P450 1A2 enzymes by St. John's Wort

3.5.1.NC] St John's Wort

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

2J) Summary: Case reports describe the onset of serotonin syndrome-like symptoms, mania, and [hypomania](#) following the addition of St. John's Wort to [sertraline](#), [fluoxetine](#), and [paroxetine](#) therapy[442][443][444][445]. A patient exhibited a syndrome resembling sedative/[hypnotic intoxication](#) after adding St. John's Wort to [paroxetine](#) therapy [446]. St. John's Wort is thought to inhibit serotonin reuptake and may have mild monoamine oxidase inhibitory activity [447][448], which when added to selective serotonin reuptake inhibitors may result in [serotonin syndrome](#).

3J) Severity: major

4J) Onset: rapid

5J) Substantiation: probable

6J) Clinical Management: Patients should be advised to wait two weeks after stopping St. John's Wort before restarting selective serotonin reuptake inhibitor therapy. If a patient plans to replace selective serotonin reuptake inhibitor (SSRI) therapy with St. John's Wort, the half-life of the specific SSRI should be taken into consideration, waiting at least 5 half-lives for the SSRI to be metabolized out of the body.

7J) Probable Mechanism: additive serotonergic effect

8J) Literature Reports

aJ) Five cases have been reported of [serotonin syndrome](#) in the elderly after combining prescription antidepressants and St. John's Wort. Case 1 developed dizziness, nausea, vomiting and a headache 4 days after starting St. John's Wort 300 milligrams (mg) three times daily combined with [sertraline](#) 50 mg daily. Her symptoms resolved 2 to 3 days after stopping all medications. Case 2 developed nausea, epigastric pain and anxiety 3 days after starting St. John's Wort 300 mg twice daily combined with [sertraline](#) 75 mg daily. His symptoms resolved in one week after discontinuing both medications, and he resumed [sertraline](#) use without complications. The third case developed nausea, vomiting, anxiety, and confusion 2 days after starting St. John's Wort 300 mg twice daily combined with [sertraline](#) 50 mg daily. His symptoms improved in 4 to 5 days after stopping both medications and taking [cyproheptadine](#) 4 mg three times daily. Case 4 developed nausea, anxiety, restless, and irritability 2 days after starting St. John's Wort 300 mg three times daily combined with [sertraline](#) 50 mg daily. [Cyproheptadine](#) 4 mg twice daily was administered for seven days, and his symptoms improved in 1 week after stopping the medication. Cases 1 through 4 resumed their prescriptive [sertraline](#) after symptoms subsided and had no further problems. Case 5 developed nausea, vomiting and restlessness 3 days after starting St. John's Wort 300 mg three times daily combined with [nefazodone](#) 100 mg twice daily. She continued to take St. John's Wort but discontinued the [nefazodone](#) and over 1 week her symptoms improved. She refused to resume therapy with [nefazodone](#), but continued therapy with St. John's Wort and mild to moderate symptoms of depression and anxiety returned [437].

bJ) A 50-year-old female taking St. John's Wort 600 mg daily experienced symptoms of sedative intoxication when she ingested a single dose of [paroxetine](#) 20 mg. She was incoherent, groggy, slow-moving, and complained of nausea and weakness. Prior to starting St. John's Wort, she had been receiving [paroxetine](#) 40 mg daily for eight months without adverse effects. After a night of sleep, she returned to her baseline mental status [438].

c) A 61-year-old female experienced restlessness and involuntary movements of her extremities after beginning [paroxetine](#) 20 milligrams (mg) two days after discontinuing St. John's Wort 600 mg daily. The patient reported agitation and [akathisia](#) 8 hours after taking the first dose of [paroxetine](#). She presented with diaphoresis and involuntary movement of all extremities with hyperreflexia and rigidity. Blood pressure, heart rate, and temperature were normal. After admission, [blood pressure increased](#) to 200/116 mmHg and heart rate increased to 145 beats per minute. [Creatine kinase](#) increased from 212 units/liter (U/L) initially to 1024 U/L. The patient was managed with supportive care and [lorazepam](#) and discharged after two days [439].

d) A 28-year-old male developed a manic syndrome following comedication with St. John's Wort and [sertraline](#). The patient was also on [testosterone](#) replacement therapy following [bilateral orchidectomy](#) 2 years earlier, but [testosterone](#) levels were subtherapeutic. The patient was prescribed [sertraline](#) 50 milligrams daily for depression following a 2 week trial of St. John's Wort per patient preference (dose not specified). Before [sertraline](#) was started, the patient was instructed to discontinue St. John's Wort, but continued it despite this advice. The patient experienced improved mood so did not see his physician, believing that he did not need further treatment. Over 2 months, the patient had elated mood, was irritable, and overspent, buying a car he could not afford, and was ultimately arrested for stealing fuel for the car. On arrest, he was referred to psychiatric services due to irritability and disinhibition. He was observed to be over-aroused, distractible, have flight of ideas, and [grandiose delusions](#), leading to a diagnosis of a [manic episode](#). The authors state the possibility of the manic state resulting from [sertraline](#) therapy alone, and that St. John's Wort may have increased the risk as a result of monoamine oxidase inhibition. Since the patient's [testosterone](#) level was subnormal, the possibility of its contribution to the manic state was considered low. However, the patient had elevated gonadotropin levels ([luteinizing hormone](#) and [follicle-stimulating hormone](#)) which may have predisposed the patient to mania [440].

e) A 42-year-old female experienced symptoms consistent with a mixed hypomanic episode following concomitant use of [fluoxetine](#), [buspirone](#), Ginkgo biloba, and St. John's Wort. The symptoms resolved following discontinuation of Ginkgo and St. John's Wort. The patient was being treated for depression following a mild [traumatic brain injury](#) with [fluoxetine](#) 20 milligrams (mg) twice daily and [buspirone](#) 15 mg twice daily. Several weeks prior to presentation, [buspirone](#) was increased to 20 mg twice daily for persistent anxiety and the patient began taking Ginkgo biloba, [melatonin](#), and St. John's Wort in unspecified doses. [Melatonin](#) was considered unlikely to have contributed to her symptoms. Ginkgo and St. John's Wort were considered possible contributors since they may potentiate antidepressants, and considering the temporal relationship between the use of the herbs and onset of symptoms and discontinuation of the herbs and resolution of symptoms. However, the [brain injury](#) was considered a possible contributor [441].

3.5.1.ND] [Sufentanil](#)

- 1) Interaction Effect: increased risk of CNS depression (ie, [respiratory depression](#), profound sedation, coma)
- 2) Summary: The concomitant use of [sufentanil](#) with other CNS depressants may result in profound sedation, [respiratory depression](#), coma, and/or death. Reserve concomitant use to clinical settings where alternative treatment options are inadequate. If combination therapy is required, reduce the initial dose of the newly prescribed medication and titrate to clinical response while monitoring for [respiratory depression](#) and sedation[78].
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical

6) Clinical Management: Reserve concomitant use of [sufentanil](#) with other CNS depressants to clinical settings where alternative treatment options are inadequate. If combination therapy is required, reduce the initial dose of the newly prescribed medication and titrate to clinical response while monitoring for [respiratory depression](#) and sedation[78].

7) Probable Mechanism: additive CNS depression

3.5.1.NE] [Sulfamethoxazole](#)

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

2) Summary: Cotrimoxazole and [fluoxetine](#) have been shown to prolong the QTc interval at the recommended therapeutic dose[435][436]. Even though no formal drug interaction studies have been done, the coadministration of drugs known to prolong the QTc interval is not recommended.

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

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

7) Probable Mechanism: additive effects on QT prolongation

3.5.1.NF] [Sulfinpyrazone](#)

1) Interaction Effect: increased risk of bleeding

2) Summary: Exercise caution when coadministering a SSRI and an antiplatelet agent or anticoagulant as this may increase the risk of bleeding events[272][173][385].

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Use caution with concomitant use of [fluoxetine](#) with anticoagulants or antiplatelet agents, as coadministration may increase bleeding risk[272][173][385].

7) Probable Mechanism: altered anticoagulant effects

8) Literature Reports

a) In a retrospective study of patients over 50 years of age with the diagnosis of acute [myocardial infarction](#) (N=27,058), SSRI use with any antiplatelet therapy significantly increased the risk of bleeding by 1.42-fold compared with [aspirin](#) use alone. Therapy with [aspirin](#), [clopidogrel](#), and an SSRI significantly increased risk by 2.35-fold compared with [aspirin](#) use alone and by 1.57-fold compared with [clopidogrel](#) and [aspirin](#) combination therapy [385].

b) In a systematic review and meta-analysis of 22 observational studies, SSRI use was associated with a significant 1.55 fold increase in risk of [upper gastrointestinal bleeding](#) (UGIB). Concomitant use of SSRIs and antiplatelet drugs was associated with a 2.48-fold increase in risk of UGIB (3 studies) [272].

3.5.1.NG] [Sulindac](#)

1) Interaction Effect: an increased risk of bleeding

2) Summary: Caution is recommended with the concomitant use of NSAIDs and antidepressants, including SSRIs due to an increased risk of [intracranial hemorrhage](#)[529] and [gastrointestinal bleeding](#) [533][534][530][531]. Bleeding events have included [epistaxis](#), ecchymosis, [hematoma](#), [petechiae](#), and life-

threatening hemorrhages [536][535][537][538]. When an SSRI and an NSAID are given concurrently, monitor the patient for signs of increased bleeding.

3) Severity: major

4) Onset: unspecified

5) Substantiation: established

6) Clinical Management: Use caution if NSAIDs and SSRIs are coadministered. Concomitant use of NSAIDs and SSRIs may cause an increased risk of [intracranial hemorrhage](#)[529] and [gastrointestinal bleeding](#) [530][531]. When an SSRI and an NSAID are given concurrently, monitor the patient for signs of increased bleeding.

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

8) Literature Reports

a) Concomitant use of NSAIDs and antidepressants, including tricyclic antidepressants, SSRIs, serotonin-norepinephrine reuptake inhibitors, and MAOIs, resulted in a 60% increased risk of [intracranial hemorrhage](#) within 30 days of concomitant use compared with antidepressant use alone. There was no significant difference between the antidepressant drug classes and the increased risk; however, there was an increased risk associated with male patients compared with female patients [529].

b) SSRIs increase the risk of upper gastrointestinal (GI) bleeding, and this effect is potentiated by concurrent use of NSAIDs or low-dose [aspirin](#). Hospitalizations for [upper GI bleeding](#) were searched among 26,005 users of antidepressant medications and compared with the number of hospitalizations in those patients who did not receive prescriptions for antidepressants. The amount of [upper GI bleeding](#) episodes was 3.6 times more than expected. Combined use of an SSRI and NSAIDs or low-dose [aspirin](#) increased the risk to 12.2 and 5.2 times, respectively. The findings of this study demonstrate an increased risk of [upper GI bleeding](#) during the use of SSRIs. Combined use of SSRIs and NSAIDs or low-dose [aspirin](#) increased the risk even further [532].

c) Two metaanalyses of incidents of upper GI bleed due to SSRIs, NSAIDs, and their combination found that SSRIs increased the risk by 1.73 [533] to 2.36 times [534], NSAIDs by 2.55 times [533], and the combination of SSRIs and NSAIDs by 4.02 [533] to 6.33 times [534].

d) The release of serotonin by [platelets](#) is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs and NSAIDs have been associated with an increased risk of bleeding [535].

3.5.1.NH] Sulpiride

1) Interaction Effect: increased risk of QT interval prolongation and [torsades de pointes](#)

2) Summary: Use caution with the concomitant use of sulpiride with other agents that prolong the QT interval. Because sulpiride by itself prolongs the QT interval, coadministration with another medication that prolongs the QT interval increases the risk of serious [ventricular arrhythmias](#) such [torsade de pointes](#) and is not recommended. If administration cannot be avoided, [monitoring of heart rate](#) and correction of any electrolyte disturbances is warranted[48].

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Use caution with the concomitant use of sulpiride with other agents that prolong the QT interval. Because sulpiride by itself prolongs the QT interval, coadministration with another medication that prolongs the QT interval increases the risk of serious [ventricular arrhythmias](#) such [torsade](#)

de pointes and is not recommended. If administration cannot be avoided, monitoring of heart rate and correction of any electrolyte disturbances is warranted[48].

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

3.5.1.NI] Sultopride

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

2J) Summary: Fluoxetine has been shown to prolong the QTc interval at the recommended therapeutic dose[304]. Even though no formal drug interaction studies have been done, the coadministration of antipsychotics and other drugs known to prolong the QTc interval, including fluoxetine, is not recommended. Several antipsychotic agents have demonstrated QT prolongation including sertindole [305], sultopride [306], and zotepine [307].

3J) Severity: major

4J) Onset: unspecified

5J) Substantiation: theoretical

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

7J) Probable Mechanism: additive effects on QT prolongation

3.5.1.NJ] Sumatriptan

1J) Interaction Effect: an increased risk of serotonin syndrome

2J) Summary: There have been case reports of weakness, hyperreflexia, and incoordination following concomitant use of sumatriptan and a serotonin specific reuptake inhibitor (SSRI)[198]. Concurrent use of a triptan and an SSRI may result in serotonin syndrome which may be life-threatening. Symptoms of serotonin syndrome may include restlessness, hallucinations, loss of coordination, fast heart beat, rapid changes in blood pressure, increased body temperature, overreactive reflexes, nausea, vomiting, and diarrhea. Clinicians should be aware that triptans may be commonly used intermittently and that either the triptan or the SSRI may be prescribed by a different physician. Discuss the risks of serotonin syndrome with patients who are prescribed this combination and monitor them closely for symptoms of serotonin syndrome [199].

3J) Severity: major

4J) Onset: delayed

5J) Substantiation: probable

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

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

8J) Literature Reports

aJ) In the Canadian post-marketing surveillance program of fluoxetine, six cases of suspected drug interactions with sumatriptan have been reported. Of these cases, two are strongly suggestive of a drug interaction. Patients demonstrated symptoms consistent with serotonin syndrome [197].

3.5.1.NK] Tacrolimus

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

2J) Summary: Concomitant use of [tacrolimus](#) with a drug that has additive effects on the QT interval may increase the risk of serious [cardiac toxicity](#), including [torsade de pointes](#). If coadministered, observe patients for signs and symptoms of QT interval prolongation, and consider obtaining an ECG and monitoring magnesium, potassium, and [calcium](#) blood levels[74][75].

3J) Severity: major

4J) Onset: unspecified

5J) Substantiation: theoretical

6J) Clinical Management: Concomitant use of [tacrolimus](#) with a drug that has additive effects on the QT interval may increase the risk of serious [cardiac toxicity](#), including [torsade de pointes](#). If coadministered, observe patients for signs and symptoms of QT interval prolongation, and consider obtaining an ECG and monitoring magnesium, potassium, and [calcium](#) blood levels[74][75].

7J) Probable Mechanism: additive effects on QT interval

3.5.1.NL| [Tamoxifen](#)

1J) Interaction Effect: decreased plasma concentration of the active metabolite of [tamoxifen](#); increased risk of QT-interval prolongation

2J) Summary: Large retrospective studies have found no significant impact of antidepressants, including [fluoxetine](#), on the risk of subsequent [breast cancer](#)[361] nor an increased risk of death from [breast cancer](#) with concomitant use of [tamoxifen](#) and [fluoxetine](#), despite an increased risk found with [paroxetine](#) [360]. When concomitant antidepressant therapy is necessary, alternatives with little or no CYP2D6 inhibition should still be considered [360]. Additionally, concomitant administration of [fluoxetine](#) and [tamoxifen](#) may result in additive effects on the QT interval and should be avoided. Consider periodic [ECG monitoring](#) in patients with risk factors for QT prolongation and [ventricular arrhythmia](#) [362].

3J) Severity: major

4J) Onset: delayed

5J) Substantiation: theoretical

6J) Clinical Management: While coadministration of [paroxetine](#), another SSRI with CYP2D6 inhibiting properties, and [tamoxifen](#) may decrease the plasma concentration of the major active metabolite of [tamoxifen](#)[358][359] and may reduce the clinical benefit of [tamoxifen](#) [360], data have not supported a significant effect of [fluoxetine](#) on [breast cancer](#) events with [tamoxifen](#) [360][361]. However, when concomitant antidepressant therapy is necessary, consider alternatives with little or no CYP2D6 inhibition [360]. Additionally, concomitant administration of [fluoxetine](#) and [tamoxifen](#) may result in additive effects on the QT interval and should be avoided. Consider periodic [ECG monitoring](#) in patients with risk factors for QT prolongation and [ventricular arrhythmia](#) [362].

7J) Probable Mechanism: inhibition of CYP2D6-mediated [tamoxifen](#) metabolism; additive QT-interval prolongation effects

8J) Literature Reports

aJ) The risk of subsequent [breast cancer](#) was not significantly increased with concurrent use of antidepressants in a retrospective review of 16,887 insured women receiving [tamoxifen](#) for at least 6 months following a diagnosis of Stage 0 to II [breast cancer](#). The median duration of [tamoxifen](#) use was 2.7 years. Of the 8089 patients who were prescribed antidepressants, the median days of overlap between antidepressant and [tamoxifen](#) use was 144 days. After a median follow-up of 6 years, 17.4% of all patients developed a subsequent [breast cancer](#). Of the 10.6% of patients who received [paroxetine](#), 25%, 50%, and 75% increases in overlapping use during the first year of [tamoxifen](#) were associated with the highest increases in the risk of subsequent [breast cancer](#) (6%, 13%, and 20%, respectively), but these increases were not significant and diminished over time. [Fluoxetine](#) was the most common antidepressant prescribed (19.9%) and was associated with a 0%, 1%, and 3% nonsignificant increase in the risk of subsequent [breast cancer](#) for the

corresponding 25%, 50%, and 75% increases in overlapping use during the first year of [tamoxifen](#). Other agents tested were grouped into categories of other SSRIs, tricyclics, and other types that included [venlafaxine](#), [trazodone](#), [bupropion](#), and tetracyclics [361].

b)) Results from a retrospective study demonstrated that concomitant use of [paroxetine](#) and [tamoxifen](#) is associated with an increased risk of death from [breast cancer](#) that is directly related to the duration of concomitant therapy, while the risk is not increased with other SSRIs, including [fluoxetine](#). Participants in the study included females at least 66 years old who were newly treated with [tamoxifen](#) for [breast cancer](#) and who also received a single SSRI antidepressant. Of the 2430 participants, 2025 initiated [tamoxifen](#) within 1 year of being diagnosed with [breast cancer](#) and the median duration of [tamoxifen](#) therapy was 4 years. [Paroxetine](#) was the most common SSRI prescribed (n=630) while others consisted of [sertraline](#) (n=541), [citalopram](#) (n=467), [venlafaxine](#) (n=365), [fluoxetine](#) (n=253), and [fluvoxamine](#) (n=174). After a mean follow-up of 2.38 years, 374 women died of [breast cancer](#). Absolute increases of 25%, 50%, and 75% in the proportion of time on [tamoxifen](#) concomitantly with [paroxetine](#) were associated with significant increases of 24%, 54%, and 91% in the risk of death from [breast cancer](#), respectively. No other SSRI was associated with an increased risk of [breast cancer](#) mortality when administered during [tamoxifen](#) therapy [360].

3.5.1.NM] [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[345] 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[345], 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](#) [345].

3.5.1.NN] [Tapentadol](#)

- 1)) Interaction Effect: increased risk of CNS depression
- 2)) Summary: Concomitant use of tapentadol, which is a CNS depressant, with another CNS depressant may result in [respiratory depression](#), hypotension, and profound sedation, potentially leading to coma or death. Assess the duration of use and the patient's degree of tolerance to CNS depressants. If tapentadol is coadministered with a CNS depressant, initiate the dose of tapentadol ER at 50 mg every 12 hours, and consider lowering the dose of the concomitant CNS depressant. Monitor for signs and symptoms of [respiratory depression](#), hypotension, and sedation[103].

- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Concomitant use of tapentadol, which is a CNS depressant, with another CNS depressant may result in [respiratory depression](#), hypotension, and profound sedation, potentially leading to coma or death. Assess the duration of use and the patient's degree of tolerance to CNS depressants. If tapentadol is coadministered with a CNS depressant, initiate the dose of tapentadol ER at 50 mg every 12 hours, and consider lowering the dose of the concomitant CNS depressant. Monitor for signs and symptoms of [respiratory depression](#), hypotension, and sedation[103].
- 7) Probable Mechanism: additive CNS depression effects

3.5.1.NO] Tapentadol

- 1) Interaction Effect: increased risk of [serotonin syndrome](#) ([hypertension](#), [hyperthermia](#), myoclonus, mental status changes)
- 2) Summary: Concurrent use of tapentadol and a selective serotonin reuptake inhibitor (SSRI) may result in [serotonin syndrome](#), which may be life-threatening. Symptoms of [serotonin syndrome](#) may include restlessness, hallucinations, loss of coordination, fast heart beat, rapid changes in blood pressure, increased body temperature, overreactive reflexes, nausea, vomiting, and diarrhea[539].
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Coadministration of tapentadol and an SSRI may result in a life-threatening condition called [serotonin syndrome](#). If these agents are used together, monitor the patient closely for symptoms of [serotonin syndrome](#) (restlessness, [hyperthermia](#), hyperreflexia, incoordination), especially during treatment initiation and dose increases[539].
- 7) Probable Mechanism: additive serotonergic effect

3.5.1.NP] Tedisamil

- 1) Interaction Effect: an increased risk of [cardiotoxicity](#) (QT prolongation, [torsades de pointes](#), [cardiac arrest](#))
- 2) Summary: Even though no formal drug interaction studies have been done, the coadministration of Class III antiarrhythmics and other drugs known to prolong the QTc interval is not recommended[300][301][302]. [Fluoxetine](#) has been shown to prolong the QTc interval at the recommended therapeutic dose [303].
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: The concurrent administration of class III antiarrhythmic agents and agents that prolong the QT interval, such as [fluoxetine](#), is not recommended.
- 7) Probable Mechanism: additive effects on QT prolongation

3.5.1.NQ] Telithromycin

- 1) Interaction Effect: an increased risk of [cardiotoxicity](#) (QT prolongation, [torsades de pointes](#), [cardiac arrest](#))
- 2) Summary: Even though no formal drug interaction studies have been done, [telithromycin](#) should be coadministered cautiously with other drugs which are also known to prolong the QTc interval, including [fluoxetine](#)[541][542].
- 3) Severity: major

- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: The concurrent administration of [telithromycin](#) with other agents that can prolong the QT interval, such as [fluoxetine](#), is not recommended.
- 7) Probable Mechanism: additive effects on QT prolongation

3.5.1.NR] Tenoxicam

- 1) Interaction Effect: an increased risk of bleeding
- 2) Summary: Caution is recommended with the concomitant use of NSAIDs and antidepressants, including SSRIs due to an increased risk of [intracranial hemorrhage](#)[529] and [gastrointestinal bleeding](#) [533][534][530][531]. Bleeding events have included [epistaxis](#), ecchymosis, [hematoma](#), [petechiae](#), and life-threatening hemorrhages [536][535][537][538]. When an SSRI and an NSAID are given concurrently, monitor the patient for signs of increased bleeding.
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: established
- 6) Clinical Management: Use caution if NSAIDs and SSRIs are coadministered. Concomitant use of NSAIDs and SSRIs may cause an increased risk of [intracranial hemorrhage](#)[529] and [gastrointestinal bleeding](#) [530][531]. When an SSRI and an NSAID are given concurrently, monitor the patient for signs of increased bleeding.
- 7) Probable Mechanism: depletion of [platelet](#) serotonin by SSRI; additive effects
- 8) Literature Reports

a) Concomitant use of NSAIDs and antidepressants, including tricyclic antidepressants, SSRIs, serotonin-norepinephrine reuptake inhibitors, and MAOIs, resulted in a 60% increased risk of [intracranial hemorrhage](#) within 30 days of concomitant use compared with antidepressant use alone. There was no significant difference between the antidepressant drug classes and the increased risk; however, there was an increased risk associated with male patients compared with female patients [529].

b) SSRIs increase the risk of upper gastrointestinal (GI) bleeding, and this effect is potentiated by concurrent use of NSAIDs or low-dose [aspirin](#). Hospitalizations for [upper GI bleeding](#) were searched among 26,005 users of antidepressant medications and compared with the number of hospitalizations in those patients who did not receive prescriptions for antidepressants. The amount of [upper GI bleeding](#) episodes was 3.6 times more than expected. Combined use of an SSRI and NSAIDs or low-dose [aspirin](#) increased the risk to 12.2 and 5.2 times, respectively. The findings of this study demonstrate an increased risk of [upper GI bleeding](#) during the use of SSRIs. Combined use of SSRIs and NSAIDs or low-dose [aspirin](#) increased the risk even further [532].

c) Two metaanalyses of incidents of upper GI bleed due to SSRIs, NSAIDs, and their combination found that SSRIs increased the risk by 1.73 [533] to 2.36 times [534], NSAIDs by 2.55 times [533], and the combination of SSRIs and NSAIDs by 4.02 [533] to 6.33 times [534].

d) The release of serotonin by [platelets](#) is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs and NSAIDs have been associated with an increased risk of bleeding [535].

3.5.1.NS] [Terbinafine](#)

- 1) Interaction Effect: elevated fluoxetine plasma concentrations and increased risk of QT-interval prolongation
- 2) Summary: Concomitant treatment of fluoxetine with other CYP2D6 inhibitors can increase fluoxetine plasma concentrations and increase the risk of adverse effects, including episodes of QT-interval prolongation, ventricular arrhythmia, and torsade de pointes. Use caution in coadministration of these drugs[173]. If concomitant use is required, initiate fluoxetine at the lowest dose possible and titrate dose carefully based on patient response [540].
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Use caution with coadministration of fluoxetine and CYP2D6 inhibitors, as increased fluoxetine plasma concentrations may increase the risk of adverse effects, including episodes of QT-interval prolongation, ventricular arrhythmia, and torsade de pointes[173]. If concomitant use is required, initiate fluoxetine at the lowest dose possible and titrate dose carefully based on patient response [540].
- 7) Probable Mechanism: inhibition of CYP2D6-mediated fluoxetine metabolism

3.5.1.NT] Terfenadine

- 1) Interaction Effect: increased risk of QT-interval prolongation
- 2) Summary: The concomitant use of terfenadine with drugs that cause QT-interval prolongation is contraindicated, as coadministration may increase the risk of QT prolongation and serious ventricular arrhythmias[174].
- 3) Severity: contraindicated
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: The concomitant use of terfenadine with drugs that cause QT-interval prolongation is contraindicated, as coadministration may increase the risk of QT prolongation and serious ventricular arrhythmias[174].
- 7) Probable Mechanism: additive QT interval effects

3.5.1.NU] Terfenadine

- 1) Interaction Effect: cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
- 2) Summary: Although 2 cases have been reported in which concomitant terfenadine and fluoxetine resulted in cardiac toxicity in patients with no previous heart disease, a study of 12 healthy males demonstrated no significant pharmacokinetic or pharmacodynamic interaction between fluoxetine and terfenadine[501][502][503]. Terfenadine and fluoxetine have been reported to cause QT prolongation at therapeutic doses. The administration of terfenadine with any other medication that may prolong the QT interval is contraindicated [504].
- 3) Severity: contraindicated
- 4) Onset: delayed
- 5) Substantiation: probable
- 6) Clinical Management: The concomitant administration of fluoxetine and terfenadine is contraindicated.
- 7) Probable Mechanism: decreased terfenadine metabolism
- 8) Literature Reports

- a) In a study of 12 healthy male volunteers, fluoxetine did not inhibit the metabolism of terfenadine. Fluoxetine 60 mg daily was given for nine days. Terfenadine 60 mg was given alone and after eight days of the nine-day fluoxetine regimen. A high dose of fluoxetine was given to

test the probability of interaction rigorously. Subject were monitored for changes in [terfenadine](#) pharmacokinetics and adverse effects. Concomitant [fluoxetine](#) resulted in a slight decrease in [terfenadine](#) plasma concentration. In addition, the area under the plasma concentration time curve for [terfenadine](#) was significantly decreased by [fluoxetine](#). No change in blood pressure, heart rate, or cardiac electrographic tracings (EKG) were observed. One subjected reported dizziness after taking [terfenadine](#) alone and one subject had an abnormal EKG at baseline and during all observations during the study [498].

b)) A 39-year old woman experienced [cardiac toxicity](#) due to a possible interaction of [terfenadine](#) and [fluoxetine](#) [499]. The patient's medications included [acyclovir](#), [beclomethasone](#), [pseudoephedrine](#), and [ibuprofen](#). During hospitalization for a substance abuse treatment program, the patient was started on [fluoxetine](#) 40 mg daily, [terfenadine](#) 60 mg twice daily, and [disulfiram](#) 250 mg daily. Approximately 14 days later, the patient underwent a routine [electrocardiogram](#) (ECG) study that revealed a prolonged QT interval of 550 milliseconds. The patient was asymptomatic and had no prior history of [heart disease](#). [Terfenadine](#) was discontinued, and an ECG taken one week later revealed a normal QT interval.

c)) A case report describes a possible interaction with [terfenadine](#) and [fluoxetine](#) in a 41-year-old male who experienced irregular heartbeat, skipped beats, and shortness of breath a month after institution of [fluoxetine](#) 20 mg daily; he had no previous history of [heart disease](#). His drug regimen included [fluoxetine](#), [terfenadine](#) 60 mg twice daily, [ibuprofen](#) 800 mg three times daily, [misoprostol](#) 100 mcg four times daily, [Midrin\(R\)](#) ([acetaminophen](#) 325 mg, [dichloralphenazone](#) 100 mg, [isometheptene](#) mucate 65 mg) as needed, and [ranitidine](#) 150 mg twice daily. A 24-hour [Holter monitor](#) showed intermittent frequent [sinus tachycardia](#), three isolated [atrial premature contractions](#), and three [couplets](#). [Terfenadine](#) was discontinued and his previously reported symptoms did not reoccur. [Fluoxetine](#) is a known enzyme inhibitor and may have inhibited [terfenadine](#) metabolism resulting in the cardiac abnormalities seen in this patient [500].

3.5.1.NV] Tetrabenazine

1)) Interaction Effect: increased risk of QT interval prolongation, [neuroleptic malignant syndrome](#), [extrapyramidal disorders](#)

2)) Summary: Tetrabenazine causes a small increase in the correct QT interval. As the degree of prolongation increases, QT prolongation can develop into torsade de pointes-type VT. The concomitant use of tetrabenazine with other drugs known for QT prolongation (eg, [olanzapine](#)) should be avoided. In a randomized, double-blind, placebo controlled crossover study of healthy subjects, the effect of a single 25 mg or 50 mg dose of tetrabenazine on the QT interval was studied with [moxifloxacin](#) as a positive control. The 50 mg dose of tetrabenazine caused an approximate 8 millisecond mean increase in QT[62]. In addition to QT prolongation, tetrabenazine may also cause adverse reactions such as [neuroleptic malignant syndrome](#) and [extrapyramidal disorders](#), which may be exaggerated when coadministered with neuroleptic drugs (eg, [olanzapine](#)) [62].

3)) Severity: major

4)) Onset: unspecified

5)) Substantiation: theoretical

6)) Clinical Management: Coadministration of tetrabenazine with [olanzapine](#) or other neuroleptic drugs may increase tetrabenazine adverse reactions, such as QT interval prolongation and increased risk of [torsade de pointes](#). Other adverse reactions, such as [neuroleptic malignant syndrome](#) and [extrapyramidal disorders](#) may be enhanced when given with a [dopamine](#) agonist such as [olanzapine](#)[62].

7)) Probable Mechanism: increased [dopamine](#) levels; additive effects on QT interval prolongation

3.5.1.NW] Tetrabenazine

1) Interaction Effect: increased plasma concentrations of tetrabenazine and increased risk of QT prolongation and [torsade de pointes](#)

2) Summary: Coadministration of [fluoxetine](#), a strong CYP2D6 inhibitor, with tetrabenazine whose active metabolites (alpha-HTBZ and beta-HTBZ) are substrates for CYP2D6 may result in markedly increased exposure to these metabolites. Although coadministration of [fluoxetine](#) and tetrabenazine was not specifically studied, following 10 days of daily administration of a strong CYP2D6 inhibitor ([paroxetine](#) 20 mg daily), a single dose of tetrabenazine 50 mg resulted in increased alpha-HTBZ and beta-HTBZ exposure in 25 healthy volunteers. When compared with tetrabenazine alone, coadministration with [paroxetine](#) caused an approximately 30% increase in C_{max} and a 3-fold increase in the AUC of the alpha-HTBZ metabolite of tetrabenazine. Subjects given [paroxetine](#) prior to tetrabenazine alone experienced a 2.4-fold increase in C_{max} and a 9-fold increase in the AUC of the beta-HTBZ metabolite of tetrabenazine. The elimination half-life for both metabolites was approximately 14 hours when tetrabenazine was coadministered with [paroxetine](#). If [fluoxetine](#) is coadministered with tetrabenazine, the total daily dose of tetrabenazine should not exceed 50 mg and single doses should not exceed 25 mg. Concomitant use of [fluoxetine](#) and tetrabenazine may also result in additive effects on the QT interval and increased risk of [torsades de pointes](#)[418]. Coadministration should be avoided [173]

3) Severity: major

4) Onset: unspecified

5) Substantiation: probable

6) Clinical Management: Avoid the concomitant use of [fluoxetine](#) with other drugs known to prolong the QT interval (eg, tetrabenazine)[173]. Concomitant use of [fluoxetine](#) and tetrabenazine may result in higher serum concentrations of the active metabolites of tetrabenazine (alpha-HTBZ and beta-HTBZ). Patients who are already receiving a stable dose of tetrabenazine should have their daily dose of tetrabenazine decreased if coadministration with [fluoxetine](#) is necessary. During coadministration, total daily doses of tetrabenazine exceeding 50 mg or single doses exceeding 25 mg are not recommended [418].

7) Probable Mechanism: inhibition of CYP2D6-mediated tetrabenazine metabolism by [fluoxetine](#) and additive QT-interval prolongation

3.5.1.NX] Thioridazine

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

2) Summary: The concomitant use of [thioridazine](#) with drugs that cause QT-interval prolongation is contraindicated, as coadministration may increase the risk of QT prolongation and serious [ventricular arrhythmias](#)[58].

3) Severity: contraindicated

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: The concomitant use of [thioridazine](#) with drugs that cause QT-interval prolongation is contraindicated, as coadministration may increase the risk of QT prolongation and serious [ventricular arrhythmias](#)[58].

7) Probable Mechanism: additive QT interval effects

3.5.1.NY] Tianeptine

1) Interaction Effect: increased risk of tricyclic antidepressant toxicity, QT prolongation and [serotonin syndrome](#)

2) Summary: [Fluoxetine](#), a potent CYP2D6 inhibitor, is associated with an increased risk of [serotonin syndrome](#), QT prolongation, and [ventricular arrhythmias](#) (including [torsade de pointes](#)). Concomitant

therapy with CYP2D6-metabolized tricyclic antidepressants (TCAs) may potentiate these risks and introduce TCA toxicity[173]; concurrent use of [fluoxetine](#) and [desipramine](#), [nortriptyline](#), and [imipramine](#) has resulted in significant increases in TCA concentrations [517][523][524][525][526][527]. Use caution with concurrent administration of [fluoxetine](#) and TCAs. If [fluoxetine](#) is added to an existing TCA regimen, consider TCA dose reduction. If [fluoxetine](#) and a TCA are coadministered or [fluoxetine](#) has been recently discontinued, consider plasma TCA monitoring. If [serotonin syndrome](#) occurs, immediately discontinue [fluoxetine](#) and TCA. If [ventricular arrhythmias](#) develop, consider [fluoxetine](#) discontinuation and cardiac evaluation [173].

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Use caution with concurrent administration of [fluoxetine](#) and TCAs, as elevated TCA plasma concentrations may occur. If [fluoxetine](#) is added to an existing TCA regimen, consider TCA dose reduction. If [fluoxetine](#) and a TCA are coadministered or [fluoxetine](#) has been recently discontinued, consider plasma TCA monitoring. If [serotonin syndrome](#) occurs, immediately discontinue [fluoxetine](#) and TCA. If [ventricular arrhythmias](#) develop, consider [fluoxetine](#) discontinuation and cardiac evaluation[173]

7) Probable Mechanism: decreased CYP2D6-mediated metabolism of tricyclic antidepressants by [fluoxetine](#); additive effects on QT prolongation; additive serotonergic effects

8) Literature Reports

a) Previously stable plasma levels of [imipramine](#) and [desipramine](#) rose more than 2- to 10-fold with [fluoxetine](#) coadministration in 2 clinical studies. This effect may persist for 3 weeks or more after [fluoxetine](#) discontinuation. Dose reduction and temporary monitoring of tricyclic antidepressant plasma concentrations may be indicated with concurrent [fluoxetine](#) treatment or recent [fluoxetine](#) discontinuation [173].

b) [Fluoxetine](#) statistically and clinically significantly increased [desipramine](#) concentrations in 18 healthy subjects. When [fluoxetine](#) (20 mg daily) was added to [desipramine](#) (50 mg daily), the mean maximum concentration of [desipramine](#) increased by 278% and the AUC increased by 342%. [Desipramine](#) trough concentrations continued to be 198% above baseline 3 weeks after [fluoxetine](#) was discontinued. The same study compared pharmacokinetics of [desipramine](#) when combined with [sertraline](#). The impact of [sertraline](#) was modest, resulting in small and short-term increases in [desipramine](#) plasma concentrations [517].

c) Concomitant administration of [fluoxetine](#) and [desipramine](#) was reported to result in an increased [desipramine](#) level and new onset of [delirium](#) in a 69-year-old male within 10 days of the addition of [fluoxetine](#) to the patient's regimen [518].

d) [Fluoxetine](#) increased the level of tricyclic antidepressants ([nortriptyline](#), [imipramine](#), [desipramine](#)) in 4 patients. After the addition of [fluoxetine](#), the ratio of antidepressant level to dose increased by 109% to 486% in the patients. Three patients developed clinical symptoms (anticholinergic effects, constipation, urinary hesitancy, sedation, unstable gait) as a result of the increased levels [519].

e) A 39-year-old female experienced symptomatic increases in her [desipramine](#) levels with concomitant [fluoxetine](#) therapy. Prior to [fluoxetine](#) therapy, the patient's measured levels of [desipramine](#) had ranged from 148 to 160 nanograms/milliliter (ng/mL; 556 to 601 nanomol/L) on a regimen of 300 mg daily. Five weeks after the addition of [fluoxetine](#) 20 mg daily, she reported anticholinergic symptoms, sedation, and confusion with a [desipramine](#) level of 527 ng/mL (1978 nanomol/L). The [desipramine](#) dose was lowered to 200 mg/day; 11 days later, the level was 244 ng/mL (916 nanomol/L); the patient reported decreased energy, impaired short-term memory, and

some "garbled" speech, as well as an episode of nausea, dizziness, and syncope. The [desipramine](#) dose was reduced to 50 mg/day, and the adverse effects resolved in 6 days. Eight days later, the [desipramine](#) level was 122 ng/mL (458 nanomol/L) [520].

f) A 33-year-old depressed male developed adverse effects of dry mouth, tinnitus, and difficulties with alertness and memory while receiving [fluoxetine](#) 40 mg daily and [desipramine](#) 150 mg daily for 5 weeks; [fluoxetine](#) was discontinued and the blood levels of [desipramine](#) decreased from 938 to 48 nanograms/mL (3521 to 180 nanomol/L) with resolution of clinical symptoms [521].

g) A 75-year-old female experienced symptomatic increases in her [desipramine](#) serum concentrations when [fluoxetine](#) was added. [Desipramine](#) serum levels ranged from 109 to 150 ng/mL (409 to 563 nanomol/L) with oral doses of 300 mg at bedtime prior to [fluoxetine](#) therapy. Following the addition of oral [fluoxetine](#) 20 mg daily to the regimen, the [desipramine](#) serum level increased to 212 ng/mL (796 nanomol/L) within five days. The [fluoxetine](#) dose was increased to 40 mg/day three days later, and the [desipramine](#) serum level was 419 ng/mL (1573 nanomol/L) after four days. A worsening of depression and severe fatigue coincided with the increases in [desipramine](#) serum levels. Withdrawal of [fluoxetine](#) and reduction in the [desipramine](#) dose to 200 mg daily reduced the [desipramine](#) serum level to 231 ng/mL (867 nanomol/L) within two weeks [522].

3.5.1.NZ] Tiaprofenic Acid

1) Interaction Effect: an increased risk of bleeding

2) Summary: Caution is recommended with the concomitant use of NSAIDs and antidepressants, including SSRIs due to an increased risk of [intracranial hemorrhage](#)[529] and [gastrointestinal bleeding](#) [533][534][530][531]. Bleeding events have included [epistaxis](#), ecchymosis, [hematoma](#), [petechiae](#), and life-threatening hemorrhages [536][535][537][538]. When an SSRI and an NSAID are given concurrently, monitor the patient for signs of increased bleeding.

3) Severity: major

4) Onset: unspecified

5) Substantiation: established

6) Clinical Management: Use caution if NSAIDs and SSRIs are coadministered. Concomitant use of NSAIDs and SSRIs may cause an increased risk of [intracranial hemorrhage](#)[529] and [gastrointestinal bleeding](#) [530][531]. When an SSRI and an NSAID are given concurrently, monitor the patient for signs of increased bleeding.

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

8) Literature Reports

a) Concomitant use of NSAIDs and antidepressants, including tricyclic antidepressants, SSRIs, serotonin-norepinephrine reuptake inhibitors, and MAOIs, resulted in a 60% increased risk of [intracranial hemorrhage](#) within 30 days of concomitant use compared with antidepressant use alone. There was no significant difference between the antidepressant drug classes and the increased risk; however, there was an increased risk associated with male patients compared with female patients [529].

b) SSRIs increase the risk of upper gastrointestinal (GI) bleeding, and this effect is potentiated by concurrent use of NSAIDs or low-dose [aspirin](#). Hospitalizations for [upper GI bleeding](#) were searched among 26,005 users of antidepressant medications and compared with the number of hospitalizations in those patients who did not receive prescriptions for antidepressants. The amount of [upper GI bleeding](#) episodes was 3.6 times more than expected. Combined use of an SSRI and NSAIDs or low-dose [aspirin](#) increased the risk to 12.2 and 5.2 times, respectively. The

findings of this study demonstrate an increased risk of [upper GI bleeding](#) during the use of SSRIs. Combined use of SSRIs and NSAIDs or low-dose [aspirin](#) increased the risk even further [532].

c) Two metaanalyses of incidents of upper GI bleed due to SSRIs, NSAIDs, and their combination found that SSRIs increased the risk by 1.73 [533] to 2.36 times [534], NSAIDs by 2.55 times [533], and the combination of SSRIs and NSAIDs by 4.02 [533] to 6.33 times [534].

d) The release of serotonin by [platelets](#) is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs and NSAIDs have been associated with an increased risk of bleeding [535].

3.5.1.OA| Ticagrelor

- 1) Interaction Effect: increased risk of bleeding
- 2) Summary: Exercise caution when coadministering a SSRI and an antiplatelet agent or anticoagulant as this may increase the risk of bleeding events[272][173][385].
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Use caution with concomitant use of [fluoxetine](#) with anticoagulants or antiplatelet agents, as coadministration may increase bleeding risk[272][173][385].
- 7) Probable Mechanism: altered anticoagulant effects
- 8) Literature Reports

a) In a retrospective study of patients over 50 years of age with the diagnosis of acute [myocardial infarction](#) (N=27,058), SSRI use with any antiplatelet therapy significantly increased the risk of bleeding by 1.42-fold compared with [aspirin](#) use alone. Therapy with [aspirin](#), [clopidogrel](#), and an SSRI significantly increased risk by 2.35-fold compared with [aspirin](#) use alone and by 1.57-fold compared with [clopidogrel](#) and [aspirin](#) combination therapy [385].

b) In a systematic review and meta-analysis of 22 observational studies, SSRI use was associated with a significant 1.55 fold increase in risk of [upper gastrointestinal bleeding](#) (UGIB). Concomitant use of SSRIs and antiplatelet drugs was associated with a 2.48-fold increase in risk of UGIB (3 studies) [272].

3.5.1.OB| Ticlopidine

- 1) Interaction Effect: increased risk of bleeding
- 2) Summary: Exercise caution when coadministering a SSRI and an antiplatelet agent or anticoagulant as this may increase the risk of bleeding events[272][173][385].
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Use caution with concomitant use of [fluoxetine](#) with anticoagulants or antiplatelet agents, as coadministration may increase bleeding risk[272][173][385].
- 7) Probable Mechanism: altered anticoagulant effects
- 8) Literature Reports

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

SSRI significantly increased risk by 2.35-fold compared with [aspirin](#) use alone and by 1.57-fold compared with [clopidogrel](#) and [aspirin](#) combination therapy [385].

b)) In a systematic review and meta-analysis of 22 observational studies, SSRI use was associated with a significant 1.55 fold increase in risk of [upper gastrointestinal bleeding](#) (UGIB). Concomitant use of SSRIs and antiplatelet drugs was associated with a 2.48-fold increase in risk of UGIB (3 studies) [272].

3.5.1.OC| [Tinzaparin](#)

1)) Interaction Effect: an increased risk of bleeding

2)) Summary: The release of serotonin by [platelets](#) is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs and anticoagulants has been associated with an increased risk of bleeding[458][457]. Bleeding events reported have included [epistaxis](#), ecchymosis, [hematoma](#), [petechiae](#), and life-threatening hemorrhages. Altered anticoagulant effects (including increased bleeding) have been reported with the coadministration of SSRIs with anticoagulants [457].

3)) Severity: major

4)) Onset: delayed

5)) Substantiation: probable

6)) Clinical Management: When [fluoxetine](#) and an anticoagulant are given concurrently, monitor patient for signs of increased bleeding. Patients who are taking an anticoagulant should be monitored closely for altered anticoagulant effects, including increased bleeding, when [fluoxetine](#) therapy is initiated or discontinued[457].

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 a significant 1.7-fold increased risk for hospitalization for nongastrointestinal bleeding; however, the rate of [gastrointestinal bleeding](#) was not significantly different [458].

3.5.1.OD| [Tiotropium](#)

1)) Interaction Effect: increased risk of anticholinergic side effects

2)) Summary: Treatment with both [tiotropium](#) and this drug may produce additive anticholinergic effects. Avoid concomitant use with other anticholinergic agents[69].

3)) Severity: major

4)) Onset: unspecified

5)) Substantiation: theoretical

6)) Clinical Management: Treatment with both [tiotropium](#) and this drug may produce additive anticholinergic effects. Avoid concomitant use with other anticholinergic agents[69].

7)) Probable Mechanism: additive anticholinergic effects

3.5.1.OE| [Tipranavir](#)

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

- 2) Summary: Although the drug interaction between [fluoxetine](#) and [tipranavir/ritonavir](#) has not been studied, coadministration of [fluoxetine](#) with [tipranavir/ritonavir](#) may result in increased [fluoxetine](#) plasma concentrations. [Fluoxetine](#) doses may need to be adjusted when [tipranavir/ritonavir](#) therapy is initiated[399].
- 3) Severity: moderate
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Concurrent administration of [fluoxetine](#) and [tipranavir/ritonavir](#) may increase [fluoxetine](#) plasma concentrations. Use caution when these agents are coadministered and consider adjusting the [fluoxetine](#) dose as needed upon initiation of [tipranavir/ritonavir](#)[399].
- 7) Probable Mechanism: unknown

3.5.1.OF] [Tirofiban](#)

- 1) Interaction Effect: increased risk of bleeding
- 2) Summary: Exercise caution when coadministering a SSRI and an antiplatelet agent or anticoagulant as this may increase the risk of bleeding events[272][173][385].
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Use caution with concomitant use of [fluoxetine](#) with anticoagulants or antiplatelet agents, as coadministration may increase bleeding risk[272][173][385].
- 7) Probable Mechanism: altered anticoagulant effects
- 8) Literature Reports

a) In a retrospective study of patients over 50 years of age with the diagnosis of acute [myocardial infarction](#) (N=27,058), SSRI use with any antiplatelet therapy significantly increased the risk of bleeding by 1.42-fold compared with [aspirin](#) use alone. Therapy with [aspirin](#), [clopidogrel](#), and an SSRI significantly increased risk by 2.35-fold compared with [aspirin](#) use alone and by 1.57-fold compared with [clopidogrel](#) and [aspirin](#) combination therapy [385].

b) In a systematic review and meta-analysis of 22 observational studies, SSRI use was associated with a significant 1.55 fold increase in risk of [upper gastrointestinal bleeding](#) (UGIB). Concomitant use of SSRIs and antiplatelet drugs was associated with a 2.48-fold increase in risk of UGIB (3 studies) [272].

3.5.1.OG] [Tolfenamic Acid](#)

- 1) Interaction Effect: an increased risk of bleeding
- 2) Summary: Caution is recommended with the concomitant use of NSAIDs and antidepressants, including SSRIs due to an increased risk of [intracranial hemorrhage](#)[529] and [gastrointestinal bleeding](#) [533][534][530][531]. Bleeding events have included [epistaxis](#), ecchymosis, [hematoma](#), [petechiae](#), and life-threatening hemorrhages [536][535][537][538]. When an SSRI and an NSAID are given concurrently, monitor the patient for signs of increased bleeding.
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: established
- 6) Clinical Management: Use caution if NSAIDs and SSRIs are coadministered. Concomitant use of NSAIDs and SSRIs may cause an increased risk of [intracranial hemorrhage](#)[529] and [gastrointestinal bleeding](#) [530][531]. When an SSRI and an NSAID are given concurrently, monitor the patient for signs of increased bleeding.

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

8J) Literature Reports

aJ) Concomitant use of NSAIDs and antidepressants, including tricyclic antidepressants, SSRIs, serotonin-norepinephrine reuptake inhibitors, and MAOIs, resulted in a 60% increased risk of [intracranial hemorrhage](#) within 30 days of concomitant use compared with antidepressant use alone. There was no significant difference between the antidepressant drug classes and the increased risk; however, there was an increased risk associated with male patients compared with female patients [529].

bJ) SSRIs increase the risk of upper gastrointestinal (GI) bleeding, and this effect is potentiated by concurrent use of NSAIDs or low-dose [aspirin](#). Hospitalizations for [upper GI bleeding](#) were searched among 26,005 users of antidepressant medications and compared with the number of hospitalizations in those patients who did not receive prescriptions for antidepressants. The amount of [upper GI bleeding](#) episodes was 3.6 times more than expected. Combined use of an SSRI and NSAIDs or low-dose [aspirin](#) increased the risk to 12.2 and 5.2 times, respectively. The findings of this study demonstrate an increased risk of [upper GI bleeding](#) during the use of SSRIs. Combined use of SSRIs and NSAIDs or low-dose [aspirin](#) increased the risk even further [532].

cJ) Two metaanalyses of incidents of upper GI bleed due to SSRIs, NSAIDs, and their combination found that SSRIs increased the risk by 1.73 [533] to 2.36 times [534], NSAIDs by 2.55 times [533], and the combination of SSRIs and NSAIDs by 4.02 [533] to 6.33 times [534].

dJ) The release of serotonin by [platelets](#) is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs and NSAIDs have been associated with an increased risk of bleeding [535].

3.5.1.OHJ [Tolmetin](#)

1J) Interaction Effect: an increased risk of bleeding

2J) Summary: Caution is recommended with the concomitant use of NSAIDs and antidepressants, including SSRIs due to an increased risk of [intracranial hemorrhage](#)[529] and [gastrointestinal bleeding](#) [533][534][530][531]. Bleeding events have included [epistaxis](#), ecchymosis, [hematoma](#), [petechiae](#), and life-threatening hemorrhages [536][535][537][538]. When an SSRI and an NSAID are given concurrently, monitor the patient for signs of increased bleeding.

3J) Severity: major

4J) Onset: unspecified

5J) Substantiation: established

6J) Clinical Management: Use caution if NSAIDs and SSRIs are coadministered. Concomitant use of NSAIDs and SSRIs may cause an increased risk of [intracranial hemorrhage](#)[529] and [gastrointestinal bleeding](#) [530][531]. When an SSRI and an NSAID are given concurrently, monitor the patient for signs of increased bleeding.

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

8J) Literature Reports

aJ) Concomitant use of NSAIDs and antidepressants, including tricyclic antidepressants, SSRIs, serotonin-norepinephrine reuptake inhibitors, and MAOIs, resulted in a 60% increased risk of [intracranial hemorrhage](#) within 30 days of concomitant use compared with antidepressant use alone. There was no significant difference between the antidepressant drug classes and the increased risk; however, there was an increased risk associated with male patients compared with female patients [529].

b)) SSRIs increase the risk of upper gastrointestinal (GI) bleeding, and this effect is potentiated by concurrent use of NSAIDs or low-dose [aspirin](#). Hospitalizations for [upper GI bleeding](#) were searched among 26,005 users of antidepressant medications and compared with the number of hospitalizations in those patients who did not receive prescriptions for antidepressants. The amount of [upper GI bleeding](#) episodes was 3.6 times more than expected. Combined use of an SSRI and NSAIDs or low-dose [aspirin](#) increased the risk to 12.2 and 5.2 times, respectively. The findings of this study demonstrate an increased risk of [upper GI bleeding](#) during the use of SSRIs. Combined use of SSRIs and NSAIDs or low-dose [aspirin](#) increased the risk even further [532].

c)) Two metaanalyses of incidents of upper GI bleed due to SSRIs, NSAIDs, and their combination found that SSRIs increased the risk by 1.73 [533] to 2.36 times [534], NSAIDs by 2.55 times [533], and the combination of SSRIs and NSAIDs by 4.02 [533] to 6.33 times [534].

d)) The release of serotonin by [platelets](#) is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs and NSAIDs have been associated with an increased risk of bleeding [535].

3.5.1.OI] Toloxatone

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

2)) Summary: Concurrent administration or overlapping therapy with [fluoxetine](#) and a monoamine oxidase (MAO) inhibitor may result in CNS toxicity or [serotonin syndrome](#), a hyperserotonergic state characterized by symptoms such as restlessness, myoclonus, changes in mental status, hyperreflexia, diaphoresis, shivering, and tremor. Serious, even fatal, reactions have been reported[252][253][254][255][256][257]. As a reversible and selective monoamine oxidase inhibitor, toloxatone may not potentiate the effects of selective serotonin reuptake inhibitors to the same frequency, extent, and duration observed with other MAOIs. However, until further studies confirm the safety and efficacy of this combined therapy, concomitant use is contraindicated.

3)) Severity: contraindicated

4)) Onset: rapid

5)) Substantiation: probable

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

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

8)) Literature Reports

a)) Concomitant use of serotonin specific reuptake inhibitors and monoamine oxidase inhibitors can produce a toxic reaction known as [serotonin syndrome](#) [247]. [Serotonin syndrome](#) is a condition of serotonergic hyperstimulation and manifests as restlessness, myoclonus, changes in mental status, hyperreflexia, diaphoresis, shivering, and tremor [247]. If the syndrome is not recognized and correctly treated, death can result.

b)) It has been suggested that [fluoxetine](#) therapy be discontinued for at least five weeks before beginning therapy with a monoamine oxidase inhibitor. A 28-year old woman discontinued [fluoxetine](#) for six weeks before starting therapy with [tranlycypromine](#). Over the next few days the patient developed fever, paresthesias, confusion, abdominal cramping, and various other CNS symptoms. Upon discontinuation of [tranlycypromine](#), the patient's symptoms began to resolve.

Blood samples taken three days after discontinuation of [tranylcypromine](#) revealed no presence of [fluoxetine](#); however, the norfluoxetine level was 84 ng/mL (284 nanomol/L) [248].

c) Adverse reactions reported when [fluoxetine](#) was given concomitantly with [phenelzine](#) (n=9) or [tranylcypromine](#) (n=4) include tremor (50%), agitation or restlessness (42%), mental status changes (42%), myoclonus (33%), diarrhea (33%), and blood pressure changes (25%) [249]. All but one of the patients were taking other medications (ie, benzodiazepines, neuroleptics, anticonvulsants, antidepressants) that may have contributed to the adverse reactions.

d) Ten hours after her last dose of [fluoxetine](#), a 45-year-old woman began [tranylcypromine](#) therapy [250]. Headache, muscle contractions, insomnia, and unsteady gait were reported on the second day. [Thioridazine](#) and tryptophan were added to her therapy. The patient experienced fever, rigidity of the arms and legs, and hyperreflexia. She died in the intensive care unit of a hospital 44 hours later.

e) Two cases reports suggested a possible interaction between [fluoxetine](#) and [selegiline](#) [251]. One case involved a first episode of mania being observed approximately one month after adding [selegiline](#) to [fluoxetine](#) therapy. The patient improved two months after both drugs were discontinued, and no further details were provided. The second case involved diaphoresis, vasoconstriction, and cyanosis of the hands which occurred in close temporal relationship to adding [fluoxetine](#) and [selegiline](#). Both drugs were discontinued, with relatively quick resolution of symptoms. Rechallenge with [fluoxetine](#) alone occurred without incident.

3.5.1.OJ] [Tramadol](#)

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

2) Summary: Concurrent use of [olanzapine](#) with [mirtazapine](#) and [tramadol](#) in a 53-year-old male resulted in symptoms of [serotonin syndrome](#)[145]. If [olanzapine](#) is used concomitantly with [mirtazapine](#) and/or [tramadol](#), monitor closely for symptoms of [serotonin syndrome](#). [Serotonin syndrome](#) can be life-threatening. If [serotonin syndrome](#) develops, discontinue the offending agents and provide supportive care and other therapy as necessary [146].

3) Severity: major

4) Onset: delayed

5) Substantiation: probable

6) Clinical Management: A case of [serotonin syndrome](#) was reported with coadministration of [olanzapine](#), [mirtazapine](#), and [tramadol](#)[145]. If 2 or more of these drugs are used concomitantly, monitor closely for symptoms of [serotonin syndrome](#) such as neuromuscular abnormalities (including hyper-reflexia, tremor, muscle rigidity, clonus, peripheral hypertonicity, and shivering), autonomic hyperactivity (including [tachycardia](#), mydriasis, diaphoresis, the presence of bowel sounds, and diarrhea), and mental status changes (including agitation and [delirium](#)). [Serotonin syndrome](#) can be life-threatening. If [serotonin syndrome](#) develops, discontinue the offending agents and provide supportive care and other therapy as necessary [146].

7) Probable Mechanism: additive serotonergic pharmacologic effects

8) Literature Reports

a) A 53-year-old male on [mirtazapine](#) and [tramadol](#) experienced [serotonin syndrome](#) 8 days after [olanzapine](#) was added to his regimen. He was on [mirtazapine](#) 45 mg/day for depression and [tramadol](#) 150 mg/day for chronic back pain. [Olanzapine](#) 10 mg/day was added for a psychotic episode. He was admitted 8 days later after being found by the police wandering the streets in inappropriate dress and in a confused state. On admission he was afebrile, tachycardic (120 bpm), and had flushing, twitching of his face, tremors, myoclonus, hyperreflexia, and an ataxic gait. He

was disorientated and agitated. He spoke with a [stutter](#). He had marked derailment, appeared perplexed, had prominent perceptual abnormalities (color of objects) and auditory hallucinations. The creatine phosphokinase was normal. All medications were discontinued and within 12 hours he significantly improved [145].

3.5.1.OK] [Tramadol](#)

1) Interaction Effect: an increased risk of seizures, opioid toxicity, and [serotonin syndrome](#) (hypertension, hyperthermia, myoclonus, mental status changes), and increased concentrations of [tramadol](#) and decreased concentrations of [tramadol](#) active metabolite, M1

2) Summary: Concomitant use of [tramadol](#) (a CYP2D6 substrate) with CYP2D6 inhibitors (eg, [fluoxetine](#)) can inhibit metabolism of [tramadol](#) to the active metabolite M1, potentially causing reduced analgesia. Increased [tramadol](#) concentrations due to inhibition of CYP2D6-mediated metabolism may cause opioid toxicity. Additionally, concomitant use of [tramadol](#) and SSRIs or serotonin [norepinephrine](#) reuptake inhibitors (SNRIs), including [fluoxetine](#), may increase the risk for seizures and [serotonin syndrome](#) even if used within recommended dosage range[464]. If concomitant use of [tramadol](#) and [fluoxetine](#) is clinically warranted, careful observation of the patient is recommended, particularly during treatment initiation and dose increases. Discontinue treatment immediately if [serotonin syndrome](#) occurs [173].

3) Severity: major

4) Onset: rapid

5) Substantiation: probable

6) Clinical Management: Use caution with concomitant use of [fluoxetine](#) and [tramadol](#). Concomitant use of [tramadol](#) with SSRIs, serotonin [norepinephrine](#) reuptake inhibitors (SNRIs), or other agents that lower the seizure threshold or impair the metabolism of [tramadol](#) may increase the risk for seizures and [serotonin syndrome](#) (including use within recommended dosage range), opioid toxicity, and potentially reduces analgesia[464]. If concomitant use of [tramadol](#) with a serotonergic agent, including SSRIs or SNRIs, is clinically warranted, careful observation is recommended, particularly during initiation and dose increases. Discontinue treatment immediately if [serotonin syndrome](#) occurs [173].

7) Probable Mechanism: increased concentration of serotonin in the nervous system and periphery; inhibition of CYP2D6 metabolism of [tramadol](#) to M1 active metabolite by [fluoxetine](#)

8) Literature Reports

a) The combination of [tramadol](#) and [fluoxetine](#) may result in [serotonin syndrome](#) and mania. A 72-year-old woman with no [cognitive deficits](#) had been treated with [fluoxetine](#) for the past 10 years. She was prescribed [tramadol](#) 150 mg daily for articular pain. After 18 days of combination therapy, the patient began to feel nervous, had a temperature of 37.2 C, piloerection, and muscular contractions. She discontinued [tramadol](#) and 21 days later her physical symptoms disappeared. She was still agitated, euphoric, hyperactive, had rapid speech, [paranoid ideation](#), and slept less than 3 hours a day. She was hospitalized and [haloperidol](#) treatment was initiated, however, her symptoms continued. She was readmitted 1 week later and treatment with [olanzapine](#) was initiated. Two weeks later, she became euthymic and continued [olanzapine](#) therapy after being released from the hospital. The potential for inducing mania and [serotonergic syndrome](#) when using [tramadol](#) combined with SSRIs must be considered [465].

3.5.1.OL] [Tranylcypromine](#)

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

2) Summary: Concomitant use of [fluoxetine](#) and an MAOI is contraindicated. Concurrent administration or overlapping therapy with [fluoxetine](#) and an MAOI 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 SSRIs and MAOIs. A minimum of 14 days should elapse after discontinuing an MAOI intended to treat psychiatric disorders before initiating therapy with [fluoxetine](#), and a minimum of 5 weeks should elapse after discontinuing [fluoxetine](#) before initiating therapy with an MAOI intended to treat psychiatric disorders[283].

3) Severity: contraindicated

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Concurrent use of [fluoxetine](#) and an MAOI is contraindicated. Wait at least 14 days after discontinuing an MAOI intended to treat psychiatric disorders before initiating [fluoxetine](#). Wait at least 5 weeks after discontinuing [fluoxetine](#) before initiating therapy with an MAOI intended to treat psychiatric disorders[283].

7) Probable Mechanism: additive serotonergic effect

3.5.1.OM] [Trazodone](#)

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

2) Summary: Both [fluoxetine](#) and [trazodone](#) affect the serotonergic neurotransmitter systems. Concomitant use may increase the risk of [serotonin syndrome](#)[173][387]. There have been several reports of [serotonin syndrome](#) due to interactions between selective serotonin reuptake inhibitors and antidepressants [392][393][394]. Additionally, concomitant administration of [fluoxetine](#) and [trazodone](#) may result in additive effects on the QT interval and should be avoided [173]. Monitoring for [serotonin syndrome](#) is warranted [387] and periodic [ECG monitoring](#) should be considered [173].

3) Severity: major

4) Onset: unspecified

5) Substantiation: probable

6) Clinical Management: Concomitant administration of [fluoxetine](#) and [trazodone](#) may result in additive serotonergic effects and may increase the risk of [serotonin syndrome](#)[173][387]. Additionally, concomitant administration of [fluoxetine](#) and [trazodone](#) may result in additive effects on the QT interval and should be avoided [173]. If coadministration is required, appropriate monitoring is warranted (including periodic [ECG monitoring](#)), particularly during treatment initiation and dose increases [387][173].

7) Probable Mechanism: additive serotonergic effects; additive QT-interval prolongation effects

8) Literature Reports

a) Five cases of elevated antidepressant levels, four involving tricyclic antidepressants ([nortriptyline](#), [imipramine](#), [desipramine](#)) and one involving [trazodone](#), have been reported. After the addition of [fluoxetine](#), the ratio of antidepressant level to dose increased by 109% to 486% in the patients on tricyclics and by 31% in the patient on [trazodone](#). The trazodone-treated patient developed sedation and unstable gait [388].

b) A 44-year-old man developed symptoms characteristic of [serotonin syndrome](#) due to a possible interaction between [fluoxetine](#) and [trazodone](#). The patient had been taking [fluoxetine](#) 40 mg daily and [trazodone](#) 100 mg daily for approximately two months before symptoms occurred. The patient experienced disorientation, tremor, diaphoresis, and anxiety, followed by uncontrollable shaking and loss of consciousness. After the patient was treated with [cyproheptadine](#) 4 mg orally, symptoms resolved over the next 30 minutes. [Trazodone](#) was discontinued and the patient continued to take [fluoxetine](#) 40 mg daily without further complications [389].

c) A 43-year-old male with [traumatic brain injury](#) developed speech dysfunction during therapy with [fluoxetine](#) and [trazodone](#). The patient was being treated with [trazodone](#) 150 mg at bedtime for chronic pain as a result of a fall. After undergoing a comprehensive psychiatric evaluation as part of rehabilitation, [fluoxetine](#) 20 mg every morning was added to the patient's regimen for treatment of symptoms of depression. Within one week of starting therapy with [fluoxetine](#), the patient began to slur his speech and later exhibited a slow rate of speech, increased pause length, prolongation of initial phonemes, and word-finding difficulties. After discontinuation of [fluoxetine](#) and tapering of [trazodone](#) therapy, the patient had marked improvement in speech difficulty and returned to normal over the next week [390].

d) The pharmacokinetic effect of [trazodone](#) and [fluoxetine cotherapy](#) was studied in 27 inpatients with a [major depressive episode](#). All were treated with [trazodone](#) 100 mg daily, followed one week later with the addition of [fluoxetine](#) 20 mg daily, [pindolol](#) 7.5 mg daily, or placebo for four weeks. [Pindolol](#) and placebo had no significant effect on the plasma concentrations of [trazodone](#) or its active metabolite, meta-chlorophenylpiperazine (mCPP). However, when [fluoxetine](#) was combined with [trazodone](#), levels of mCPP increased from a mean baseline value of 11.3 ng/mL to 38.3 ng/mL (57.5 nanomol/L to 194.7 nanomol/L) in four weeks. This increase was also associated with an improvement in the clinical response to the antidepressants [391].

3.5.1.ON] [Treprostinil](#)

- 1) Interaction Effect: increased risk of bleeding
- 2) Summary: Exercise caution when coadministering a SSRI and an antiplatelet agent or anticoagulant as this may increase the risk of bleeding events[272][173][385].
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Use caution with concomitant use of [fluoxetine](#) with anticoagulants or antiplatelet agents, as coadministration may increase bleeding risk[272][173][385].
- 7) Probable Mechanism: altered anticoagulant effects
- 8) Literature Reports

a) In a retrospective study of patients over 50 years of age with the diagnosis of acute [myocardial infarction](#) (N=27,058), SSRI use with any antiplatelet therapy significantly increased the risk of bleeding by 1.42-fold compared with [aspirin](#) use alone. Therapy with [aspirin](#), [clopidogrel](#), and an SSRI significantly increased risk by 2.35-fold compared with [aspirin](#) use alone and by 1.57-fold compared with [clopidogrel](#) and [aspirin](#) combination therapy [385].

b) In a systematic review and meta-analysis of 22 observational studies, SSRI use was associated with a significant 1.55 fold increase in risk of [upper gastrointestinal bleeding](#) (UGIB). Concomitant use of SSRIs and antiplatelet drugs was associated with a 2.48-fold increase in risk of UGIB (3 studies) [272].

3.5.1.OO] [Trifluoperazine](#)

- 1) Interaction Effect: an increased risk of [cardiotoxicity](#) (QT prolongation, [torsades de pointes](#), [cardiac arrest](#))
- 2) Summary: Although citing no data, the manufacturers of some phenothiazines state that concomitant use with other drugs which prolong the QT interval is not recommended. Q and T wave distortions have been observed in patients taking phenothiazines[311][312][313] . Other phenothiazines may have similar

effects, though no reports are available. [Fluoxetine](#) has been shown to prolong the QTc interval at the recommended therapeutic dose [314].

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

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

7) Probable Mechanism: additive effects on QT prolongation

3.5.1.OP] [Trimethoprim](#)

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

2) Summary: Cotrimoxazole and [fluoxetine](#) have been shown to prolong the QTc interval at the recommended therapeutic dose[435][436]. Even though no formal drug interaction studies have been done, the coadministration of drugs known to prolong the QTc interval is not recommended.

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

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

7) Probable Mechanism: additive effects on QT prolongation

3.5.1.OQ] [Trimipramine](#)

1) Interaction Effect: increased risk of tricyclic antidepressant toxicity, QT prolongation and [serotonin syndrome](#)

2) Summary: [Fluoxetine](#), a potent CYP2D6 inhibitor, is associated with an increased risk of [serotonin syndrome](#), QT prolongation, and [ventricular arrhythmias](#) (including [torsade de pointes](#)). Concomitant therapy with CYP2D6-metabolized tricyclic antidepressants (TCAs) may potentiate these risks and introduce TCA toxicity[173]; concurrent use of [fluoxetine](#) and [desipramine](#), [nortriptyline](#), and [imipramine](#) has resulted in significant increases in TCA concentrations [517][523][524][525][526][527]. Use caution with concurrent administration of [fluoxetine](#) and TCAs. If [fluoxetine](#) is added to an existing TCA regimen, consider TCA dose reduction. If [fluoxetine](#) and a TCA are coadministered or [fluoxetine](#) has been recently discontinued, consider plasma TCA monitoring. If [serotonin syndrome](#) occurs, immediately discontinue [fluoxetine](#) and TCA. If [ventricular arrhythmias](#) develop, consider [fluoxetine](#) discontinuation and cardiac evaluation [173].

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Use caution with concurrent administration of [fluoxetine](#) and TCAs, as elevated TCA plasma concentrations may occur. If [fluoxetine](#) is added to an existing TCA regimen, consider TCA dose reduction. If [fluoxetine](#) and a TCA are coadministered or [fluoxetine](#) has been recently discontinued, consider plasma TCA monitoring. If [serotonin syndrome](#) occurs, immediately discontinue [fluoxetine](#) and TCA. If [ventricular arrhythmias](#) develop, consider [fluoxetine](#) discontinuation and cardiac evaluation[173]

7) Probable Mechanism: decreased CYP2D6-mediated metabolism of tricyclic antidepressants by [fluoxetine](#); additive effects on QT prolongation; additive serotonergic effects

8) Literature Reports

a) Previously stable plasma levels of [imipramine](#) and [desipramine](#) rose more than 2- to 10-fold with [fluoxetine](#) coadministration in 2 clinical studies. This effect may persist for 3 weeks or more after

fluoxetine discontinuation. Dose reduction and temporary monitoring of tricyclic antidepressant plasma concentrations may be indicated with concurrent **fluoxetine** treatment or recent **fluoxetine** discontinuation [173].

b)) Fluoxetine statistically and clinically significantly increased **desipramine** concentrations in 18 healthy subjects. When **fluoxetine** (20 mg daily) was added to **desipramine** (50 mg daily), the mean maximum concentration of **desipramine** increased by 278% and the AUC increased by 342%. **Desipramine** trough concentrations continued to be 198% above baseline 3 weeks after **fluoxetine** was discontinued. The same study compared pharmacokinetics of **desipramine** when combined with **sertraline**. The impact of **sertraline** was modest, resulting in small and short-term increases in **desipramine** plasma concentrations [517].

c)) Concomitant administration of fluoxetine and desipramine was reported to result in an increased **desipramine** level and new onset of **delirium** in a 69-year-old male within 10 days of the addition of **fluoxetine** to the patient's regimen [518].

d)) Fluoxetine increased the level of tricyclic antidepressants (**nortriptyline**, **imipramine**, **desipramine**) in 4 patients. After the addition of **fluoxetine**, the ratio of antidepressant level to dose increased by 109% to 486% in the patients. Three patients developed clinical symptoms (anticholinergic effects, constipation, urinary hesitancy, sedation, unstable gait) as a result of the increased levels [519].

e)) A 39-year-old female experienced symptomatic increases in her desipramine levels with concomitant fluoxetine therapy. Prior to **fluoxetine** therapy, the patient's measured levels of **desipramine** had ranged from 148 to 160 nanograms/milliliter (ng/mL; 556 to 601 nanomol/L) on a regimen of 300 mg daily. Five weeks after the addition of **fluoxetine** 20 mg daily, she reported anticholinergic symptoms, sedation, and confusion with a **desipramine** level of 527 ng/mL (1978 nanomol/L). The **desipramine** dose was lowered to 200 mg/day; 11 days later, the level was 244 ng/mL (916 nanomol/L); the patient reported decreased energy, impaired short-term memory, and some "garbled" speech, as well as an episode of nausea, dizziness, and syncope. The **desipramine** dose was reduced to 50 mg/day, and the adverse effects resolved in 6 days. Eight days later, the **desipramine** level was 122 ng/mL (458 nanomol/L) [520].

f)) A 33-year-old depressed male developed adverse effects of dry mouth, tinnitus, and difficulties with alertness and memory while receiving fluoxetine 40 mg daily and desipramine 150 mg daily for 5 weeks; fluoxetine was discontinued and the blood levels of desipramine decreased from 938 to 48 nanograms/mL (3521 to 180 nanomol/L) with resolution of clinical symptoms [521].

g)) A 75-year-old female experienced symptomatic increases in her desipramine serum concentrations when fluoxetine was added. Desipramine serum levels ranged from 109 to 150 ng/mL (409 to 563 nanomol/L) with oral doses of 300 mg at bedtime prior to fluoxetine therapy. Following the addition of oral fluoxetine 20 mg daily to the regimen, the desipramine serum level increased to 212 ng/mL (796 nanomol/L) within five days. The fluoxetine dose was increased to 40 mg/day three days later, and the desipramine serum level was 419 ng/mL (1573 nanomol/L) after four days. A worsening of depression and severe fatigue coincided with the increases in desipramine serum levels. Withdrawal of fluoxetine and reduction in the desipramine dose to 200 mg daily reduced the desipramine serum level to 231 ng/mL (867 nanomol/L) within two weeks [522].

3.5.1.OR] **Triptorelin**

- 1) Interaction Effect: increased risk of QT-interval prolongation
- 2) Summary: Use caution with coadministration of gonadotropin-releasing hormone (GnRH) agonists with QT-interval prolonging drugs. Androgen deprivation caused by GnRH agonists may prolong the QT interval and cause additive effects when administered with QT-interval prolonging drugs[141][142][143]. If concurrent therapy is necessary, monitor patients closely for signs and symptoms of [cardiac toxicity](#), including changes in the ECG.
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Use caution with coadministration of gonadotropin-releasing hormone (GnRH) agonists with QT-interval prolonging drugs, as additive effects on the QT interval may occur[141][142][143].
- 7) Probable Mechanism: additive effects on the QT interval

3.5.1.OS] Tryptophan

- 1) Interaction Effect: an increased risk of [serotonin syndrome](#) ([hypertension](#), [hyperthermia](#), myoclonus, mental status changes)
- 2) Summary: Potentially life-threatening [serotonin syndrome](#) has been reported with SSRIs when used concomitantly with other serotonergic drugs, such as hydroxytryptophan or tryptophan. If coadministration is clinically warranted, monitor for the development of [serotonin syndrome](#), especially during treatment initiation and dose increases[237].
- 3) Severity: major
- 4) Onset: rapid
- 5) Substantiation: theoretical
- 6) Clinical Management: Potentially life-threatening [serotonin syndrome](#) has been reported with SSRIs when used concomitantly with other serotonergic drugs, such as hydroxytryptophan or tryptophan. If coadministration is clinically warranted, monitor for the development of [serotonin syndrome](#), especially during treatment initiation and dose increases[237].
- 7) Probable Mechanism: additive serotonergic effect
- 8) Literature Reports

a) In a case series, the concurrent use of [fluoxetine](#) 50 to 100 mg daily and L-tryptophan 1 to 4 g daily resulted in all five patients experiencing central nervous system toxicity (agitation, poor concentration, nausea, diarrhea, paresthesias, palpitations, chills, headaches, aggressive behavior, and severe insomnia) within a few days. Tryptophan was discontinued and the symptoms disappeared [238].

3.5.1.OT] [Valdecocixib](#)

- 1) Interaction Effect: an increased risk of bleeding
- 2) Summary: Caution is recommended with the concomitant use of NSAIDs and antidepressants, including SSRIs due to an increased risk of [intracranial hemorrhage](#)[529] and [gastrointestinal bleeding](#) [533][534][530][531]. Bleeding events have included [epistaxis](#), ecchymosis, [hematoma](#), [petechiae](#), and life-threatening hemorrhages [536][535][537][538]. When an SSRI and an NSAID are given concurrently, monitor the patient for signs of increased bleeding.
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: established
- 6) Clinical Management: Use caution if NSAIDs and SSRIs are coadministered. Concomitant use of NSAIDs and SSRIs may cause an increased risk of [intracranial hemorrhage](#)[529] and [gastrointestinal](#)

bleeding [530][531]. When an SSRI and an NSAID are given concurrently, monitor the patient for signs of increased bleeding.

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

8) Literature Reports

a) Concomitant use of NSAIDs and antidepressants, including tricyclic antidepressants, SSRIs, serotonin-norepinephrine reuptake inhibitors, and MAOIs, resulted in a 60% increased risk of **intracranial hemorrhage** within 30 days of concomitant use compared with antidepressant use alone. There was no significant difference between the antidepressant drug classes and the increased risk; however, there was an increased risk associated with male patients compared with female patients [529].

b) SSRIs increase the risk of upper gastrointestinal (GI) bleeding, and this effect is potentiated by concurrent use of NSAIDs or low-dose **aspirin**. Hospitalizations for **upper GI bleeding** were searched among 26,005 users of antidepressant medications and compared with the number of hospitalizations in those patients who did not receive prescriptions for antidepressants. The amount of **upper GI bleeding** episodes was 3.6 times more than expected. Combined use of an SSRI and NSAIDs or low-dose **aspirin** increased the risk to 12.2 and 5.2 times, respectively. The findings of this study demonstrate an increased risk of **upper GI bleeding** during the use of SSRIs. Combined use of SSRIs and NSAIDs or low-dose **aspirin** increased the risk even further [532].

c) Two metaanalyses of incidents of upper GI bleed due to SSRIs, NSAIDs, and their combination found that SSRIs increased the risk by 1.73 [533] to 2.36 times [534], NSAIDs by 2.55 times [533], and the combination of SSRIs and NSAIDs by 4.02 [533] to 6.33 times [534].

d) The release of serotonin by **platelets** is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs and NSAIDs have been associated with an increased risk of bleeding [535].

3.5.1.OU] **Valproic Acid**

1) Interaction Effect: decreased **olanzapine** plasma concentrations

2) Summary: Concomitant use of **olanzapine** 5 to 20 mg/day and **valproate** up to 2000 mg/day for 4 weeks resulted in significantly decreased **olanzapine** plasma concentrations in subjects with **bipolar or schizoaffective disorder** (n=18). In this study, increased **valproate** concentrations and smoking were associated with lower **olanzapine** concentrations. Older age was associated with higher **olanzapine** concentrations. Concurrent use with **valproate** was well-tolerated, with mild adverse effects that resolved over time. Induction, competitive inhibition, and protein binding displacement are all postulated mechanisms for this interaction. Because of the decreased **olanzapine** concentrations with concomitant use, monitoring **olanzapine** levels may be necessary[109].

3) Severity: moderate

4) Onset: delayed

5) Substantiation: established

6) Clinical Management: Concomitant use of **olanzapine** and **valproate** has resulted in decreased **olanzapine** plasma concentrations. Therefore, monitoring **olanzapine** concentrations may be warranted[109].

7) Probable Mechanism: unknown

8) Literature Reports

a) Concomitant use of **olanzapine** and **valproate** resulted in decreased **olanzapine** plasma concentrations in subjects with **bipolar or schizoaffective disorder** (n=18). A consistent **olanzapine**

dose of 5 to 20 mg/day was given for 1 month prior to [valproate](#) initiation. [Valproate](#) was adjusted based on clinical response and maintained at a stable dose of 600 to 2000 mg/day. After 2 and 4 weeks of coadministration, a mean baseline [olanzapine](#) concentration of 32.9 +/- 9.7 nanogram/mL (ng/mL; 105.3 +/- 31 nanomol/L) had decreased to 27.4 +/- 9.8 ng/mL (87.7 +/- 31 nanomol/L) and 26.9 +/- 9.2 ng/mL (86.1 +/- 29.4 nanomol/L). In an analysis adjusted for age, smoking, [valproate](#) treatment duration, and individual variances, an increase in [valproate](#) concentrations was associated with a decrease in [olanzapine](#) concentrations that was dependent on the number of treatment weeks. With a 1 mcg/mL (7 mcmol/L) [valproate](#) concentration increase at 2 and 4 weeks, [olanzapine](#) concentrations decreased 0.37 ng/mL (1.18 nanomol/L) and 0.21 ng/mL (0.67 nanomol/L). [Olanzapine](#) concentrations were 5.9 ng/mL (18.9 nanomol/L) lower in smokers compared with nonsmokers. Age progression was associated with higher [olanzapine](#) concentrations. Sex did not affect [olanzapine](#) concentrations. Concurrent use of [olanzapine](#) and [valproate](#) was well-tolerated with only mild adverse effects [109].

3.5.1.OV] Vandetanib

- 1) Interaction Effect: increased risk of QT-interval prolongation
- 2) Summary: Vandetanib is associated with QT-interval prolongation. [Torsades de pointes](#), [ventricular tachycardia](#), and sudden death have also been reported in patients taking vandetanib. Therefore, avoid concurrent use of other QT-interval-prolonging agents as this may increase the risk of additive QT-interval prolongation and [torsade de pointes](#). If coadministration is required, monitor ECG more frequently than during vandetanib monotherapy[121].
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Concurrent use of vandetanib with another drug known to prolong QT interval should be avoided due to increased risk of additive QT-interval prolongation and [ventricular arrhythmias](#). Monitor ECG frequently if coadministration is required[121].
- 7) Probable Mechanism: additive effects on QT interval

3.5.1.OW] Vasopressin

- 1) Interaction Effect: an increased risk of [cardiotoxicity](#) (QT prolongation, [torsades de pointes](#), [cardiac arrest](#))
- 2) Summary: [Fluoxetine](#) and [vasopressin](#) have been shown to prolong the QTc interval at the recommended therapeutic dose[296][297]. Even though no formal drug interaction studies have been done, the coadministration of drugs known to prolong the QTc interval is not recommended.
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: The concurrent administration of [fluoxetine](#) and [vasopressin](#) is not recommended.
- 7) Probable Mechanism: additive effects on QT prolongation

3.5.1.OX] Vemurafenib

- 1) Interaction Effect: increased risk of QT-interval prolongation
- 2) Summary: Do not start vemurafenib treatment in patients who are receiving another drug known to prolong the QT interval. Vemurafenib is known to increase the QT interval, which may lead to an increased risk of serious cardiac adverse events, including [torsade de pointes](#). Coadministration of vemurafenib with

another drug that prolongs the QT interval may result in additive effects on the QT interval and further increase the risk of [torsade de pointes](#)[49].

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Do not start vemurafenib treatment in patients who are receiving another drug known to prolong the QT interval, as concurrent use of such agents may lead to an increased risk of serious cardiac adverse events, including [torsade de pointes](#)[49].

7) Probable Mechanism: additive effects on QT interval

3.5.1.OY| [Venlafaxine](#)

1) Interaction Effect: increased [venlafaxine](#) exposure; increased risk of [serotonin syndrome](#) ([hypertension](#), [hyperthermia](#), myoclonus, mental status changes); increased risk of QT-interval prolongation

2) Summary: The concomitant use of [fluoxetine](#), a CYP2D6 inhibitor, with [venlafaxine](#), a CYP2D6 substrate, may increase [venlafaxine](#) exposure and increase the risk of adverse effects. Coadministration of [fluoxetine](#) and [venlafaxine](#) may also result in additive serotonergic effects and increase the risk of [serotonin syndrome](#)[173][456]. Additionally, concomitant administration of [fluoxetine](#) and [ritonavir](#) may result in additive effects on the QT interval and should be avoided. If concomitant use is required, consider periodic [ECG monitoring](#) [173]. Discontinue [fluoxetine](#) and [venlafaxine](#) if [serotonin syndrome](#) occurs [173][456].

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Concurrent use of [fluoxetine](#), a CYP2D6 inhibitor, and [venlafaxine](#), a CYP2D6 substrate, may increase [venlafaxine](#) exposure and increase the risk of adverse effects. Coadministration of [fluoxetine](#) and [venlafaxine](#) may also result in additive serotonergic effects and increase the risk of [serotonin syndrome](#)[173][456]. Additionally, concomitant administration of [fluoxetine](#) and [ritonavir](#) may result in additive effects on the QT interval and should be avoided. If concomitant use is required, consider periodic [ECG monitoring](#) [173]. Discontinue [fluoxetine](#) and [venlafaxine](#) if [serotonin syndrome](#) occurs [173][456].

7) Probable Mechanism: inhibition of CYP2D6-mediated metabolism of [venlafaxine](#) by [fluoxetine](#); additive serotonergic effect; additive QT-interval prolongation effects

3.5.1.OZ| [Vilazodone](#)

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

2) Summary: [Serotonin syndrome](#) has been reported with vilazodone monotherapy and in combination with other serotonergic drugs; coadministration with another serotonergic drug may increase risk for [serotonin syndrome](#)[239]. 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 [146]. 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 [239].

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[239].

7) Probable Mechanism: additive serotonergic effects

3.5.1.PA] Vinflunine

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

2) Summary: Vinflunine is associated with QT-interval prolongation. Concomitant administration of vinflunine with other drugs that prolong the QT interval may have additive prolonging effects on the QT interval and is not recommended[92]. If concomitant use is required, consider a baseline ECG and on-treatment monitoring when vinflunine is coadministered with other QT-prolonging agents.

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Concomitant administration of vinflunine and QT-prolonging drugs may result in additive QT-interval prolongation effects and is therefore not recommended[92]. If concomitant use is required, consider a baseline ECG and on-treatment monitoring.

7) Probable Mechanism: additive QT interval effects

3.5.1.PB] Vorapaxar

1) Interaction Effect: increased risk of bleeding

2) Summary: Exercise caution when coadministering a SSRI and an antiplatelet agent or anticoagulant as this may increase the risk of bleeding events[272][173][385].

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Use caution with concomitant use of [fluoxetine](#) with anticoagulants or antiplatelet agents, as coadministration may increase bleeding risk[272][173][385].

7) Probable Mechanism: altered anticoagulant effects

8) Literature Reports

a) In a retrospective study of patients over 50 years of age with the diagnosis of acute [myocardial infarction](#) (N=27,058), SSRI use with any antiplatelet therapy significantly increased the risk of bleeding by 1.42-fold compared with [aspirin](#) use alone. Therapy with [aspirin](#), [clopidogrel](#), and an SSRI significantly increased risk by 2.35-fold compared with [aspirin](#) use alone and by 1.57-fold compared with [clopidogrel](#) and [aspirin](#) combination therapy [385].

b) In a systematic review and meta-analysis of 22 observational studies, SSRI use was associated with a significant 1.55 fold increase in risk of [upper gastrointestinal bleeding](#) (UGIB). Concomitant use of SSRIs and antiplatelet drugs was associated with a 2.48-fold increase in risk of UGIB (3 studies) [272].

3.5.1.PC] Vortioxetine

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

2) Summary: The concomitant use of [fluoxetine](#) (a strong CYP2D6 inhibitor) with vortioxetine (a CYP2D6 substrate) may increase the exposure of vortioxetine and lead to an increase in adverse events. Additionally, coadministration of vortioxetine, a serotonergic antidepressant, with another serotonergic drug, such as [fluoxetine](#), may result in additive serotonergic effects and increase the risk of [serotonin syndrome](#). Reduce the vortioxetine dose to one-half of the original dose when used concomitantly with [fluoxetine](#) and closely monitor the patient for symptoms of [serotonin syndrome](#), particularly during treatment initiation and dosage increases. If coadministration with [fluoxetine](#) is discontinued, increase the vortioxetine dose back to its original strength[328].

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: The concomitant use of [fluoxetine](#), a strong CYP2D6 inhibitor, with vortioxetine, a CYP2D6 substrate, may increase the exposure of vortioxetine and lead to an increase in adverse events. Additionally, coadministration of vortioxetine, a serotonergic antidepressant, with another serotonergic drug, such as [fluoxetine](#), may result in additive serotonergic effects and increase the risk of [serotonin syndrome](#). Reduce the vortioxetine dose to one-half of the original dose when used concomitantly with [fluoxetine](#) and closely monitor the patient for symptoms of [serotonin syndrome](#), particularly during treatment initiation and dosage increases. If coadministration with [fluoxetine](#) is discontinued, increase the vortioxetine dose back to its original strength[328].

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

3.5.1.PD] [Warfarin](#)

1) Interaction Effect: an increased risk of bleeding

2) Summary: Concomitant use of [fluoxetine](#) and [warfarin](#) may result in an increased INR[578]. Case-control and cohort studies have shown that the combined use of SSRIs, including [fluoxetine](#), and anticoagulants, including [warfarin](#), has been associated with an increased risk of bleeding [579][580]. Due to this additive effect, closely monitor patients taking [warfarin](#) for altered anticoagulant effects, including increased INR and bleeding, when [fluoxetine](#) therapy is initiated or discontinued [579][578].

3) Severity: major

4) Onset: delayed

5) Substantiation: probable

6) Clinical Management: Concomitant use of [fluoxetine](#) and [warfarin](#) may result in an increased INR[578]. Coadministration may also result in increased risk of bleeding, as each drug by itself is associated with bleeding. Due to this additive effect, closely monitor patients taking [warfarin](#) for altered anticoagulant effects, including increased INR and bleeding, when [fluoxetine](#) therapy is initiated or discontinued [579][578].

7) Probable Mechanism: additive effects

8) Literature Reports

a) According to a retrospective cohort study (n=234), there was an increased risk of clinically relevant bleeding (hospital admission due to bleeding) in patients receiving [warfarin](#) for [atrial fibrillation](#) during concomitant SSRI therapy or within 2 weeks following SSRI therapy termination. Patients with a mean age of 72 +/- 7 years receiving [warfarin](#) plus SSRI (n=117) were matched with randomly selected patients who received [warfarin](#) only (n=117). SSRI included [fluoxetine](#), [citalopram](#), [paroxetine](#), [sertraline](#), [fluvoxamine](#), or [escitalopram](#). Nine patients experienced 11 bleeding episodes during 213.9 treatment years in the [warfarin](#) plus SSRI group, and 10 patients experienced 14 bleedings during 586.4 treatment years in the warfarin-only group. The corresponding total incidences of bleedings were 51.4 and 23.9 per 1000 treatment

years, respectively. The risk for first bleedings during treatment with [warfarin](#) plus SSRI was increased significantly by 3.5 times compared with [warfarin](#) only. The SSRI implicated in patients experiencing bleeding at the time of concomitant administration were [sertraline](#) or [citalopram](#). The addition of an SSRI was not associated with a change in [warfarin](#) dose or INR. The results of the study may be limited by earlier bleeding events, unknown patient adherence, and exclusion of [clopidogrel](#), [dipyridamole](#), corticosteroids and anticoagulants other than [warfarin](#) in the model [580].

b)) In 6 reported cases, INR increased during combined [fluoxetine](#) and [warfarin](#) therapy. In a seventh case, severe bruising of the lower legs occurred in a woman initially treated with [fluoxetine](#) and, secondarily, started on [warfarin](#) [581][582].

c)) An 83-year-old man died from [cerebral hemorrhage](#) secondary to increased [warfarin](#) concentrations. The patient had been taking [warfarin](#) 30 mg per week for [atrial fibrillation](#) with a target INR between 2 and 3. The patient's other drugs included [lisinopril](#), [furosemide](#), potassium, [digoxin](#), and [acetaminophen](#). After being seen for symptoms of depression, anxiety, and insomnia, the patient was given [fluoxetine](#) 20 mg per day and [diazepam](#) 2.5 mg 3 to 4 times per day. Eight days later, the patient's INR increased to 4.8, and the dose of [warfarin](#) was decreased to 27.5 mg per week. The patient was later seen for symptoms of drug [delirium](#), including confusion, incoherence, and speaking irrationally. At this point, the INR was 3.64 and [fluoxetine](#) was discontinued. The next day the patient presented to the hospital with left-sided weakness and later died from complications of a large interparenchymal hemorrhage. The authors proposed that the addition of [fluoxetine](#) to the patient's regimen resulted in increased serum levels of both [warfarin](#) and [diazepam](#), resulting in [delirium](#) and loss of anticoagulant control [583].

3.5.1.PE] [Ziprasidone](#)

- 1)) Interaction Effect: increased risk of QT-interval prolongation
- 2)) Summary: The concomitant use of [ziprasidone](#) with drugs that cause QT-interval prolongation is contraindicated, as coadministration may increase the risk of QT prolongation and serious [ventricular arrhythmias](#)[63][64].
- 3)) Severity: contraindicated
- 4)) Onset: unspecified
- 5)) Substantiation: theoretical
- 6)) Clinical Management: The concomitant use of [ziprasidone](#) with drugs that cause QT-interval prolongation is contraindicated, as coadministration may increase the risk of QT prolongation and serious [ventricular arrhythmias](#)[63][64].
- 7)) Probable Mechanism: additive QT interval effects

3.5.1.PF] [Ziprasidone](#)

- 1)) Interaction Effect: increased risk of QT-interval prolongation and increased risk of [serotonin syndrome](#) ([hypertension](#), [hyperthermia](#), [myoclonus](#), [mental status changes](#))
- 2)) Summary: The concomitant use of [ziprasidone](#) with other drugs that prolong the QT interval is contraindicated because coadministration may result in additive risk for QT-interval prolongation. [Serotonin syndrome](#) has also been reported with [ziprasidone](#) monotherapy and in combination with other serotonergic drugs[64][63]; coadministration with another serotonergic drug may increase the risk for [serotonin syndrome](#).
- 3)) Severity: contraindicated
- 4)) Onset: unspecified
- 5)) Substantiation: theoretical

6J) Clinical Management: The concomitant use of [ziprasidone](#) with other drugs that prolong the QT interval is contraindicated because coadministration may result in additive risk for QT-interval prolongation. [Serotonin syndrome](#) has also been reported with [ziprasidone](#) monotherapy and in combination with other serotonergic drugs[64][63]; coadministration with another serotonergic drug may increase the risk for [serotonin syndrome](#).

7J) Probable Mechanism: additive QT interval effects; additive serotonergic effect

3.5.1.PG| [Zolmitriptan](#)

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

2J) Summary: [Serotonin syndrome](#) may the result from concomitant use of [fluoxetine](#) and serotonergic agents, such as a triptans or other antidepressants. Monitor patients for symptoms of [serotonin syndrome](#), including neuromuscular abnormalities, autonomic instability, and mental status changes, especially during treatment initiation and dose increases. [Serotonin syndrome](#) can be life-threatening. If [serotonin syndrome](#) develops, discontinue [fluoxetine](#) and any concomitant serotonergic agent and initiate supportive care[173].

3J) Severity: major

4J) Onset: unspecified

5J) Substantiation: theoretical

6J) Clinical Management: Exercise caution with coadministration of [fluoxetine](#) and serotonergic agents, such as a triptans or other antidepressants, because it may result in a life-threatening condition called [serotonin syndrome](#). If these agents are used together, discuss the risks of [serotonin syndrome](#) with the patient and monitor closely for symptoms of [serotonin syndrome](#) (mental status changes, autonomic instability, neuromuscular symptoms, seizures, and gastrointestinal symptoms), especially during treatment initiation and dose increases. If [serotonin syndrome](#) develops, discontinue [fluoxetine](#) and any concomitant serotonergic agent and initiate supportive care[173]

7J) Probable Mechanism: additive serotonergic effect

3.5.1.PH| [Zolpidem](#)

1J) Interaction Effect: an increased risk of hallucinations

2J) Summary: Short-term combined therapy with [fluoxetine](#) and [zolpidem](#) was determined to be safe by a study involving 29 healthy women. After a single dose of [zolpidem](#) followed by one washout day, the subjects were given a daily dose of [fluoxetine](#) on days three through 27, then [zolpidem](#) was added each evening on days 28 through 32. There were no significant changes in either [fluoxetine](#) or [zolpidem](#) plasma concentrations, and both medications were tolerated well, either individually or combined[351]. However, the publication of five case reports from the Washington Poison Center elucidates potential interactions between [zolpidem](#) and various antidepressant medications. Five patients reported hallucinations after concurrent use of [zolpidem](#) and antidepressant medication. The hallucination episodes all lasted longer than one hour, but resolved without further [sequelae](#) [352].

3J) Severity: moderate

4J) Onset: delayed

5J) Substantiation: theoretical

6J) Clinical Management: Observe patients for hallucinatory activity. Alternative anti-insomnia medication may be warranted.

7J) Probable Mechanism: unknown

8J) Literature Reports

aJ) A study conducted by Lorex Pharmaceuticals and Boston Research and Science Consulting demonstrates the safety of concomitant short-term therapy with [fluoxetine](#) and [zolpidem](#). In this study, 29 healthy female volunteers were given a single evening dose of [zolpidem](#) 10 mg,

followed by one washout day. This was followed by a daily morning dose of [fluoxetine](#) 20 mg on days 3 through 27. On days 28 through 32, a daily evening dose of [zolpidem](#) was added. Steady state plasma concentrations of [fluoxetine](#) and norfluoxetine were reached on day 24 of [fluoxetine](#) dosing as determined by serial venous blood sampling. There were no significant differences in area under concentration curve (AUC), peak concentration (C_{max}), or time to reach peak concentration (T_{max}) after one or five consecutive doses of [zolpidem](#) in conjunction with [fluoxetine](#) administration. The following pharmacokinetic mean parameters were observed for [zolpidem](#): AUC 917.04 ng/hr/mL on day 28, 978.77 ng/hr/mL on day 32, C_{max} 167.94 ng/mL (546.3 nanomol/L) on day 28, 175.91 ng/mL (572.26 nanomol/L) on day 32, T_{max} 1.67 hr on day 28, 1.54 hr on day 32. For [fluoxetine](#) the following were noted: AUC 2674.53 ng/hr/mL on day 27, 2879.63 ng/hr/mL on day 32, C_{max} 133.48 ng/mL (431.51 nanomol/L) on day 27, 142.23 ng/mL (459.79 nanomol/L) on day 32, T_{max} 8.28 hr on day 27, 9.04 hr on day 32. The only statistically significant difference was a higher half-life value for [zolpidem](#) on day 32, the fifth consecutive dose of [zolpidem](#) in the presence of [fluoxetine](#) [349].

b) The Washington Poison Center reports that they received five different calls from patients experiencing hallucinations after concurrent use of [zolpidem](#) and antidepressant medication. Four of the five reports came from patients taking serotonin reuptake inhibitors in addition to [zolpidem](#). The antidepressant medications being taken were [desipramine](#), [fluoxetine](#), [sertraline](#), [venlafaxine](#), and [bupropion](#). In each case, the hallucinatory activity lasted longer than one hour, but the patients' symptoms resolved without further [sequelae](#). The authors concluded that the mechanism by which [zolpidem](#) might cause hallucinations has not been firmly established [350].

3.5.1.PI] Zotepine

- 1) Interaction Effect: an increased risk of [cardiotoxicity](#) (QT prolongation, [torsade de pointes](#), [cardiac arrest](#))
- 2) Summary: [Fluoxetine](#) has been shown to prolong the QTc interval at the recommended therapeutic dose[304]. Even though no formal drug interaction studies have been done, the coadministration of antipsychotics and other drugs known to prolong the QTc interval, including [fluoxetine](#), is not recommended. Several antipsychotic agents have demonstrated QT prolongation including sertindole [305], sultopride [306], and zotepine [307].
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: The concurrent administration of [fluoxetine](#) and antipsychotics is not recommended.
- 7) Probable Mechanism: additive effects on QT prolongation

3.5.1.PJ] Zuclopenthixol

- 1) Interaction Effect: increased risk of QT prolongation
- 2) Summary: Avoid the concomitant use of zuclopenthixol and other drugs known to significantly increase the QT interval. Additionally, drugs known to cause electrolyte disturbances (eg, hypokalemia) or drugs known to increase the plasma concentration of zuclopenthixol should be used cautiously. Cases of QT prolongation, [ventricular arrhythmias](#) and fibrillation, [ventricular tachycardia](#), [torsade de pointes](#), and sudden death have been reported with zuclopenthixol[90][91].
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical

6) Clinical Management: Avoid the concomitant use of zuclopenthixol and other drugs known to significantly increase the QT interval. Additionally, drugs known to cause electrolyte disturbances (eg, hypokalemia) or drugs known to increase the plasma concentration of zuclopenthixol should be used cautiously. Cases of QT prolongation, [ventricular arrhythmias](#) and fibrillation, [ventricular tachycardia](#), [torsade de pointes](#), and sudden death have been reported with zuclopenthixol[90][91].

7) Probable Mechanism: additive QT prolongation

3.5.2] Drug-Food Combinations

3.5.2.A] Ethanol

1) Interaction Effect: excessive central nervous system depression

2) Summary: Coadministration of [olanzapine](#) and ethanol will potentiate the orthostatic hypotension observed with [olanzapine](#) alone. Although a single dose of ethanol (45 mg/70 kg) had no effect on [olanzapine](#) pharmacokinetics, these drugs should not be taken concomitantly due to the central nervous system depressive effects of both drugs[587].

3) Severity: moderate

4) Onset: rapid

5) Substantiation: theoretical

6) Clinical Management: Concurrent use of [olanzapine](#) and ethanol should be avoided if at all possible. If these two are taken in combination, extreme caution should be used.

7) Probable Mechanism: additive central nervous system depression

3.5.4] Drug-Tobacco Combinations

3.5.4.A] Tobacco

1) Interaction Effect: decreased exposure of CYP1A2 substrates

2) Summary: Cigarette smoking releases polycyclic aromatic hydrocarbons that induce CYP1A2 substrate metabolism[589][599], which may reduce CYP1A2 substrate bioavailability. Advise patients to stop smoking during treatment with a CYP1A2 substrate due to the potential reduction in efficacy [588]. If CYP1A2 substrate therapy is required in patients who smoke, consider monitoring for reduced efficacy [589] and adjusting the CYP1A2 substrate dosage if needed [590].

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: CYP1A2 substrate bioavailability may be reduced with tobacco smoking. Advise patients to stop smoking during treatment due to the potential reduction in CYP1A2 substrate efficacy[588]. If therapy with a CYP1A2 substrate is required in patients who smoke, consider monitoring for reduced efficacy [589] and adjusting the CYP1A2 substrate dosage if needed [590].

7) Probable Mechanism: induction of CYP1A2-mediated metabolism by tobacco smoke

8) Literature Reports

a) Smoking 7 to 12 cigarettes/day produced maximum enzyme induction and a significantly lower mean [clozapine](#) concentration/dose (C/D) ratio in smokers than in nonsmokers (2.8 vs 6 nanograms/mL/mg/day), and similarly with [olanzapine](#) C/D ratio in another study (6.1 vs 12.8 nanograms/mL/mg/day). Smoking more than 12 cigarettes/day did not produce any further induction nor lower C/D ratio of [clozapine](#) or [olanzapine](#) [591].

b) Among patients treated with [mirtazapine](#) 30 mg/day for 4 weeks, smokers had significantly lower concentrations of S(+)-[mirtazapine](#) (23 vs 39 nmol/L) and [mirtazapine](#) S(+)/R(-) ratio (0.28

vs 0.37) than nonsmokers. These effects from smoking remained significant after multivariate analysis [590].

c) In patients receiving stable [clozapine](#) 100 mg/day, heavy smokers (30 or more cigarettes/day) had a significantly higher mean plasma [clozapine](#) concentration coefficient of variation (CV) than smokers (30% vs 16%); however, no difference was seen in patients receiving stable [clozapine](#) 300 or 600 mg/day in a study of patients with [schizophrenia](#) or [schizoaffective disorder](#) (N=47) [592].

d) In a study of patients receiving an average [clozapine](#) dose of 304 mg/day (N=18), [clozapine](#) and norclozapine (active metabolite) plasma concentrations were significantly lower in smokers (median of 25 cigarettes or 4 pipes/day) compared with nonsmokers. The [clozapine](#) plasma concentration in smokers was a significant 3.2-fold lower and norclozapine was 2.3-fold lower compared with plasma concentration in nonsmokers [593].

e) Induction of CYP1A2 activity by cigarette smoking significantly reduced [olanzapine](#) plasma concentrations and clinical effectiveness in smokers (10 to 40 cigarettes/day), compared with nonsmokers in a study of adults with thought disorder (N=17). After 15 days of [olanzapine](#) 10 mg/day, the dose-corrected steady-state [olanzapine](#) plasma concentration (C:D) ratio was about 5-fold lower in smokers compared with nonsmokers (1.56 vs 7.9 nanograms/mL/mg). At the same time, Brief Psychiatric Rating Scale total scores were significantly higher for nonsmokers than for smokers (30.4% vs 12.5%) and were positively correlated with the steady-state plasma [olanzapine](#) C:D ratio. Smoking induced a significant 6-fold higher level of CYP1A2 activity in smokers compared with nonsmokers and the index was closely correlated with the steady-state plasma [olanzapine](#) C:D ratio[594].

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 [589].

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. [595]. However, in another study of volunteers (N=5), intense, short-term (5 days) passive smoking did not effect [theophylline](#) disposition [596]. 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 [597].

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) [598].

4.0] Clinical Applications

[Monitoring Parameters](#)

[Patient Instructions](#)

[Place In Therapy](#)

Mechanism of Action / Pharmacology

Therapeutic Uses

Comparative Efficacy / Evaluation With Other Therapies

4.1] Monitoring Parameters

A]) Therapeutic

1]) Physical Findings

a]) Improvement in signs and symptoms of [depressive episodes](#) associated with bipolar 1 disorder or treatment-resistant depression are indicative of efficacy.

b]) Reassess the need for continued pharmacotherapy periodically, especially if treatment continues beyond 8 weeks [2].

B]) Toxic

1]) Laboratory Parameters

a]) Measure fasting plasma glucose at baseline and periodically during treatment [2]

b]) Measure lipid profile at baseline and periodically during treatment [2].

c]) In patients with a history of a clinically significant low WBC or drug-induced [leukopenia/neutropenia](#), monitor CBC frequently during the first few months of therapy [2], with differential.

2]) Physical Findings

a]) Based on available data on the use of atypical antipsychotics, the American Diabetes Association, the American Psychiatric Association, the American Association of Clinical Endocrinologists, and the North American Association for the Study of Obesity developed a consensus position statement that recommends baseline and periodic [monitoring for obesity and diabetes](#), as listed below [608]:

1]) Obtain personal and family history of obesity, diabetes, dyslipidemia, hypertension, and cardiovascular disease prior to treatment and review annually with patient [608].

2]) Track weight [2] and BMI at baseline, at week 4, at week 8, at week 12, following initiation or change in therapy, and quarterly thereafter [608][2].

3]) Measure waist circumference at baseline and annually thereafter [608].

4]) Measure blood pressure at baseline, at week 12, then annually thereafter, or more frequently in patients with a higher baseline risk for the development of hypertension [608].

b]) Examine patient for [tardive dyskinesia](#) before initiation and then annually. Patients at higher risk for [tardive dyskinesia](#) (ie, elderly, patients who have experienced acute dystonic reactions, [akathisia](#), or other clinically significant extrapyramidal side effects) should be examined every 6 months throughout the duration of treatment [609].

- c) Monitor closely for clinical worsening of depression, suicidality, or unusual changes in behavior, particularly during the initial few months of therapy or at times of dose changes, either increases or decreases [2]. Such monitoring should include at least weekly face-to-face contact with patients or their family members or caregivers during the initial 4 weeks of treatment, then visits every other week for the next 4 weeks, then at 12 weeks, and then as clinically indicated beyond 12 weeks [610].
- d) Monitor patients with a history of [neuroleptic malignant syndrome](#) (NMS) carefully for the recurrence of NMS [2].
- e) Monitor for signs and symptoms of [serotonin syndrome](#) [2].
- f) Screen patients with depressive symptoms for [bipolar disorder](#) risk factors before treatment initiation, including intake of personal and family history of suicide, [bipolar disorder](#), and depression [2].
- g) Observe patients closely for symptoms of mania or [hypomania](#) during treatment [2].
- h) Consider performing ECG at baseline and periodically during treatment in patients with risk factors for QT prolongation and [ventricular arrhythmia](#) [2].

4.2] Patient Instructions

A) [Olanzapine/Fluoxetine](#) (By mouth)

[Fluoxetine](#) Hydrochloride/[Olanzapine](#)

Treats depression. This medicine contains an SSRI.

When This Medicine Should Not Be Used:

This medicine is not right for everyone. Do not use it if you have had an [allergic reaction](#) to [olanzapine](#) or [fluoxetine](#).

How to Use This Medicine:

Capsule

Take your medicine as directed. Your dose may need to be changed several times to find what works best for you. It is best to take this medicine in the evening.

This medicine should come with a Medication Guide. Ask your pharmacist for a copy if you do not have one.

Missed dose: Take a dose as soon as you remember. If it is almost time for your next dose, wait until then and take a regular dose. Do not take extra medicine to make up for a missed dose.

Store the medicine in a closed container at room temperature, away from heat, moisture, and direct light.

Drugs and Foods to Avoid:

Ask your doctor or pharmacist before using any other medicine, including over-the-counter medicines, vitamins, and herbal products.

Do not use this medicine together with [pimozide](#) or [thioridazine](#). Do not use this medicine within 14 days of using an MAO inhibitor (MAOI), and do not start an MAOI for at least 5 weeks after you stop using [fluoxetine](#).

Some foods and medicines can affect how [olanzapine/fluoxetine](#) works. Tell your doctor if you are also using any of the following:

[Buspirone](#), [digitoxin](#), [dolasetron](#), [fentanyl](#), [levodopa](#), [lithium](#), [mefloquine](#), [methadone](#), [pentamidine](#), [probutol](#), St John's wort, [tacrolimus](#), [tramadol](#), tryptophan, or [vinblastine](#)

Other medicine to treat depression (such as [fluvoxamine](#)), medicine to treat mental illness, triptan medicine to treat migraine headaches, medicine for seizures (such as [carbamazepine](#), [phenytoin](#)), blood pressure medicine, medicine for heart rhythm problems, an antibiotic, a diuretic (water pill),

an NSAID pain or [arthritis](#) medicine (such as [aspirin](#), [celecoxib](#), [diclofenac](#), [ibuprofen](#), [naproxen](#)), or a blood thinner (such as [warfarin](#))

Do not drink alcohol while you are using this medicine.

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 if you have liver disease, bleeding problems, [diabetes](#), high cholesterol, [glaucoma](#), prostate problems, or a history of [breast cancer](#), mania, seizures, or severe constipation. Make sure your doctor knows if you have had a heart rhythm problem (such as QT prolongation), or if you have had a [heart attack](#), [heart failure](#), low blood pressure, or a [stroke](#).

Do not breastfeed while you are using this medicine.

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:

[Neuroleptic malignant syndrome](#) (a nerve and muscle problem)

High blood sugar, cholesterol, or [triglyceride](#) levels

[Serotonin syndrome](#) (may be life-threatening when used with certain other medicines)

[Tardive dyskinesia](#) (a muscle problem that may become permanent)

Higher risk of bleeding

Low sodium levels in the blood

Heart rhythm changes

This medicine may make you dizzy or drowsy. Do not drive or do anything else that could be dangerous until you know how this medicine affects you.

This medicine may make it more difficult for your body to cool down. Be careful to not become overheated during exercise or hot weather, because you could have [heat stroke](#).

Do not stop using this medicine suddenly. Your doctor will need to slowly decrease your dose before you stop it completely.

Your doctor will do lab tests at regular visits to check on the effects of this medicine. Keep all appointments.

Keep all medicine out of the reach of children. Never share your medicine with anyone.

Possible Side Effects While Using This Medicine:

Call your doctor right away if you notice any of these side effects:

[Allergic reaction](#): Itching or hives, swelling in your face or hands, swelling or tingling in your mouth or throat, chest tightness, trouble breathing

Anxiety, restlessness, fever, sweating, muscle spasms, nausea, vomiting, diarrhea, seeing or hearing things that are not there

Confusion, weakness, and muscle stiffness or twitching

Eye pain, trouble seeing

Fast, pounding, or uneven heartbeat

Feeling very thirsty or hungry, change in how much or how often you urinate

Fever, chills, [cough](#), sore throat, and body aches

Jerky muscle movement you cannot control (often in your face, tongue, or jaw)

Lightheadedness, dizziness, or fainting

Seizures or tremors

Trouble sleeping, unusual dreams

Unusual behavior, thoughts of hurting yourself or others

Unusual bleeding or bruising

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

Blurred vision

Sexual problems

Sleepiness or unusual drowsiness

Trouble swallowing

Weight gain, increased appetite

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

4.3] Place In Therapy

A) Depression Associated with Bipolar I Disorder

1) The combination of [olanzapine](#) and [fluoxetine](#) is indicated in adults and adolescents, aged 10 years or older, for the treatment of acute [depressive episodes](#) associated with bipolar I disorder.. The need for continued use of [olanzapine/fluoxetine](#) should be periodically reevaluated [1].

B) Treatment-Resistant Depression

1) Combination [olanzapine](#) and [fluoxetine](#) is indicated for the treatment of treatment-resistant [major depressive disorder](#) in adults who experienced failure to 2 separate previous trials of antidepressant therapy of adequate dose and duration in the current episode. The need for continued use [olanzapine/fluoxetine](#) should be periodically reevaluated [1].

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

4.4] Mechanism of Action / Pharmacology

A) Mechanism of Action

1) Although the exact mechanism of the combination of [olanzapine](#) and [fluoxetine](#) is unknown, the enhanced antidepressant effect is probably related to serotonin, [norepinephrine](#), and [dopamine](#) activation. Increased [norepinephrine](#) and [dopamine](#) release in the prefrontal cortex compared with either drug alone, as well as increases in serotonin, have been demonstrated in animal studies [2].

2) [Olanzapine](#) is an atypical antipsychotic and [fluoxetine](#) is an SSRI. [Fluoxetine](#) is an inhibitor of the serotonin transporter and is a weak inhibitor of [norepinephrine](#) and [dopamine](#) transporters. [Olanzapine](#) binds with high affinity to serotonin 5HT_{2A/2C} and 5HT₆, [dopamine](#) D₁₋₄, [histamine](#) H-1, and adrenergic alpha-1 receptors. [Olanzapine](#) binds with moderate affinity to serotonin 5HT₃ and muscarinic M₁₋₅ and with weak affinity to GABA-A, benzodiazepine, and beta-adrenergic receptors [2]

3) The therapeutic and adverse effects of [olanzapine](#) may be due to its antagonism of certain receptors, such as anticholinergic-like effects related to muscarinic M₁₋₅ receptor antagonism, somnolence effects related to [histamine](#) H-1 receptor antagonism, and orthostatic hypotension due to alpha-1 adrenergic and [histamine](#) H-1 receptor antagonism. [Fluoxetine](#) does not contribute to the above effects because of its relatively low affinity for muscarinic, alpha-1 adrenergic, and [histamine](#) H-1 receptors [2].

4.5] Therapeutic Uses

4.5.1] FDA Uses

4.5.1.A] Bipolar disorder, depressed phase

FDA Labeled Indication

1] Overview

FDA Approval: Adult, yes; **Pediatric, yes (10 to 17 years)**

Efficacy: Adult, Effective; Pediatric, Evidence favors efficacy

Recommendation: Adult, Class IIa; Pediatric, Class IIb

Strength of Evidence: Adult, Category B; Pediatric, Category B

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

2] Summary:

[Olanzapine/fluoxetine](#) is indicated in adults and adolescents 10 to 17 years of age for the acute treatment of [depressive episodes](#) associated with bipolar I disorder [2].

In an 8-week, randomized, double-blind study, [olanzapine](#) monotherapy and combination [olanzapine/fluoxetine](#) treatment demonstrated significantly greater mean improvements in Montgomery-Asberg Depression Rating Scale total scores compared with placebo in adults with bipolar I depression (n=833) [3].

Efficacy of [olanzapine/fluoxetine](#) in adults was established in 2 identically designed, 8-week, randomized, double-blind clinical studies (n=788) [4].

Efficacy of [olanzapine/fluoxetine](#) in adolescents aged 10 to 17 years with [depressive episodes](#) associated with bipolar I disorder was established in an 8-week, randomized, double-blind study (n=255) where treatment with [olanzapine/fluoxetine](#) resulted in a significant reduction in the mean total score on the Children's Depressive Rating Scale-Revised from baseline compared with placebo (-28.43 vs -23.4) [2].

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

3] Adult:

a)] Both [olanzapine](#) monotherapy and [olanzapine](#) plus [fluoxetine](#) combination therapy were more effective than placebo in the treatment of [bipolar depression](#). In a randomized, double-blind, placebo-controlled, multicenter, international study, patients with bipolar I disorder, depressed and a score of at least 20 on the Montgomery-Asberg Depression Rating Scale (MADRS) received [olanzapine](#) (n=370; 5 to 20 mg/day; mean modal dose, 9.7 mg/day), [olanzapine](#) plus [fluoxetine](#) (n=86; 6 and 25 mg/day, 6 and 50 mg/day, or 12 and 50 mg/day; mean dose, 7.4 and 39.3 mg/day) or placebo (n=377) for 8 weeks. The primary objective of the study compared [olanzapine](#) monotherapy with placebo with regard to change in the MADRS total score from baseline to 8 weeks. Throughout all 8 weeks of the study, treatments with both [olanzapine](#) and [olanzapine/fluoxetine](#) combination produced significantly greater reductions in depressive symptoms (as measured by the MADRS) as compared with placebo (p less than 0.001, all values). Also, a significantly greater improvement in the mean MADRS score at weeks 4, 6, and 8 was observed with [olanzapine/fluoxetine](#) combination therapy as compared with [olanzapine](#) monotherapy (p=0.01, p=0.02, p=0.01, respectively). The rate of response (defined as at least a 50% improvement in the MADRS total score and completion of at least 4 weeks of study) was significantly higher in olanzapine-treated patients as compared with placebo (39% vs 30.4%, respectively; p=0.02). Additionally, the response rate was significantly higher in the [olanzapine/fluoxetine](#) group as compared with both the placebo (56.1% vs 30.4%; p less than 0.001)

and [olanzapine](#) groups (56.1% vs 39%; $p=0.006$). There were no statistically significant differences between groups with regard to rates of treatment-emergent mania. Adverse events were similar between the combination therapy and monotherapy groups, however, the [olanzapine/fluoxetine](#) group had a significantly higher rate of nausea and diarrhea [3].

b) The efficacy of [olanzapine/fluoxetine](#) for the treatment of [depressive episodes](#) associated with [bipolar disorder](#) was established in 2 identically designed, 8-week, randomized, double-blind, controlled studies ($n=788$) of patients who met DSM-IV criteria for Bipolar I Disorder, Depressed utilizing flexible dosing of [olanzapine/fluoxetine](#) (6/25, 6/50, or 12/50 mg/day), [olanzapine](#) (5 to 20 mg/day), and placebo. These studies included patients (18 years and older) with or without psychotic symptoms and with or without a rapid cycling course. The primary rating instrument used to assess depressive symptoms in these studies was the Montgomery-Asberg Depression Rating Scale (MADRS), a 10-item clinician-rated scale with total scores ranging from 0 to 60. The primary outcome measure of these studies was the change from baseline to endpoint in the MADRS total score. In both studies, [olanzapine/fluoxetine](#) was statistically significantly superior to both [olanzapine](#) monotherapy and placebo in reduction of the MADRS total score [4].

4) Pediatric:

a) In an 8-week, randomized, double-blind study in adolescents age 10 to 17 years with acute [depressive episodes](#) associated with bipolar I disorder ($n=255$), treatment with [olanzapine/fluoxetine](#) resulted in a significant reduction in the mean total score on the clinician-rated Children's Depressive Rating Scale-Revised (CDRS-R) from baseline compared with placebo. Adolescents included in the study met DSM-IV-TR criteria for bipolar I disorder, depressed, and included patients with or without psychotic symptoms. Patients were randomized to receive either placebo, or initiated with [olanzapine](#) 3 mg/[fluoxetine](#) 25 mg/day and then force-titrated to [olanzapine](#) 12 mg/[fluoxetine](#) 50 mg/day over 2 weeks. After 2 weeks, flexible dosing was permitted in the range of [olanzapine](#) 6 to 12 mg/[fluoxetine](#) 25 to 50 mg. At baseline, the mean CDRS-R score was 54.6 ± 10 in the [olanzapine/fluoxetine](#) group and 53.7 ± 8.2 in placebo. The mean daily dose was [olanzapine](#) 7.7 mg/[fluoxetine](#) 37.6 mg. Using the CDRS-R, an 17-item scale with total scores ranging from 17 to 113, the least squares mean change from baseline to week 8 (primary outcome) was reduced by -28.43 ± 1.1 in the [olanzapine/fluoxetine](#) group compared with a reduction of -23.4 ± 1.5 in placebo (treatment difference, -5; 95% CI, -8.3 to -1.8) [2].

4.5.1.B] [Major depressive disorder](#), Treatment-resistant

FDA Labeled Indication

1) 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](#)

2) Summary:

Indicated for the acute treatment of treatment-resistant [major depressive disorder](#) in adults who experienced failure to 2 separate previous trials of antidepressant therapy [4].

Pooled results of 2 parallel, 8-week, double-blind studies revealed [olanzapine/fluoxetine](#) combination therapy provided significant improvement in treatment-resistant depression compared with [olanzapine](#) or [fluoxetine](#) monotherapy (n=605) [5].

A 12-week, double-blind, randomized study revealed [olanzapine/fluoxetine](#) combination therapy was significantly more effective for rapid improvement of treatment-resistant depression compared with [olanzapine](#), [fluoxetine](#) or [venlafaxine](#) monotherapy, but the statistical advantage was sustainable over [olanzapine](#) monotherapy only by the end of the study (n=483) [6].

Despite significant, rapid-onset, improvement with [olanzapine/fluoxetine](#) combination therapy, there was no difference between [olanzapine/fluoxetine](#) combination therapy compared with [olanzapine](#), [fluoxetine](#) or [nortriptyline](#) monotherapy at the end of an 8-week, multicenter, double-blind, randomized study for treatment-resistant depression (n=500) [7].

Reduced symptoms of [major depressive disorder](#) in patients with non-treatment resistant and treatment-resistant depression [8]

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

3) Adult:

a) Pooled results of 2 parallel, 8-week, double-blind studies revealed [olanzapine/fluoxetine](#) combination therapy provided significant improvement in treatment-resistant depression compared with [olanzapine](#) or [fluoxetine](#) monotherapy (n=605). Eligible adult patients must meet DSM-IV criteria for [major depressive disorder](#), recurrent, and nonpsychotic. All patients had a total score of 22 or greater for the 17-item Hamilton Rating Scale for Depression (HAM-D 17) and a documented failure to respond to at least 6 weeks of therapeutically dosed antidepressant, except [fluoxetine](#) occurring within the current [depressive episode](#). After a 3- to 14-day screening phase, patients entered an 8-week, open-label, lead-in phase to confirm [fluoxetine](#) resistance initiated at 25 mg/day for a minimum of 1 day, titrated to 50 mg/day by lead-in week 2. Patients who could not tolerate [fluoxetine](#) 50 mg/day were discontinued. Nonresponders to [fluoxetine](#) (defined as less than a 25% improvement in the interactive voice response (IVR) HAM-D 17 score, or an IVR HAM-D 17 score less than 18 or greater than 15% decrease between lead-in week 7 and 8) proceeded to the double-blind treatment phase and were randomized equally to 1 of 3 treatment groups: [olanzapine/fluoxetine](#) 6 mg/50 mg (n=200), [fluoxetine](#) 50 mg alone (n=206), or [olanzapine](#) 6 mg alone (n=199) daily for 8 weeks. The primary outcome was the mean change in the Montgomery-Asberg Depression Rating Scale (MADRS) score from baseline to endpoint. Analysis included 598 patients with baseline and at least 1 post baseline measurement. The mean baseline MADRS score was 30 +/- 6.6. Mean modal doses were [olanzapine](#) 8.6 +/- 4.7 mg/[fluoxetine](#) 48.8 +/- 7.8 mg, [fluoxetine](#) alone 49.5 +/- 4.9 mg and [olanzapine](#) alone 8.7 +/- 4.8 mg. At week 8, pooled results revealed combination treatment with [olanzapine/fluoxetine](#) combination therapy provided significant improvement in mean change of MADRS score (-12.7 +/- 10.3) compared with [fluoxetine](#) alone (-9 +/- 9.8) and [olanzapine](#) alone (-8.8 +/- 9.1) (both p less than 0.001). Pooled response rates were also significantly better with combination treatment 40.4% (80/198) compared with [fluoxetine](#) alone 29.6% (60/203) and [olanzapine](#) alone 25.9% (51/197) (overall p=0.006). Common adverse events occurring at 10% or greater in the pooled [olanzapine/fluoxetine](#) combination therapy group included weight gain, increased appetite, dry mouth, somnolence, peripheral edema, and hypersomnia, which were significantly higher than that of [fluoxetine](#) monotherapy (p less than 0.001) [5].

b) A 12-week, double-blind, randomized study revealed [olanzapine/fluoxetine](#) combination therapy was significantly more effective for rapid improvement of treatment-resistant depression compared with [olanzapine](#), [fluoxetine](#) or [venlafaxine](#) monotherapy, but the statistical advantage was sustainable over [olanzapine](#) monotherapy only by the end of the study (n=483). Eligible adult

patients required DSM-IV diagnosis of unipolar, nonpsychotic, [major depressive disorder](#) and SSRI treatment failure after at least 6 weeks of treatment at a therapeutic dose. After verification of enrollment criteria during phase 1, patients entered the 7-week, open-label, lead-in phase and received [venlafaxine](#) 75 to 375 mg/day to confirm treatment resistance, defined as less than a 30% improvement in the Montgomery-Asberg Depression Rating Scale (MADRS) score. Patients with confirmed treatment resistance (age 45.7 +/- 10.8 years; 72.5% female) were then randomized equally to 1 of 4 groups of the acute treatment, double-blind phase: [olanzapine/fluoxetine](#) combination therapy (6 dose options; n=302), [olanzapine](#) alone (n=62), [fluoxetine](#) alone (n=60) and [venlafaxine](#) alone (n=59). The 4 highest [olanzapine/fluoxetine](#) combination therapy doses were pooled for analysis (6/25, 6/50, 12/25, and 12 mg/50 mg). The primary outcome was the mean change in MADRS score from baseline to endpoint of the pooled data from the 4 highest [olanzapine/fluoxetine](#) combination therapy doses compared with each monotherapy group. Analysis included patients with baseline and at least 1 post baseline measurement. The mean baseline MADRS score for all treatment groups was 30 +/- 6.8. The mean modal doses were 7.9 mg/day, 37.5 mg/day and 275.4 mg/day in the [olanzapine](#), [fluoxetine](#) and [venlafaxine](#) monotherapy groups. At week 1, improvement (decrease) in mean change in MADRS score from baseline to endpoint was significantly better with [olanzapine/fluoxetine](#) combination therapy compared with [olanzapine](#), [fluoxetine](#) and [venlafaxine](#) monotherapy (-7.2, -4.8, -4.7, -3.7, respectively; all p=0.03 or less), and remained statistically significant through treatment week 6. However, at week 12, a significant difference in mean change in MADRS score was sustained only between [olanzapine/fluoxetine](#) combination therapy compared with [olanzapine](#) alone (p less than 0.001), and not with [fluoxetine](#) alone (p=0.062) or [venlafaxine](#) alone (p=0.795). Common adverse effects occurring at 10% incidence or greater in the [olanzapine/fluoxetine](#) combination group included weight gain, somnolence, increased appetite, dizziness, dry mouth, asthenia, peripheral edema and headache. More patients in the combination therapy group discontinued due to weight gain [6].

c) Despite significant and rapid-onset improvement with [olanzapine/fluoxetine](#) combination therapy, there was no difference between [olanzapine/fluoxetine](#) combination therapy compared with [olanzapine](#), [fluoxetine](#) or [nortriptyline](#) monotherapy at the end of an 8-week, multicenter, double-blind, randomized study for treatment-resistant depression (n=500). Eligible adult patients required DSM-IV, unipolar, nonpsychotic, [major depressive disorder](#), a total Montgomery-Asberg Depression Rating Scale (MADRS) score of 20 or greater at the beginning and end of the screening period, and at least 1 previous failure after at least 4 weeks of SSRI treatment at therapeutic dosage. After a 2- to 7-day, screening/washout period, patients proceeded to the 7-week, lead-in phase (n=946; age 42.5 +/- 10.8 years; 67.3% female) with [nortriptyline](#) (titrated to therapeutic plasma level within 2 weeks of initiation, maximum 75 mg daily if tolerated) to confirm treatment resistance, defined as less than a 30% improvement (decrease) in the MADRS score. Those with confirmed treatment resistance were tapered off [nortriptyline](#) (except for the [nortriptyline](#) monotherapy group) and randomized in a 2:2:2:1 ratio to [olanzapine/fluoxetine](#) combination therapy (n=146), [olanzapine](#) alone (n=144), [fluoxetine](#) alone (n=142) or [nortriptyline](#) alone (n=68) once daily for an 8-week, acute-treatment phase. [Lorazepam](#) 2 mg/day or less was permitted as needed for anxiety. The primary outcome was the mean change in MADRS score from baseline (acute treatment phase) to endpoint. Despite a statistically significant improvement in MADRS score with [olanzapine/fluoxetine](#) combination therapy at week 2 compared with all other monotherapy groups ([olanzapine](#) p=0.029, [fluoxetine](#) and [nortriptyline](#) p less than 0.001) and a sustained improvement throughout the treatment period, there was no difference between all treatment groups in mean change in MADRS score at the end of week 8; data provided in the Mean Change in MADRS Scores from Baseline table. The most common adverse events (10% incidence or greater) in the [olanzapine/fluoxetine](#) combination therapy group were asthenia, somnolence, weight gain, increased appetite, headache, anxiety, tremor, nervousness, insomnia, and nausea [7]:

Mean Change in MADRS Scores
from Baseline

Therapy	Mean Modal Dose, mg/day (+/- SD)	Baseline MADRS Score (+/- SD)	Mean Change in MADRS (+/- SE)
olanzapine/fluoxetine	8.5 (3.1)/35.6 (12.7)	28.5 (7.5)	-8.71 (0.7)
olanzapine	8.3 (3.1)	28.4 (7.3)	-6.95 (0.71)
fluoxetine	35.8 (12.8)	28.4 (7.3)	-8.51 (0.7)
nortriptyline	103.5 (33.9)	28.8 (6.5)	-7.46 (0.98)

KEY: MADRS = Montgomery-Asberg Depression Rating Scale;
SE = standard error; SD = standard deviation

d) Combination treatment with [olanzapine](#) and [fluoxetine](#) effectively reduced symptoms of [major depressive disorder](#) in patients with non-treatment-resistant and treatment-resistant depression. In an open-label, multicenter, 76-week study, patients (n=560) with [major depressive disorder](#), including treatment-resistant depression, received combination therapy with [olanzapine](#) and [fluoxetine](#) at mean doses of 7.5 mg/day and 46.1 mg/day, respectively. Efficacy was assessed by mean change from baseline in the Montgomery-Asberg Depression Rating Scale (MADRS) total score and the Clinical Global Impression-Severity of Illness scale (CGI-S) score. At 76 weeks, there was a 67.7% (21.8 points) mean reduction in the total MADRS score and the CGI-S mean score was reduced by 49.3% (2.2 points). Mean change scores for both the MADRS and CGI-S were significantly different from baseline at all time points (p=0.0001). At endpoint, 61.6% of patients were considered responders (defined as at least a 50% decrease in MADRS total score from baseline to endpoint) and throughout the study period, 56.3% of patients achieved remission (defined as 2 consecutive MADRS total scores of 8 or less at any time). However, 14.8% of patients who remitted, relapsed by endpoint. Patients with treatment-resistant depression exhibited a similar pattern of response to patients with non-treatment-resistant depression. Somnolence (47.7%), weight gain (39.8%), dry mouth (37.1%), increased appetite (32%), headache (22.3%), [rhinitis](#) (22.1%), asthenia (19.3%), and tremor (18.8%) were the most commonly reported adverse events associated with treatment [8].

4.6] Comparative Efficacy / Evaluation With Other Therapies

4.6.A] [Fluoxetine](#)

4.6.A.1] Depression - [Schizophrenia](#)

a) Results of an 8-week, double-blind trial demonstrated that patients receiving both [olanzapine](#) and [fluoxetine](#) in combination demonstrated greater improvement in Montgomery-Asberg Depression Rating Scale (MADRS) and Clinical Global Impression (CGI) total scores than patients receiving either medication alone. Twenty-eight patients with nonpsychotic treatment-refractory depression received [olanzapine](#) (5 to 20 milligrams/day) and/or [fluoxetine](#) (20 to 60 milligrams/day). In addition, there were no significant differences in adverse events among the 3 different treatment groups [612].

4.6.B] [Olanzapine](#)

4.6.B.1] Depression - [Schizophrenia](#)

a) Results of an 8-week, double-blind trial demonstrated that patients receiving both [olanzapine](#) and [fluoxetine](#) in combination demonstrated greater improvement in Montgomery-Asberg Depression Rating

Scale (MADRS) and Clinical Global Impression (CGI) total scores than patients receiving either medication alone. Twenty-eight patients with nonpsychotic treatment-refractory depression received [olanzapine](#) (5 to 20 milligrams/day) and/or [fluoxetine](#) (20 to 60 milligrams/day). In addition, there were no significant differences in adverse events among the 3 different treatment groups [613].

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