

DRUGDEX-EV 2410

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## **SERTRALINE**

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### **0.0] Overview**

#### **1] Class**

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

Antidepressant  
Central Nervous System Agent

#### **2] Dosing Information**

**a)** [Sertraline](#) Hydrochloride

##### **1] Adult**

**a)** [Dysthymia](#)

**1)** 50 mg orally daily as a single dose in the morning or the evening; MAX 200 mg/day (off-label dosage)[46]

**b)** [Major depressive disorder](#)

**1)** 50 mg/day orally as a single dose in the morning or the evening; may be increased at intervals of at least 1 week to a MAX dosage of 200 mg/day [13]

**c)** [Obsessive-compulsive disorder](#)

**1)** Initial, 50 mg/day orally as a single dose in the morning or the evening; may increase at intervals of at least 1 week to a MAX dosage of 200 mg/day (FDA dosage) [13]

**2)** Initial, 50 mg orally once daily; may increase by 50 mg/day once every week to usual target dose of 200 mg/day; MAX 200 to 400 mg/day, especially in rapid metabolizers or those with inadequate response after 8 weeks (guideline dosage) [20]

**d)** [Panic disorder](#)

1j) Initial, 25 mg/day orally as a single dose in the morning or the evening for 1 week, then increase to 50 mg/day; may then be increased at intervals of at least 1 week to a MAX dosage of 200 mg/day [13]

e) [Posttraumatic stress disorder](#)

1j) Initial, 25 mg/day orally as a single dose in the morning or the evening for 1 week, then increase to 50 mg/day; may then be increased at intervals of at least 1 week to a MAX dosage of 200 mg/day [13]

f) [Premenstrual dysphoric disorder](#)

1j) Daily dosing, 50 mg/day orally as a single dose in the morning or the evening throughout the menstrual cycle; may be increased at 50-mg increments/menstrual cycle up to 150 mg/day [13]; OR

2j) Luteal phase dosing, 50 mg/day orally only during the luteal phase; may be increased up to 100 mg/day if needed; if 100-mg dosage is necessary, each new luteal-phase dosing cycle should begin with 50 mg/day for 3 days before increasing to 100-mg/day dose [13]

g) [Social phobia](#)

1j) Initial, 25 mg/day orally as a single dose in the morning or the evening for 1 week, then increase to 50 mg/day; may then be increased at intervals of at least 1 week to a MAX dosage of 200 mg/day [13]

2j) Pediatric

a) [Obsessive-compulsive disorder](#)

1j) (6 to 12 years) Initial, 25 mg/day orally as a single dose in the morning or the evening; may increase at intervals of at least 1 week to a MAX dosage of 200 mg/day [13]

2j) (13 to 17 years) Initial, 50 mg/day orally as a single dose in the morning or the evening; may increase at intervals of at least 1 week to a MAX dose of 200 mg/day [13]

3j) Contraindications

a) [Sertraline](#) Hydrochloride

1j) Concomitant use of [disulfiram](#) with oral concentrate [60]

2j) Concomitant use of MAOIs, including [linezolid](#) or IV methylene blue, within 14 days of [sertraline](#) discontinuation or use of [sertraline](#) within 14 days of discontinuing an MAOI; increased risk of [serotonin syndrome](#) [60]

3j) Concomitant use of [pimozide](#) [60]

4)) Hypersensitivity to [sertraline](#) or any other component of the product [60]

4)) Serious Adverse Effects

a)) [Sertraline](#) Hydrochloride

- 1)) [Anaphylaxis](#)
- 2)) Depression, Exacerbation
- 3)) [Gastrointestinal hemorrhage](#)
- 4)) Hemorrhage, Abnormal
- 5)) [Hyponatremia](#)
- 6)) Mania
- 7)) [Rhabdomyolysis](#)
- 8)) Seizure
- 9)) [Serotonin syndrome](#)
- 10)) [Stevens-Johnson syndrome](#)
- 11)) Suicidal thoughts
- 12)) Suicide

5)) Clinical Applications

a)) [Sertraline](#) Hydrochloride

1)) FDA Approved Indications

- a)) [Major depressive disorder](#)
- b)) [Obsessive-compulsive disorder](#)
- c)) [Panic disorder](#)
- d)) [Posttraumatic stress disorder](#)
- e)) [Premenstrual dysphoric disorder](#)
- f)) [Social phobia](#)

2)) Non-FDA Approved Indications

- a)) [Dysthymia](#)

1.0) Dosing Information

[Drug Properties](#)  
[Storage and Stability](#)  
[Adult Dosage](#)  
[Pediatric Dosage](#)

### 1.1] Drug Properties

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

B)] Synonyms

[Sertraline](#)

[Sertraline](#) HCl

[Sertraline](#) Hydrochloride

C)] Physicochemical Properties

1)] [Sertraline](#) Hydrochloride

a)] Molecular Weight

1)] 342.7 [106]

b)] Solubility

1)] Slightly soluble in water and isopropyl alcohol; sparingly soluble in ethanol [106]

### 1.2] Storage and Stability

A)] [Sertraline](#) Hydrochloride

1)] Preparation

a)] Oral route

1)] Dilute the oral concentrate in 4 ounces (one-half cup) using only water, ginger ale, lemon/lime soda, lemonade, or orange juice. Dilute immediately prior to use [13].

B)] Oral route

1)] Solution/Tablet

a)] Store at a controlled room temperature, 25 degrees C (77 degrees F), with excursions permitted between 15 and 30 degrees C (59 and 86 degrees F) [13].

### 1.3] Adult Dosage

#### 1.3.1] Normal Dosage

##### 1.3.1.A] Important Note

J) Beers Criteria: Use caution or avoid use as potentially inappropriate in older adults [1].

### 1.3.1.B] **Sertraline Hydrochloride**

#### 1.3.1.B.1] **Oral route**

##### 1.3.1.B.1.a] **Dysthymia**

1) Off-label dosage: Begin with 50 mg daily orally as a single dose in the morning or the evening; may titrate up to a maximum of 200 mg/day [46].

##### 1.3.1.B.1.b] **Major depressive disorder**

1) Initial dosage and titration: 50 mg orally daily as a single dose in the morning or the evening. May be increased at intervals of at least 1 week [13].

2) Maximum dosage: 200 mg daily [13].

3) Duration of use: Treatment of depression generally requires several months or longer of continued pharmacologic intervention. It is unknown whether the dose of **sertraline** required to maintain euthymia is the same as that needed to induce remission of depression [13].

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

##### 1.3.1.B.1.c] **Obsessive-compulsive disorder**

#### 1) FDA Dosage

a) Initial dosage and titration: 50 mg orally daily as a single dose in the morning or the evening. May be increased at intervals of at least 1 week [13].

b) Maximum dosage: 200 mg daily [13].

c) Duration of use: Because of the chronic nature of this disorder, therapy should be continued for responding patients with periodic reassessment of the need for continued therapy [13].

#### 2) Guideline Dosage

a) Usual dosage: 200 mg/day [20].

b) Initial dosage and titration: 50 mg/day orally once daily. May increase by 50 mg/day once every week during the first month of therapy. If little or no response is seen in first 4 weeks, continue to increase weekly or biweekly to the maximum dosage tolerated, with a period of at least 4 to 6 weeks at the highest comfortably tolerated dosage [20].

c) Maintenance dosage: Continue effective dosage for 1 to 2 years before considering discontinuation [20].

d) Maximum dosage: 200 to 400 mg/day, especially in rapid metabolizers or those with no or minimal side effects and inadequate response after 8 weeks [20].

e) Discontinuation: Gradually reduce dose over several months or more [20].

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

**1.3.1.B.1.d] Panic disorder**

1)) Initial dosage and titration: 25 mg orally daily for 7 days, as a single dose in the morning or the evening. After 1 week, increase to 50 mg once daily. May be further increased at intervals of at least 1 week [13].

2)) Maintenance dosage: Use the lowest effective dosage [13].

3)) Maximum dosage: 200 mg daily [13].

4)) Duration of use: Because of the chronic nature of this disorder, therapy should be continued for responding patients with periodic reassessment of the need for continued therapy [13].

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

**1.3.1.B.1.e] Posttraumatic stress disorder**

1)) Initial dosage and titration: 25 mg orally daily for 7 days, as a single dose in the morning or the evening. After 1 week, increase to 50 mg once daily. May be further increased at intervals of at least 1 week [13].

2)) Maximum dosage: 200 mg daily [13].

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

**1.3.1.B.1.f] Premenstrual dysphoric disorder****1)) Daily Dosing**

a)) Initial dosage: 50 mg daily as a single dose in the morning or the evening throughout the menstrual cycle. If needed, the dosage may be increased at 50-mg increments per menstrual cycle up to 150 mg once daily [13].

**2)) Luteal Phase Dosing**

a)) Initial dosage: 50 mg daily as a single dose in the morning or the evening only during the luteal phase. The dosage may be increased up to 100 mg once daily, if needed. If the 100-mg dosage is necessary, each new luteal-phase dosing cycle should begin with 50 mg/day for 3 days before increasing the dosage to 100 mg/day [13].

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

**1.3.1.B.1.g] Social phobia**

1)) Initial dosage and titration: 25 mg orally daily for 7 days, as a single dose in the morning or the evening. After 1 week, increase to 50 mg once daily. May be further increased at intervals of at least 1 week [13].

2)) Maintenance dosage: Use the lowest effective dosage [13]

3)) Maximum dosage: 200 mg daily [13].

4)) Duration of use: Periodic determinations should be made to assess the need for long-term treatment [13]

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

**1.3.1.B.2] Severe major depression with psychotic features; Adjunct**

a) Treatment with [olanzapine](#) plus [sertraline](#) produced higher remission rates compared with [olanzapine](#) monotherapy in patients with [major depression](#) with psychotic features in the 12-week randomized STOP-PD study (N=259). Patients meeting the DSM-IV-TR criteria for unipolar [major depression](#) with psychotic features, with the presence of at least 1 delusional belief, a Delusional Assessment Scale score of 2 or higher on one of the conviction items, a score of 3 or higher on the delusion severity rating item of the [Schedule of Affective Disorders and Schizophrenia](#) (SADS), moderately severe to severe depression based on a score of 21 or higher on the 17-item Hamilton Depression Scale (HAM-D), and without history of [dementia](#) or cognition impairment were eligible for the study. Eligible patients (age 58 +/- 17.7 years; 60 years or older, 54.8%) were randomized to initial therapy of [olanzapine](#) 5 milligrams/day (mg/day) plus [sertraline](#) 50 mg/day (n=129) or [olanzapine](#) 5 mg/day plus matching placebo (n=130) with dose increases allowed every 3 days as tolerated. Doses were increased to reach a target dose of [olanzapine](#) 10 mg/day plus [sertraline](#) 100 mg/day by the end of week 1, [olanzapine](#) 15 mg/day plus [sertraline](#) 150 mg/day by the end of week 2, and a maximum of [olanzapine](#) 20 mg/day plus [sertraline](#) 200 mg/day by the beginning of week 3. Frail elderly patients initially received [olanzapine](#) 2.5 mg/day plus [sertraline](#) 25 mg/day or matching placebo. Temporary dose reductions or slower titrations were allowed if adverse effects were intolerable; however, the attempt to achieve a minimum daily target dose of [olanzapine](#) 15 mg/day plus [sertraline](#) 150 mg/day or placebo was required. The use of adjunctive [lorazepam](#) of up to 4 mg per day was allowed. There was no significant difference in the mean daily dose of between treatment arms. The final dose of [olanzapine](#) was 14.3 +/- 5.3 mg and 168.9 +/- 44.1 mg for [sertraline](#) in the active treatment arm. Remission was defined as a HAM-D score of 10 or less at two consecutive assessments, and the absence of delusions (SADS delusional score of 1). Based on the intent-to-treat analysis, 41.9% of patients in the combination arm achieved remission (primary endpoint) compared with 23.9% of the patients in the [olanzapine](#) plus placebo arm (p=0.002). The increase in the rates of remission over the course of the study (treatment x time effect) was significantly greater in the combination therapy arm compared with the monotherapy arm (odds ratio (OR), 1.28). Subgroup analysis of treatment x time effect was comparable between the younger (n=117; mean age 41.3 +/-10.8 years; OR, 1.25) and the older population (n=142; mean age 71.7 +/- 7.8 years; OR, 1.34). In the 3-way interaction among age, treatment and time was nonsignificant (OR, 1.05). The combination therapy arm was associated with significantly greater improvements in the Clinical Global Impressions, Severity of Illness Scale (CGI-S) scores (p=0.02) and HAM-D scores compared with the monotherapy arm; but not significant with the improvements in SADS scores. The most common adverse effects included significant weight gain (2.7 kg or more during the previous month; 54.3% vs 53.4%), somnolence/sedation (28.7% vs 30.8%), and orthostatic dizziness (15.5% vs 10%) in the combination and monotherapy arms, respectively. Stratified by age, the younger patient subgroup experienced a higher incidence of weight gain (65% vs 45.1%; p=0.001) and lower incidence of pedal edema (4.3% vs 13.4%) compared with the older patient subgroup. Overall, the number needed to treat to achieve 1 additional remission with combination therapy is 5.5 patients [11].

### 1.3.2] Dosage in [Renal Failure](#)

#### A) [Sertraline](#) Hydrochloride

1) Impairment: Dosage adjustment is not necessary. [Sertraline](#) is extensively metabolized, so only minimal amounts of unchanged drug are eliminated in the urine [13].

### 1.3.3] Dosage in [Hepatic Insufficiency](#)

#### A) [Sertraline](#) Hydrochloride

1j) Impairment: A lower or less frequent dose should be used as [sertraline](#) is extensively metabolized in the liver [13].

## 1.4] Pediatric Dosage

### 1.4.1] Normal Dosage

#### 1.4.1.A] Important Note

j) Beers Criteria: Use caution or avoid use as potentially inappropriate in older adults [1].

#### 1.4.1.B] [Sertraline](#) Hydrochloride

##### 1.4.1.B.1] Oral route

##### 1.4.1.B.1.a] [Obsessive-compulsive disorder](#)

##### 1j) 6 to 12 Years

a) Initial dosage and titration: 25 mg orally once daily in the morning or the evening. May be increased at intervals of at least 1 week. Dosage adjustments in children should take into consideration their lower body weight [13]

b) Maximum dosage: 200 mg daily [13].

##### 2j) 13 to 17 Years

a) Initial dosage and titration: 50 mg orally once daily in the morning or the evening. May be increased at intervals of at least 1 week however. Dosage adjustments in children should take into consideration their lower body weight [13].

b) Maximum dosage: 200 mg daily [13]

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

#### 1.4.3] Dosage in [Hepatic Insufficiency](#)

##### A) [Sertraline](#) Hydrochloride

1j) Impairment: A lower or less frequent dosage interval should be used as [sertraline](#) is extensively metabolized in the liver [13].

## 2.0] Pharmacokinetics

[Onset and Duration](#)

[Drug Concentration Levels](#)

[ADME](#)

### 2.1] Onset and Duration

#### A) Onset

##### 1j) Initial Response

a) Depression, regular release: 2 weeks [469].



**2)) Peak Response**

**a))** Depression, regular release: 6 weeks [470][471].

**2.2) Drug Concentration Levels****A)) Time to Peak Concentration**

**1))** Oral, regular release: 4 to 8 hours [472][471][476].

**a))** The C<sub>max</sub> after continuous administration of [sertraline](#) 200 mg/day was 165 ng/mL (children 6 to 12 years), 123 ng/mL (adolescents), and 142 ng/mL (adults) [472].

**b))** A study of 22 young (less than 45 years) and elderly (greater than 65 years) healthy male and female volunteers reported no statistically significant difference in C<sub>max</sub> or T<sub>max</sub> between the young and elderly groups after continuous administration of 200 mg for 21 days [477].

**c))** The time of administration (morning versus evening) did NOT affect mean peak plasma [sertraline](#) concentration (C<sub>max</sub>) or time to reach C<sub>max</sub> (T<sub>max</sub>) in 22 healthy male volunteers who received single doses of 100 mg. Although no specific recommendation can be made, it appears that [sertraline](#) may be administered in the morning or evening without bioavailability differences [478].

**d))** A mean peak plasma [sertraline](#) concentration of 54.5 ng/mL was observed 4 hours after a single 100-milligram oral dose. After single 200- and 400-milligram doses, the mean peak plasma levels were 105.4 and 253.2 ng/mL, respectively, at 6 hours post-dosing [476].

**B)) Area Under the Curve**

**1))** 2296 to 3107 ng-hr/mL [472].

**a))** The AUC was 3107 ng-hr/mL (children 6 to 12 years), 2296 ng-hr/mL (adolescents 13 to 17 years), and 2570 ng-hr/mL (adults) after chronic dosing with 200 milligrams daily [472].

**2.3) ADME****2.3.1) Absorption****A)) Bioavailability**

**1))** Oral, regular release: complete [472][471].

**a))** Single dose bioavailability studies have shown that the tablets and oral solution are approximately equal [472].

**b))** The time of day of administration (morning versus evening) did NOT affect the area under the curve (AUC), mean peak plasma [sertraline](#) concentration (C<sub>max</sub>), time to reach C<sub>max</sub> (T<sub>max</sub>), mean terminal elimination half-life, or mean elimination rate constant, in 22 healthy male volunteers who received single doses of 100mg. Although no specific recommendation can be made, it appears that [sertraline](#) may be administered in the morning or evening without bioavailability differences [478].

**B)) Effects of Food**

1) small [472].

a) For the tablet, food increased the mean peak plasma concentration by 25%, and it decreased the time to peak plasma concentrations from a mean of 8 hours to a mean of 5.5 hours post-dose [472].

### 2.3.2] Distribution

#### A) Distribution Sites

##### 1) Protein Binding

a) 99% [471].

#### B) Distribution Kinetics

##### 1) Volume of Distribution

a) 20 L/kg [471].

### 2.3.3] Metabolism

#### A) Metabolism Sites and Kinetics

##### 1) Liver, extensive [472].

a) [Sertraline](#) undergoes extensive first-pass metabolism [472].

b) [Sertraline](#) is primarily metabolized via N-demethylation to desmethylsertraline, which is weakly active. Both compounds are further metabolized to their corresponding ketones and then hydroxylated. The alpha-hydroxy ketone metabolite is excreted in the urine and feces [471].

#### B) Metabolites

1) Desmethylsertraline, weakly active [471].

2) Alcohol metabolites, inactive [471].

3) Oxime metabolites, inactive [471].

### 2.3.4] Excretion

#### A) Kidney

##### 1) Renal Excretion (%)

a) 40% to 45% [472].

2) None of the dose is recovered as unchanged [sertraline](#) [472]. The alpha-hydroxy ketone metabolite of [sertraline](#) is primarily recovered in the urine [471].

#### B) Other

**1) OTHER EXCRETION**

**a)** Feces, 40% to 45% [472].

**b)** About 12-14% of [sertraline](#) is found unchanged in the feces along with the alpha-hydroxy ketone metabolite [471][472].

**2.3.5] Elimination Half-life****A) Parent Compound****1) ELIMINATION HALF-LIFE**

**a)** 24 hours [471][476].

**1)** The half-life after continuous administration of sertraline 200 mg/day was 26.2 hours (children 6 to 12 years), 27.8 hours (adolescents), and 27.2 hours (adults) [472].

**2)** A study of 22 young (less than 45 years) and elderly (greater than 65 years) healthy male and female volunteers reported similar pharmacokinetic parameters; however, young males exhibited a 50% shorter half-life (mean 22 hours) compared to the other groups (32 to 36 hours) [477].

**3)** The time of day of administration (morning versus evening) did NOT affect mean terminal elimination half-life or mean elimination rate constant in 22 healthy male volunteers who received single doses of 100 mg [478].

**B) Metabolites**

**1)** Desmethylsertraline, 62 to 104 hours [471][476][472].

**2.3.6] Extracorporeal Elimination****A) Hemodialysis**

**1)** Dialyzable: No[483]

**a)** In 2 patients undergoing [hemodialysis](#) with a Baxter CA-110 hollow fiber dialysis filter, no [sertraline](#) was detected in the dialysate. The arterial blood flow was maintained at about 300 mL/min; the dialysis time was 4 and 3.63 hours for patient 1 and 2, respectively [483].

**3.0] Cautions**

[Contraindications](#)

[Precautions](#)

[Adverse Reactions](#)

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

[Drug Interactions](#)

**3.0.A] Black Box WARNING**

## Sertraline Hydrochloride

## Oral (Solution; Tablet)

## Suicidality and Antidepressant Drugs

Antidepressants increased the risk compared to placebo of suicidal thinking and behavior (suicidality) in children, adolescents, and young adults in short-term studies of major depressive disorder (MDD) and other psychiatric disorders. Anyone considering the use of sertraline hydrochloride or any other antidepressant in a child, adolescent, or young adult must balance this risk with the clinical need. Short-term studies did not show an increase in the risk of suicidality with antidepressants compared to placebo in adults beyond age 24; there was a reduction in risk with antidepressants compared to placebo in adults aged 65 and older. Depression and certain other psychiatric disorders are themselves associated with increases in the risk of suicide. Patients of all ages who are started on antidepressant therapy should be monitored appropriately and observed closely for clinical worsening, suicidality, or unusual changes in behavior. Families and caregivers should be advised of the need for close observation and communication with the prescriber. Sertraline hydrochloride is not approved for use in pediatric patients except for patients with obsessive compulsive disorder (OCD) [21].

**3.1] Contraindications****A) Sertraline Hydrochloride**

- 1) Concomitant use of [disulfiram](#) with oral concentrate [60]
- 2) Concomitant use of MAOIs, including [linezolid](#) or IV methylene blue, within 14 days of [sertraline](#) discontinuation or use of [sertraline](#) within 14 days of discontinuing an MAOI; increased risk of [serotonin syndrome](#) [60]
- 3) Concomitant use of [pimozide](#) [60]
- 4) Hypersensitivity to [sertraline](#) or any other component of the product [60]

**3.2] Precautions****A) Sertraline Hydrochloride**

- 1) Black box warning: [Suicidal ideation](#) and behavior or worsening depression in children, adolescents, and young adults may occur during the first few months of therapy or following changes in dosage; monitoring recommended and discontinuation may be necessary [60]
- 2) Beers Criteria: Avoid use in elderly patients with a history of falls or fractures (unless safer alternatives are not available) as ataxia and impaired psychomotor performance may occur. If prescribed, use with caution in elderly patients as this may cause or exacerbate SIADH or [hyponatremia](#); monitoring recommended when starting or changing doses [1].
- 3) Concomitant use: Alcohol use not recommended [60]

- 4)) Endocrine and metabolic: New onset [diabetes mellitus](#) has been reported [60]
- 5)) Endocrine and metabolic: [Hyponatremia](#), usually the result of SIADH, has occurred, especially with volume-depletion, elderly age, or concurrent diuretic therapy; discontinuation recommended with symptomatic [hyponatremia](#) [60]
- 6)) Endocrine and metabolic: Loss of glycemic control, including [hypoglycemia](#) and [hyperglycemia](#), has been reported in patients with and without preexisting [diabetes](#); monitoring recommended [60]
- 7)) Gastrointestinal: [Gastrointestinal hemorrhage](#) has been reported; risk may be increased with concomitant use of [aspirin](#), NSAIDs, [warfarin](#), and other anticoagulants [60]
- 8)) Hematologic: Bleeding events, including life-threatening hemorrhages, have been reported with SSRIs; risk may be increased with concomitant use of [aspirin](#), NSAIDs, [warfarin](#), and other anticoagulants [60]
- 9)) Hepatic: Liver disease or impairment increases risk of [drug toxicity](#); dosage adjustment may be necessary [60]
- 10)) Immunologic: Use caution in patients with [latex allergy](#) as oral concentrate dropper dispenser contains dry natural rubber [60]
- 11)) Neurologic: Use caution in patients with seizure disorder, although seizures have been reported rarely and usually in patients with personal or family history of seizure disorder [60]
- 12)) Ophthalmic: Angle closure attacks may occur in patients with anatomically narrow angles who do not have a patent [iridectomy](#) [60]
- 13)) Psychiatric: Use caution in patients with [bipolar disorder](#) due to risk of precipitation of a mixed episode; mania and [hypomania](#) have been reported [60]
- 14)) [Serotonin syndrome](#): [Serotonin syndrome](#) has been reported, often with concurrent use with other serotonergic drugs (eg, triptans, tricyclic antidepressants, [fentanyl](#), [lithium](#), [tramadol](#), [buspirone](#), tryptophan, and St John's wort), MAOIs (including methylene blue IV and [linezolid](#)), and other drugs that impair serotonin metabolism; monitoring recommended and discontinue if suspected [60]
- 15)) Withdrawal: Serious discontinuation symptoms have been reported upon abrupt withdrawal; gradual reduction recommended when possible [60]

### 3.3] Adverse Reactions

#### 3.3.1] Cardiovascular Effects

##### 3.3.1.A] [Sertraline](#) Hydrochloride

###### 3.3.1.A.1] Angina pectoris

- a)) The incidence of total cardiovascular events (angina, chest pain, edema, palpitations, syncope, postural dizziness, [congestive heart failure](#) (CHF), [myocardial infarction](#) (MI), [tachycardia](#), bradycardia, and blood pressure changes) and major cardiovascular events involving death or requiring hospitalization (MI, CHF, [stroke](#), or angina) was no different in sertraline-treated patients compared with placebo in a postmarketing 16-week randomized placebo-controlled trial among patients (n=372) with [major depressive disorder](#) and recent history of MI or [unstable angina](#) requiring

hospitalization. Patients randomized to [sertraline](#) received 50 to 200 mg/day (mean daily dose was 89 mg/day) [13].

b) An 81-year-old woman developed nausea and severe, crushing, retrosternal chest pain with shortness of breath and diaphoresis 1 hour after taking the third dose of [sertraline](#) 50 mg. The pain worsened over the subsequent 2 hours and required hospitalization. The cardiovascular examination was normal; all laboratory tests including serial cardiac enzymes were also normal. The [electrocardiogram](#) revealed normal sinus rhythm with nonspecific ST-T wave changes. This patient was diagnosed with [unstable angina](#) which was treated with acetylsalicylic acid, IV [heparin](#), IV [nitroglycerin](#), and [diltiazem](#); [sertraline](#) was stopped. Four days later [cardiac catheterization](#) revealed 90% and 50% stenosis of the right coronary artery and circumflex artery, respectively. Although it is difficult to attribute angina to [sertraline](#), the authors suggest that increased presynaptic serotonin in patients with atherosclerotic coronary arteries causes vasoconstriction. This results from the inability of the endothelium to produce sufficient endothelium-derived relaxing factor to counteract the vasoconstriction caused by serotonin [64].

#### 3.3.1.A.2] [Atrioventricular block](#)

a) In postmarketing evaluation, [atrioventricular block](#) has been temporally associated with use of [sertraline](#), although no causal relationship has been established [13].

#### 3.3.1.A.3] [Chest pain](#)

a) Incidence: 1% or greater [13]

b) During premarketing use of [sertraline](#) in clinical trials of over 4000 patients, chest pain occurred on one or more occasions in at least 1% of patients exposed to multiple doses of [sertraline](#) [13].

#### 3.3.1.A.4] [Palpitations](#)

a) Incidence: 1% or greater [13]

b) During premarketing use of [sertraline](#) in clinical trials of over 4000 patients, palpitations occurred on one or more occasions in at least 1% of patients exposed to multiple doses of [sertraline](#) [13].

c) Palpitations were the cause of therapy discontinuation in 1% of patients with [premenstrual dysphoric disorder](#) with luteal-phase dosing (n=136) [13].

#### 3.3.1.A.5] [Prolonged QT interval](#)

a) Postmarketing

1) In postmarketing evaluation, QT-interval prolongation has been temporally associated with use of [sertraline](#), although no causal relationship has been established [21]

#### 3.3.1.A.6] [Syncope](#)

a) Three patients with [neurally mediated syncope](#), which was exacerbated following the use of [sertraline](#) has been reported [63].

#### 3.3.1.A.7] [Torsades de pointes](#)

a) Postmarketing

1) In postmarketing evaluation, [Torsade de pointes](#) has been temporally associated with use of [sertraline](#), although no causal relationship has been established [21]

### 3.3.1.A.8] Ventricular tachycardia

#### a) Adult Clinical Trial

1) (Oral route:) electrocardiographic abnormalities, 2 in 8 patients; T-wave flattening, 1 in 8 patients; clinically significant QT interval prolongation, 1 in 8 patients.[65].

#### b) Adult Case Reports and Postmarketing

1) In postmarketing evaluation, [ventricular tachycardia](#), including torsades de pointe-type [arrhythmias](#), have been temporally associated with use of [sertraline](#), although no causal relationship has been established [21].

## 3.3.2] Dermatologic Effects

### 3.3.2.A] Sertraline Hydrochloride

#### 3.3.2.A.1] Acneiform eruption

##### a) Adult Case Reports

1) Acneiform eruptions developed on the face of a 38-year-old woman with no history of acne within 12 days of [sertraline](#) 50 mg/day initiation for [depressive disorder](#). With a primary diagnosis of [paranoid schizophrenia](#), maintenance medications included [risperidone](#) and [topiramate](#). The lesions resolved within 5 days of [sertraline](#) discontinuation. The episode scored a 5 on the Naranjo probability scale [98].

#### 3.3.2.A.2] Stevens-Johnson syndrome

##### a) Adult Case Reports and Postmarketing

1) A 96-year-old woman developed cutaneous and mucosal eruptions 3 weeks after she began taking [sertraline](#) and arginine chlorhydrate for depression. Erythematous, atypical flat lesions were found on the face, trunk, and proximal limbs. Painful, oral erosions and [conjunctivitis](#) were also present. [Skin biopsy](#) revealed total necrosis of the epidermis. The [skin lesions](#) disappeared a week after [sertraline](#) and arginine chlorhydrate were withdrawn. The diagnosis of this skin reaction was classified as [Stevens-Johnson syndrome](#) because of the distribution, atypical flat appearance, and total necrolysis of the epidermis [99].

2) Reported in postmarketing surveillance [13]

#### 3.3.2.A.3] Sweating

##### a) Incidence: 3% to 11% [13]

##### b) Adult Clinical Trials

- 1) [Major depressive disorder](#) (oral route): Increased sweating, 8% vs 3% with placebo [13]
- 2) [Obsessive compulsive disorder](#) (oral route): Increased sweating, 6% vs 1% with placebo [13]
- 3) [Panic disorder](#) (oral route): Increased sweating, 5% vs 1% with placebo [13]
- 4) [Posttraumatic stress disorder](#) (oral route): Increased sweating, 4% vs 2% with placebo [13]
- 5) [Social anxiety disorder](#) (oral route): Increased sweating, 11% vs 2% with placebo [13]

6) **Premenstrual dysphoric disorder** (oral route): Increased sweating, 3% to 6% vs less than 1% with placebo [13]

c) Adult Case Reports

1) A **sertraline** dose increase to 150 mg/day coincided with progressive worsening of night sweats in a young woman with depression. Symptoms resolved within 4 days of abrupt **sertraline** discontinuation. Due to withdrawal symptoms, the patient restarted **sertraline** and noted mild daytime sweating. The sweating did not recur after switching **sertraline** to **fluoxetine** [100].

### 3.3.3] Endocrine/Metabolic Effects

#### 3.3.3.A] **Sertraline** Hydrochloride

##### 3.3.3.A.1] Decreased uric acid level

a) A small mean decrease in serum uric acid (7%) has been associated with **sertraline** therapy, although the clinical significance is unknown [13].

##### 3.3.3.A.2] **Diabetes mellitus**

a) **Sertraline** hydrochloride has been associated with new-onset **diabetes mellitus** and with loss of glycemic control (including both **hyperglycemia** and **hypoglycemia**) in patients with and without preexisting **diabetes**. Monitor for signs and symptoms of glucose fluctuations during **sertraline** therapy, especially in patients with **diabetes**. Dose adjustment of **insulin** or concomitant oral hypoglycemic drug may be required in **diabetes** patients [78].

##### 3.3.3.A.3] **Galactorrhea**

a) Summary

1) **Sertraline** therapy has been associated with **galactorrhea**. The probable mechanism for SSRI-induced **galactorrhea** is increased serum prolactin. This may result from direct stimulation of postsynaptic serotonin receptors in the hypothalamus or presynaptic serotonin receptor mediated inhibition of **dopamine** release [81][82].

b) **Galactorrhea** associated with **sertraline** was reported in a 37-year-old woman with a 1-year history of depression. She initially received **fluoxetine** 20 mg daily. Because intolerable nausea developed, she was switched to **sertraline** 50 mg daily. After 2 weeks, the dosage was increased to 100 mg daily. **Galactorrhea** developed approximately 5 weeks after beginning treatment. **Sertraline** was discontinued, and lactation ceased 21 days later. She was receiving no other medications; no other etiology for **galactorrhea** was identified [82]. Sixteen anecdotal cases of **galactorrhea** associated with **sertraline** have been reported during the 2 years after marketing. Elevated prolactin levels associated with **sertraline** have been reported in approximately 36 patients [81].

##### 3.3.3.A.4] **Gynecomastia**

a) **Gynecomastia** has been reported in less than 0.1% of patients receiving **sertraline** during premarketing clinical trials [13]. Breast pain and **breast enlargement** have also been reported [82].

##### 3.3.3.A.5] **Hyperglycemia**



a) **Sertraline** hydrochloride has been associated with new-onset **diabetes mellitus** and with loss of glycemic control (including both **hyperglycemia** and **hypoglycemia**) in patients with and without preexisting **diabetes**. Monitor for signs and symptoms of glucose fluctuations during **sertraline** therapy, especially in patients with **diabetes**. Dose adjustment of **insulin** or concomitant oral hypoglycemic drug may be required in **diabetes** patients [78].

b) **Hyperglycemia** was reported following the administration of **sertraline** for the treatment of depressive symptoms in a 54-year-old Caucasian woman with diet-controlled, type-II **diabetes**. Following the initiation of **sertraline** (12.5 mg/day, titrated weekly to 50 mg/day), the woman's fasting glucose levels (attained via a **glucometer**) increased from an average of 116.3 mg/dL (6.5 mmol/L) to 180.3 mg/dL (10 mmol/L). Laboratory studies revealed an increase in fasting serum glucose from an average of 115.4 mg/dL (6.4 mmol/L) 6 months before treatment to 131 mg/dL (7 mmol/L) with treatment. During **sertraline** therapy, the patient lost 4 pounds and reported a reduction in carbohydrate craving (Sansone & Sansone, 2003).

#### 3.3.3.A.6] **Hyponatremia**

a) **Hyponatremia** has been reported during treatment with SSRIs, including **sertraline**, and serotonin **norepinephrine** reuptake inhibitor (SNRI) agents. In most cases, low sodium levels appear to be the result of the syndrome of **inappropriate antidiuretic hormone secretion** (SIADH), and levels lower than 110 mmol/L have been reported. The elderly, patients on diuretics, and patients who are otherwise volume depleted may be at greater risk. Discontinuation of **sertraline** may be necessary [13].

b) The use of **sertraline** by elderly patients has been associated with cases of clinically significant **hyponatremia** [83]. **Hyponatremia** secondary to syndrome of **inappropriate antidiuretic hormone secretion** (SIADH) has also been reported following therapy. This effect has been reported with all of the SSRIs [13], but appears most frequently in patients over 65 years of age [84][85][86][87][88][89][90].

#### 3.3.3.A.7] **Hypothyroidism**

a) **Hypothyroidism** has been temporally associated with the postmarketing use of **sertraline**, although no causal relationship has been established [13].

b) Patients with thyroid disease who are also receiving treatment for depression should have thyroid function tested periodically. There are reports of small decreases in **serum thyroxine** levels and small increases in serum **thyrotropin** levels after starting treatment with **sertraline** and other antidepressants (McCowen et al, 1997).

#### 3.3.3.A.8] **Poor glycemic control**

a) **Sertraline** hydrochloride has been associated with new-onset **diabetes mellitus** and with loss of glycemic control (including both **hyperglycemia** and **hypoglycemia**) in patients with and without preexisting **diabetes**. Monitor for signs and symptoms of glucose fluctuations during **sertraline** therapy, especially in patients with **diabetes**. Dose adjustment of **insulin** or concomitant oral hypoglycemic drug may be required in **diabetes** patients [78].

#### 3.3.3.A.9] **Summary**

a) **Sertraline** use has been associated with small mean increases in total cholesterol (approximately 3%) and **triglycerides** (approximately 5%). Decreases in serum uric acid have occurred, but the clinical significance of this is unknown. Weight loss and weight gain have also been reported. **Hyponatremia** secondary to syndrome of **inappropriate antidiuretic hormone secretion** (SIADH) may occur following therapy with all of the SSRIs, including **sertraline**. Elderly patients and patients who are volume depleted, including patients taking diuretics, may be at greater risk [13].

### 3.3.3.A.10] Syndrome of inappropriate antidiuretic hormone secretion

#### a) Summary

1) **Sertraline** has been associated with syndrome of inappropriate antidiuretic hormone secretion (SIADH). The majority of cases have occurred in patients over 70 years of age. Onset occurs between 3 days and 4 months after beginning therapy [79][80].

b) Of the 25 case reports of SSRI-induced syndrome of inappropriate antidiuretic hormone secretion (SIADH) which have been published, the majority occurred in patients over 70 years of age. Based on published reports, the onset of SIADH was between 3 days and 4 months after starting therapy. Symptoms included confusion, lethargy, dizziness, fatigue, anorexia, delirium, and abdominal pain. Abnormal laboratory findings consisted of a decreased serum osmolality (median 251 (milliosmole/liter) mOsm/L; range 214 to 272 mOsm/L), decreased serum sodium concentration (median, 118 mEq/L or 118 mmol/L; range, 98 to 130 mEq/L or 98 to 130 mmol/L), and urine osmolality (median 392.5 mOsm/L; 229 to 613 mOsm/L). In all but 1 case, the SSRI was stopped, and fluids were restricted before hyponatremia resolved; 1 patient was also treated with sodium chloride 3%. Patients in their fifties generally recovered in 2 to 4 days versus patients in their eighties required up to 14 days for complete recovery. Of the 6 patients rechallenged with an SSRI, 3 developed a decrease in serum sodium consistent with SIADH, and 3 tolerated rechallenge without adverse events. Many case reports did not adequately report symptoms, laboratory results, and exclusion of other causes making it difficult to attribute SIADH to the SSRI [79].

c) Three days after starting **sertraline** 50 mg daily, a 78-year-old woman was diagnosed with the syndrome of inappropriate antidiuretic hormone (SIADH). Clinically, she was encephalopathic and had myoclonus. Her serum sodium decreased from 136 mEq/L (136 mmol/L) on day 1 to 119 mEq/L (119 mmol/L) on day 3 of **sertraline**. Urinary sodium and osmolality were 125 mEq/L (125 mmol/L) and 474 milliosmoles/kilogram (mOsm/kg), respectively, compared with a plasma osmolality of 262 mOsm/kg. Treatment consisted of: (1) stopping **sertraline**, (2) administering 200 mL of sodium chloride 3%, (3) restricting fluid intake to 1000 mL/day, and (4) initiating demeclocycline 300 mg twice daily. Encephalopathy and myoclonus improved rapidly; the serum sodium returned to 138 mEq/L (138 mmol/L) within 3 days. Other drugs and medical conditions were considered unlikely causes of the SIADH. Two other cases of SIADH induced by **sertraline** have been reported although symptoms occurred later, after 5 days and 4 months; discontinuation of **sertraline** and fluid restriction resulted in resolution of symptoms in these cases [80].

### 3.3.3.A.11] Weight gain

a) Incidence: 1% or greater [13]

b) During premarketing use of **sertraline** in clinical trials of over 4000 patients, weight gain occurred on one or more occasions in at least 1% of patients exposed to multiple doses of **sertraline** [13].

### 3.3.3.A.12] Weight loss

a) Incidence: 2% or greater [13]

b) Minimal weight loss (mean 1 to 2 pounds) occurred during controlled clinical studies with **sertraline** vs smaller changes in weight loss with placebo [13].

c) Among pediatric patients treated with **sertraline** in controlled clinical trials, weight loss was reported at an incidence of at least 2%, and occurred at a rate of at least twice that of placebo (n=281 treated with **sertraline**) [13].

d) In a pooled analysis of two 10-week placebo-controlled trials for major depressive disorder in patients 6 to 17 years of age, a difference in weight change of roughly 1 kg occurred between **sertraline**

and placebo, representing a slight weight loss for sertraline-treated patients and a slight weight gain among placebo patients. Of note, a greater percentage of sertraline-treated patients experienced a weight loss of greater than 7% of body weight compared with placebo (children: 7% vs 0%; adolescents 2% vs 1%). Following completion of these 2 trials, a subset of patients (sertraline n=99; placebo n=122) continued in a 24-week flexible-dose, open-label extension study. Placebo patients starting on sertraline experienced a mean weight loss of 0.5 kg during the first 8 weeks, a finding similar to sertraline patients in the initial trial. Following 12 weeks of sertraline therapy, patients began to gain weight compared with baseline. For subjects completing 34 weeks of sertraline therapy (n=68), weight gain was similar to that expected using data from age-adjusted peers. Regular monitoring of weight and growth is recommended in pediatric patients receiving long-term SSRI therapy [13].

### 3.3.4] Gastrointestinal Effects

#### 3.3.4.A] Sertraline Hydrochloride

##### 3.3.4.A.1] Abdominal pain

a) Incidence: 6% to 7% [13]

b) In placebo-controlled clinical trials of 5193 patients, abdominal pain was reported in a greater percentage of patients treated with sertraline compared with patients treated with placebo in certain groups: posttraumatic stress disorder (6% vs 5%), and premenstrual dysphoric disorder (PMDD) with continuous daily dosing (7% vs less than 1%). The incidence of pain reported with sertraline was equal to or less than that reported with placebo in patients with major depressive disorder, obsessive compulsive disorder, panic disorder, social anxiety disorder, and PMDD with luteal-phase dosing. All patients received between 50 and 200 mg/day of sertraline except for the PMDD populations, of which the continuous-dosing group received 50 to 150 mg/day and the luteal-phase dosing group received 50 to 100 mg/day during the luteal phase of their menstrual cycle [13].

c) Abdominal pain was the cause of therapy discontinuation in 1% of patients with social anxiety disorder (n=344) [13].

##### 3.3.4.A.2] Constipation

a) Incidence: 3% to 8% [13]

b) In placebo-controlled clinical trials of 5193 patients, constipation was reported in a greater percentage of patients treated with sertraline compared with patients treated with placebo for major depressive disorder (8% vs 6%), obsessive compulsive disorder (6% vs 4%), panic disorder (7% vs 3%), and for PMDD with luteal-phase dosing only (5% vs 3%). The incidence of constipation reported with sertraline was equal to that reported with placebo in patients with posttraumatic stress disorder (3%). All patients received between 50 and 200 mg/day of sertraline except for the PMDD populations, of which the continuous-dosing group received 50 to 150 mg/day and the luteal-phase dosing group received 50 to 100 mg/day during the luteal phase of their menstrual cycle [13].

##### 3.3.4.A.3] Diarrhea

a) Incidence: 13% to 24% [13]

b) In placebo-controlled clinical trials of 5193 patients, diarrhea/loose stools were reported in a greater percentage of patients treated with sertraline compared with patients treated with placebo for major depressive disorder (18% vs 9%), obsessive compulsive disorder (24% vs 10%), panic disorder (20% vs 9%), posttraumatic stress disorder (24% vs 15%), social anxiety disorder (21% vs 8%), premenstrual dysphoric disorder (PMDD) with continuous daily dosing (13% vs 3%), and for PMDD with luteal-phase dosing only (13% vs 7%). All patients received between 50 and 200 mg/day

of [sertraline](#) except for the PMDD populations, of which the continuous-dosing group received 50 to 150 mg/day and the luteal-phase dosing group received 50 to 100 mg/day during the luteal phase of their menstrual cycle [13].

c) Diarrhea was the cause of therapy discontinuation in 2% of patients with [major depressive disorder](#) (n=861), [obsessive compulsive disorder](#) (n=533), and [premenstrual dysphoric disorder](#) with continuous daily dosing (n=121), and in 1% of patients with [panic disorder](#) (n=430) [13].

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

##### a) General Information

1) [Sertraline](#), other SSRIs, and serotonin [norepinephrine](#) reuptake inhibitors (SNRIs) have demonstrated an increased risk of bleeding including [gastrointestinal hemorrhage](#). [Aspirin](#), [warfarin](#), and other agents that inhibit [platelets](#) or blood coagulation factors may increase this risk and should be used cautiously with [sertraline](#) therapy. Patients should be warned about the risk of using these agents together [60].

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

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

a) Sertraline-induced [bruxism](#) has occurred after exposure to daily doses ranging from 6.25 to 150 mg, with onset within the first few weeks to months [91][92]. Dose reduction from 25 mg/day to 6.25 mg/day failed to relieve symptoms in one 36-year-old woman with [atypical depression](#) and posttraumatic stress. A 73-year-old woman with longstanding anxiety disorder and depression had her 100-mg/day [sertraline](#) discontinued, with an 18-month trial of 40-mg/day oral [paroxetine](#). [Paroxetine](#) alleviated the [bruxism](#) but the patient's mood deteriorated. Replacement of [paroxetine](#) with [fluvoxamine](#) (dosage not reported) resulted in an exacerbation of tooth grinding. The addition of oral [buspirone](#) (dosage not reported) failed to alleviate her [bruxism](#) [93].

#### 3.3.4.A.6] [Increased appetite](#)

a) Incidence: 1% or greater [13]

b) During premarketing use of [sertraline](#) in clinical trials of over 4000 patients, increased appetite occurred on one or more occasions in at least 1% of patients exposed to multiple doses of [sertraline](#) [13].

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

a) Incidence: 6% to 13% [13]

b) In placebo-controlled clinical trials of 5193 patients, [dyspepsia](#) was reported in a greater percentage of patients treated with [sertraline](#) compared with patients treated with placebo for [major depressive disorder](#) (6% vs 3%), [obsessive compulsive disorder](#) (10% vs 4%), [panic disorder](#) (10% vs 8%), [social anxiety disorder](#) (13% vs 5%), [premenstrual dysphoric disorder](#) (PMDD) with continuous daily dosing (7% vs 2%), and for PMDD with luteal-phase dosing only (7% vs 3%). The incidence of [dyspepsia](#) reported with [sertraline](#) was equal to that reported with placebo in patients with [posttraumatic stress disorder](#) (6%). All patients received between 50 and 200 mg/day of [sertraline](#) except for the PMDD populations, of which the continuous-dosing group received 50 to 150 mg/day and the luteal-phase dosing group received 50 to 100 mg/day during the luteal phase of their menstrual cycle [13].

c) [Dyspepsia](#) was the cause of therapy discontinuation in 1% of patients with [panic disorder](#) (n=430) [13].

**3.3.4.A.8] Loss of appetite**

a) Incidence: 3% to 11% [13]

b) In placebo-controlled clinical trials of 5193 patients, anorexia was reported in a greater percentage of patients treated with [sertraline](#) compared with patients treated with placebo for [major depressive disorder](#) (3% vs 2%), [obsessive compulsive disorder](#) (11% vs 2%), [panic disorder](#) (7% vs 2%), [posttraumatic stress disorder](#) (8% vs 2%), [social anxiety disorder](#) (6% vs 3%), [premenstrual dysphoric disorder](#) (PMDD) with continuous daily dosing (3% vs 2%), and for PMDD with luteal-phase dosing only (5% vs 0%). All patients received between 50 and 200 mg/day of [sertraline](#) except for the PMDD populations, of which the continuous-dosing group received 50 to 150 mg/day and the luteal-phase dosing group received 50 to 100 mg/day during the luteal phase of their menstrual cycle [13].

**3.3.4.A.9] Nausea**

a) Incidence: 13% to 30% [13]

b) In placebo-controlled clinical trials of 5193 patients, nausea was reported in a greater percentage of patients treated with [sertraline](#) compared with patients treated with placebo for [major depressive disorder](#) (26% vs 12%), [obsessive compulsive disorder](#) (30% vs 11%), [panic disorder](#) (29% vs 18%), [posttraumatic stress disorder](#) (21% vs 11%), [social anxiety disorder](#) (22% vs 8%), [premenstrual dysphoric disorder](#) (PMDD) with continuous daily dosing (23% vs 9%), and for PMDD with luteal-phase dosing only (13% vs 3%). All patients received between 50 and 200 mg/day of [sertraline](#) except for the PMDD populations, of which the continuous-dosing group received 50 to 150 mg/day and the luteal-phase dosing group received 50 to 100 mg/day during the luteal phase of their menstrual cycle [13].

c) The SSRIs produce nausea and vomiting in 20% to 25% and 2% to 3% of patients, respectively. In the majority of patients, nausea gradually decreases or resolves over approximately 3 weeks. However, in others, reduction of the dose or discontinuation of the drug is required. For this group, [ondansetron](#) may facilitate continued treatment with the SSRI. The proposed mechanism for SSRI-induced nausea and vomiting is increased serotonin levels within the chemoreceptor trigger zone and area postrema in the brainstem, the primary areas within the brain associated with nausea and vomiting [95].

d) Nausea was the cause of therapy discontinuation in patients with [major depressive disorder](#) (4%, n=861), [obsessive compulsive disorder](#) (3%, n=533), [panic disorder](#) (3%, n=430), [posttraumatic stress disorder](#) (2%, n=374), [social anxiety disorder](#) (2%, n=344), [premenstrual dysphoric disorder](#) with continuous daily dosing (2%, n=121), and [premenstrual dysphoric disorder](#) with luteal-phase dosing (1%, n=136) [13].

**3.3.4.A.10] Nausea and vomiting**

a) Summary

1) During placebo-controlled clinical trials, nausea and vomiting were reported in adults with [sertraline](#) therapy at an incidence greater than 2% [13]. Mild nausea and vomiting were noted 4 to 6 hours after single doses of 100 mg in one study, and were reported as a frequent side effect in another [94][74].

b) Incidence: 2% to 30% [95][13]

c) The SSRIs produce nausea and vomiting in 20% to 25% and 2% to 3% of patients, respectively. In the majority of patients, nausea gradually decreases or resolves over approximately 3 weeks. However, in others, reduction of the dose or discontinuation of the drug is required. For this group, [ondansetron](#) may facilitate continued treatment with the SSRI. The proposed mechanism for SSRI-induced nausea

and vomiting is increased serotonin levels within the chemoreceptor trigger zone and area postrema in the brainstem, the primary areas within the brain associated with nausea and vomiting [95].

d) In placebo-controlled clinical trials of 5193 patients, nausea was reported in a greater percentage of patients treated with [sertraline](#) compared with patients treated with placebo for [major depressive disorder](#) (26% vs 12%), [obsessive compulsive disorder](#) (30% vs 11%), [panic disorder](#) (29% vs 18%), [posttraumatic stress disorder](#) (21% vs 11%), [social anxiety disorder](#) (22% vs 8%), [premenstrual dysphoric disorder](#) (PMDD) with continuous daily dosing (23% vs 9%), and for PMDD with luteal-phase dosing only (13% vs 3%). All patients received between 50 and 200 mg/day of [sertraline](#) except for the PMDD populations, of which the continuous-dosing group received 50 to 150 mg/day and the luteal-phase dosing group received 50 to 100 mg/day during the luteal phase of their menstrual cycle [13].

e) Nausea was the cause of therapy discontinuation in patients with [major depressive disorder](#) (4%, n=861), [obsessive compulsive disorder](#) (3%, n=533), [panic disorder](#) (3%, n=430), [posttraumatic stress disorder](#) (2%, n=374), [social anxiety disorder](#) (2%, n=344), [premenstrual dysphoric disorder](#) with continuous daily dosing (2%, n=121), and [premenstrual dysphoric disorder](#) with luteal-phase dosing (1%, n=136) [13].

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

a) [Pancreatitis](#) has been temporally associated with the postmarketing use of [sertraline](#), although no causal relationship has been established [13].

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

a) Incidence: 6% to 16% [13]

b) Several studies have reported dry mouth as an occasional adverse effect of [sertraline](#) in therapeutic doses [65][74][94], while the manufacturer reports this effect as common [13].

c) In placebo-controlled clinical trials of 5193 patients, dry mouth was reported in a greater percentage of patients treated with [sertraline](#) compared with patients treated with placebo for [major depressive disorder](#) (16% vs 9%), [obsessive compulsive disorder](#) (14% vs 9%), [panic disorder](#) (15% vs 10%), [posttraumatic stress disorder](#) (11% vs 6%), [social anxiety disorder](#) (12% vs 4%), [premenstrual dysphoric disorder](#) (PMDD) with continuous daily dosing (6% vs 3%), and for PMDD with luteal-phase dosing only (10% vs 3%). All patients received between 50 and 200 mg/day of [sertraline](#) except for the PMDD populations, of which the continuous-dosing group received 50 to 150 mg/day and the luteal-phase dosing group received 50 to 100 mg/day during the luteal phase of their menstrual cycle [13].

d) Dry mouth was the cause of therapy discontinuation in 1% of patients with [major depressive disorder](#) (n=861) [13].

### 3.3.5] Hematologic Effects

#### 3.3.5.A] [Sertraline Hydrochloride](#)

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

a) [Agranulocytosis](#) has been reported with [sertraline](#) therapy in postmarketing surveillance, although a causal relationship has not been established [13].

##### 3.3.5.A.2] [Aplastic anemia](#)

a) [Aplastic anemia](#) and [pancytopenia](#) have been reported with [sertraline](#) therapy in postmarketing surveillance, although a causal relationship has not been established[13].



### 3.3.5.A.3] Hemorrhage, Abnormal

a) Incidence: less than 0.1% [61]

b) General Information

1) Increased risk of [gastrointestinal bleeding](#) due to interference with serotonin reuptake [60].

2) Bleeding events include ecchymoses, [hematomas](#), [epistaxis](#), [petechiae](#), [gastrointestinal bleeding](#), and life-threatening hemorrhages [60].

3) Risk may be increased by the concomitant use of drugs that affect coagulation (eg, NSAIDs, [aspirin](#), [warfarin](#)) [60].

4) Rare occurrences (incidence less than 0.1%) of bruising, ecchymoses, [epistaxis](#), prolonged bleeding time and [rectal bleeding](#) have been associated with [sertraline](#) therapy. The majority of cases have been reported in patients taking [fluoxetine](#), but case reports are also available for [paroxetine](#), [sertraline](#), and [fluvoxamine](#) [61].

c) Prevention and Management

1) Use caution when coadministering drugs that affect coagulation with [sertraline](#) [60].

2) Consider discontinuation of [sertraline](#) 2 weeks prior to surgery (particularly, breast or orthopedic surgery) in patients in a stable phase of depression that are at a high risk of bleeding. Gradual tapering of treatment is recommended to minimize discontinuation syndrome. Restart therapy as soon as possible when there is no longer perioperative bleeding risk [62].

3) Use of an antidepressant agent that is less likely to or does not increase the clinical risk of bleeding (eg, [bupropion](#), [mirtazapine](#)) may be considered [62].

4) Take into account the type of surgery, type of antidepressant, risk of suicide, severity of depression, risk factors for bleeding, and potential for discontinuation syndrome when determining management plan [62]

d) Adult Clinical Trials

1) [Facelift surgery](#), [CABG](#) surgery (oral route): No significant relationship between serotonergic antidepressant use and a risk of perioperative bleeding in 4 studies (review article) [62]

2) Orthopedic, spinal, breast, or [CABG](#) surgery (oral route): Some increased risk of bleeding associated with serotonergic antidepressant use in 6 studies; clinical significance unclear (review article) [62]

### 3.3.5.A.4] Pancytopenia

a) [Pancytopenia](#) and [aplastic anemia](#) have been reported with [sertraline](#) therapy in postmarketing surveillance, although a causal relationship has not been established[13].

### 3.3.5.A.5] Purpura

a) Incidence: 2% or greater (pediatric) [13]

b) There have been several reports of [purpura](#) in patients taking [sertraline](#), although a causal relationship has not been established [13].

c) Among pediatric patients treated with [sertraline](#) in controlled clinical trials, [purpura](#) was reported at an incidence of at least 2% and occurred at a rate of at least twice that of placebo (n=281 treated with [sertraline](#)) [13].

### 3.3.6] Hepatic Effects

#### 3.3.6.A] [Sertraline](#) Hydrochloride

##### 3.3.6.A.1] Increased liver enzymes

a) Incidence: 0.8% [13]

b) Asymptomatic elevations in serum transaminases have been reported infrequently (0.8%) within the first 9 weeks of [sertraline](#) treatment and have promptly diminished upon discontinuation of the drug [13].

##### 3.3.6.A.2] [Liver failure](#)

a) In postmarketing evaluation, [liver failure](#) has been temporally associated with the use of [sertraline](#), although no causal relationship has been established [13].

### 3.3.7] Immunologic Effects

#### 3.3.7.A] [Sertraline](#) Hydrochloride

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

a) In postmarketing surveillance, [anaphylactoid reactions](#) have been associated with use of [sertraline](#), although a causal relationship has not been established [13].

##### 3.3.7.A.2] [Angioedema](#)

a) In postmarketing surveillance, [angioedema](#) has been associated with use of [sertraline](#), although a causal relationship has not been established [13].

##### 3.3.7.A.3] [Lupus erythematosus](#)

a) Lupus-like syndrome has been reported with [sertraline](#) therapy in postmarketing surveillance, although a causal relationship has not been established [106].

### 3.3.8] Musculoskeletal Effects

#### 3.3.8.A] [Sertraline](#) Hydrochloride

##### 3.3.8.A.1] [Arthralgia](#)

a) Incidence: 0.1% to 1% [103]

b) Arthralgia was reported in 0.1% to 1% of over 4000 adult patients exposed to multiple doses of [sertraline](#) in clinical trials; a causal relationship cannot be determined [103].

##### 3.3.8.A.2] [Fracture of bone](#)

a) In a case-control study including fracture cases (n=124,655) during the year 2000 and age- and gender-matched controls (n=373,962), there was an increased risk of any fracture in participants who were using an average standard daily dose of [sertraline](#) (adjusted odds ratio (OR), 1.25; 95% CI, 1.16 to 1.34) compared with those who were not exposed to [sertraline](#). [Sertraline](#) use was associated with



an increased risk of hip fracture (adjusted OR, 1.76; 95% CI, 1.52 to 2.03), [forearm fracture](#) (adjusted OR, 1.35; 95% CI, 1.13 to 1.62), and [spine fracture](#) (adjusted OR, 1.74; 95% CI, 1.26 to 2.41) [104].

**b)** In a population-based, randomly selected, prospective cohort study adjusted for potential covariates, an increased risk of fragility fracture was reported at the 5-year follow-up in patients 50 years of age or older who used daily SSRIs (n=137; mean age of 65.1 years), including [sertraline](#), compared with those who did not use an SSRI (n=4871; mean age of 65.7 years). Daily SSRI use was associated with a significant 2.1-fold increased risk of fragility fracture (95% CI, 1.3 to 3.4). Daily dose of SSRI use was associated with a 1.5-fold increased risk of fragility fracture (95% CI, 1.1 to 2.1). Daily SSRI users who were recurrent (ie, treated with SSRIs at baseline and at 5-year follow-up) had a significant 2.1-fold increased risk of fragility fracture (95% CI, 1.1 to 4). Fractures were reported at the following sites: forearm (40%), ankle and foot (21%), hip (13%), rib (13%), femur (9%), and back (4%). None were reported at the skull, toes, or fingers [105].

### 3.3.8.A.3] Fracture of bone, Nonvertebral

**a)** In a prospective, population-based, cohort study (n=7983) with a mean follow-up of 8.4 years, there was an increased risk of nonvertebral fracture in adult participants older than 55 years of age (mean age of 77.5 years) who were currently using an SSRI ([citalopram](#), [escitalopram](#), [fluoxetine](#), [fluvoxamine](#), [paroxetine](#), or [sertraline](#)) compared with those who were not exposed to antidepressants. Current SSRI use was associated with an increased risk of nonvertebral fracture (adjusted hazard ratio (HR), 2.35; 95% CI, 1.32 to 4.18) compared with no antidepressant use. Current SSRI use was also associated with an increased risk of nonvertebral fracture (adjusted HR, 2.07; 95% CI, 1.23 to 3.5) compared with past antidepressant use (n=1217). In addition, duration of SSRI use showed a 9% increase in fracture risk per extra month on an SSRI (95% CI, 3% to 16%; p for trend=0.004). Fractures of the hip (most frequent), wrist, humerus, and pelvis were reported [102].

### 3.3.8.A.4] Muscle weakness

**a)** Incidence: 0.1% to 1% [103]

**b)** Muscle weakness was reported in 0.1% to 1% of over 4000 adult patients exposed to multiple doses of [sertraline](#) in clinical trials; a causal relationship cannot be determined [103].

### 3.3.8.A.5] Myalgia

**a)** Incidence: 1% or greater [103]

**b)** Myalgia was reported in at least 1% of over 4000 adult patients exposed to multiple doses of [sertraline](#) in clinical trials; a causal relationship cannot be determined [103].

### 3.3.8.A.6] Rhabdomyolysis

**a)** A 71-year-old woman developed [rhabdomyolysis](#) within 2 months after starting [sertraline](#) 50 mg/day for depression. The patient's medical history included [vascular dementia](#), depression, [hypertension](#), [heart failure](#), [cardiac pacemaker](#) implantation, and negative history of nicotine or alcohol use. Medications included a 2-month history of [sertraline](#) 50 mg/day for depression, amisulpride 50 mg, [diazepam](#) 2 mg/day, nicergoline 30 mg/day, [amlodipine](#) 5 mg/day, [aspirin](#) 100 mg/day, candesartan 16 mg/day, and [atenolol](#) 25 mg/day. Within 2 months after the initiation of [sertraline](#) 50 mg/day, the patient presented with muscular weakness and reduced mobilization. The following week, the patient was admitted to the cardiac unit to undergo a scheduled pacemaker replacement, and the laboratory analysis revealed markedly elevated serum [creatinine kinase](#) (CK) of 7952 international units/L (normal, 180 international units/L or less), AST of 362 international units/L (normal, 38 international units/L or less), [LDH](#) of 1021 international units/L (normal, 240 to 480

international units/L) and myoglobin of 2322 units/L (normal, 19 to 72 units/L), and BUN of 73 mg/dL or 26.1 mmol/L (normal, 10 to 50 mg/dL or 4 to 18 mmol/L). The patient was diagnosed with iatrogenic [rhabdomyolysis](#). Two days after admission, amisulpride and [sertraline](#) were discontinued, and the patient was started on [rehydration therapy](#). Six days after admission, she was discharged from the hospital. Upon discharge, laboratory levels were improved but remained elevated (CK, 839 international units/L; AST, 94 international units/L; [LDH](#), 804 international units/L; myoglobin, 91 units/L; and BUN, 54 mg/dL or 19.3 mmol/L). One month later, CK, AST, and myoglobin levels normalized. Upon rechallenged with [sertraline](#) 50 mg/day, the patient experienced increase in CK (1327 international units/L), AST (52 international units/L), and myoglobin levels (324 units/L). Therefore, [sertraline](#) was discontinued. The laboratory values normalized within a week. The Naranjo probability scale indicated a probable causal relationship between the [sertraline](#) treatment and the onset of [rhabdomyolysis](#) [101].

### 3.3.8.A.7] Summary

a) [Sertraline](#) has been frequently associated with myalgia, and infrequently associated with arthralgia and muscle weakness [103]. [Sertraline](#) use was associated with an increased risk of hip, forearm, and [spine fracture](#) in a case-controlled study [104]. An increased risk of fragility fracture has been reported in a prospective cohort study of SSRIs, including [sertraline](#) [105]. An increased risk of nonvertebral fracture has been reported in a prospective cohort study of SSRI use, including [paroxetine](#), in adult participants older than 55 years of age [102].

## 3.3.9] Neurologic Effects

### 3.3.9.A] [Sertraline](#) Hydrochloride

#### 3.3.9.A.1] Asthenia

- a) Incidence: 1% or greater [13]
- b) During premarketing use of [sertraline](#) in clinical trials of over 4000 patients, asthenia occurred on one or more occasions in at least 1% of patients exposed to multiple doses of [sertraline](#) [13].

#### 3.3.9.A.2] CVA - cerebrovascular accident due to [cerebral artery occlusion](#)

- a) [Cerebrovascular spasm](#) (including reversible cerebrovascular constriction syndrome and Call-Fleming syndrome) has been reported with [sertraline](#) therapy in postmarketing surveillance, although a causal relationship has not been established [13].

#### 3.3.9.A.3] Dizziness

- a) Incidence: 6% to 17% [13]
- b) Dizziness is one the most frequently reported adverse effects of [sertraline](#). In placebo-controlled clinical trials of 5193 patients, dizziness was reported in a greater percentage of patients treated with [sertraline](#) compared with patients treated with placebo for [major depressive disorder](#) (12% vs 7%), [obsessive compulsive disorder](#) (17% vs 9%), [posttraumatic stress disorder](#) (8% vs 5%), [social anxiety disorder](#) (14% vs 6%), [premenstrual dysphoric disorder](#) (PMDD) with continuous daily dosing (6% vs 3%), and for PMDD with luteal-phase dosing only (7% vs 5%). Patients with [panic disorder](#) taking [sertraline](#) experienced dizziness at the same rate as placebo (10%). All patients received between 50 and 200 mg/day of [sertraline](#) except for the PMDD populations, of which the continuous-dosing group received 50 to 150 mg/day and the luteal-phase dosing group received 50 to 100 mg/day during the luteal phase of their menstrual cycle [13].

c) Dizziness was the cause of therapy discontinuation in 1% of patients with [obsessive compulsive disorder](#) (n=533) [13].

### 3.3.9.A.4] [Dystonia](#), Mandibular

#### a) Summary

1) Mandibular [dystonia](#) has been noted in several case reports during therapeutic [sertraline](#) use. Withdrawal of therapy and/or treatment with [diphenhydramine](#) has been helpful in symptom abatement. Patients on multiple drug therapies should be carefully monitored for interactions or potentiation (Stanislav & Childs, 1999)[69][70][71].

b) "Sneering" movements developed in the upper mouth area 7.5 months after [sertraline](#) was initiated for depression in a patient with [traumatic brain injury](#). The patient described this as a painful pulling sensation of the upper lip. Other [dyskinesias](#) or tics were not identified. Symptoms resolved 3 days after [sertraline](#) was stopped. [Sertraline](#) was restarted 10 days later with reappearance of the sneering movement 24 hours later. Two days after stopping [sertraline](#), the abnormal movement resolved completely. All other medications were continued during and after identification of this movement disorder (Stanislav & Childs, 1999).

c) A case of mandibular [dystonia](#) was reported 2 days after the addition of [metoclopramide](#) 10 mg 3 times daily in a 14-year-old female who had been treated for 2 months with [sertraline](#) 100 mg/day [69].

d) In a case report, [dystonia](#) was reported in a 24-year-old man treated for [posttraumatic stress disorder](#). The patient started on [trazodone](#) 25 mg at bedtime for 2 weeks and then this dose was increased to 50 mg. Three days after starting the higher dosages, he presented to the emergency department with his mouth immobile in an open position, complaining of jaw stiffness and feeling as if his face was "frozen." The symptoms were relieved by administration of a single 50-mg dose of IV [diphenhydramine](#). Because the same adverse effect was noted over a year after he began treatment with [sertraline](#) 25 mg, which was increased to 75 mg daily, the authors hypothesized that the mechanism causing the [dystonia](#) was common to both drugs, possibly associated with enhancement of serotonergic neurotransmission that impairs nigrostriatal [dopamine](#) activity [70].

e) A 22-year-old woman developed mandibular [dystonia](#) characterized by periauricular pain, jaw tightness, and teeth clenching and grinding after the second dose of [sertraline](#) 50 mg daily. Symptoms were relieved by [diphenhydramine](#) 50 mg. A third dose of [sertraline](#) was administered with similar results; [benztropine](#) 2 mg relieved symptoms. This patient was also taking [metoclopramide](#) 15 mg 4 times daily for [gastroesophageal reflux](#) which had caused no adverse effects over 6 months. A possible explanation for this reaction may be an additive effect of [sertraline](#) and [metoclopramide](#) resulting in [dystonia](#). This case is intended to alert clinicians that patients receiving this combination may be at increased risk of [dystonia](#) [71].

f) Torticollis and jaw stiffness, responsive to treatment with [diphenhydramine](#), and [akathisia](#) have been reported [72].

### 3.3.9.A.5] Extrapyramidal sign

#### a) Summary

1) Extrapyramidal reactions (EPRs) including acute dystonic reactions, [neuroleptic malignant syndrome](#), [akathisia](#), and [dyskinesias](#) were reported with 1 or more SSRIs. The majority of case reports involved [fluoxetine](#); however, all of the SSRIs were implicated in at least 1 EPR [67][68].

b) Extrapyramidal reactions occurred more frequently in women (about 75%) possibly due to more frequent use of SSRIs. In many, but not all, case reports, the dose of the SSRI was increased to the maximum recommended dose within 7 days or near maximum doses were used. The majority of

reactions occurred within the first week or during the second to fourth week of treatment. Possible mechanisms by which SSRIs cause extrapyramidal reactions include: (1) Central serotonergic activity which inhibits dopaminergic activity resulting in clinically significant effects; and (2) Concurrent use of an SSRI and antipsychotic may cause EPRs by a pharmacokinetic interaction, a pharmacodynamic interaction, or a combination of the two [67].

**c)** The majority of extrapyramidal reactions (EPRs) occur within the first few days to first month of treatment. Therefore, careful monitoring for EPRs is recommended weekly during the first 4 weeks of treatment with SSRIs and periodically thereafter. EPRs generally resolve within a few days after reducing the dose or stopping the SSRI [67][68]. In a limited number of case reports, [propranolol](#) and/or benzodiazepines were used to treat [akathisia](#); the dose of [propranolol](#) ranged from 40 to 90 mg daily, and the dose of [clonazepam](#) was 1.5 mg daily [68]. In single case reports, dystonic reactions responded to an unspecified dose of IM trihexyphenidyl or [diphenhydramine](#) 50 mg. [Parkinsonism](#) characterized by increasing rigidity and tremor frequently occurred with high doses of the SSRI or during concomitant treatment with a neuroleptic agent. In all cases, symptoms disappeared after reducing the dose or stopping the SSRI. In contrast to neuroleptic-induced [dyskinesias](#), SSRI-induced [dyskinesias](#) resolve spontaneously over days to weeks after the SSRI is stopped [68].

### 3.3.9.A.6] Headache

**a)** Incidence: 25% [13]

**b)** Headache has been reported in 25% of patients receiving [sertraline](#) (n=2799) in placebo-controlled clinical trials compared with 23% of placebo-treated patients (n=2394) [13].

### 3.3.9.A.7] Hyperactive behavior

**a)** Incidence: 2% or greater [13]

**b)** Among pediatric patients treated with [sertraline](#) in controlled clinical trials, hyperkinesia was reported at an incidence of at least 2% and occurred at a rate of at least twice that of placebo (n=281 treated with [sertraline](#)) [13].

### 3.3.9.A.8] Impaired psychomotor performance

**a)** Summary

**1)** In controlled studies, the manufacturer reported that [sertraline](#) did not cause sedative effects and did not interfere with psychomotor performance [13]; however, subjective drowsiness was reported with [sertraline](#) in a study testing psychomotor function, although the impairment was less than that of [amitriptyline](#) [74]. In a retrospective chart review, nursing home patients treated with [fluoxetine](#) and other SSRIs, including [paroxetine](#) and [sertraline](#), were also found to have an increased risk of falls compared with patients who were not on antidepressants [75].

**b)** A retrospective chart review of 2428 nursing home residents treated with antidepressants assessed the incidence of falls before and after the initiation of antidepressant therapy. Results were then compared with those not treated (n=847). Antidepressant treatment included tricyclic antidepressants (TCAs; n=665), SSRIs (n=612), and [trazodone](#) (n=304). The rate of falls for treated patients was higher than that for patients who were not treated, both before and after the initiation of antidepressant therapy. This suggests that nursing home patients with depression or related conditions are at a greater risk of falls than those without such conditions. Patients on TCAs had the highest rate of falls, with an adjusted rate ratio of 2 (95% CI, 1.8 to 2.2). The SSRIs had a adjusted rate ratio of 1.8 (95% CI, 1.6 to 2, p=0.001) and [trazodone](#) had a ratio of 1.2 (95% CI, 1 to 1.4, p less than 0.001). No significant differences in incidence were seen among medications of the same class. It

was noted, however, that patients receiving a dose of 20 mg daily of [fluoxetine](#), or an equivalent dose of another SSRI, had a statistically significant increase in the incidence of falls than those receiving lower doses [75].

c) The acute effects of single doses of [sertraline](#) 100 mg, [amitriptyline](#) 50 mg, and placebo on psychomotor performance were evaluated in 12 subjects over 50 years of age in a double-blind, placebo-controlled crossover study. While performance was clearly impaired by [amitriptyline](#), [sertraline](#) caused no significant impairment. In addition, [sertraline](#) slightly improved objective measures of alertness. Although subjective drowsiness was reported with both drugs, the effect was less with [sertraline](#) [74].

### 3.3.9.A.9] Insomnia

a) Incidence: 12% to 28% [13]

b) Insomnia is one of the most frequently reported adverse effects of [sertraline](#). In placebo-controlled clinical trials of 5193 patients, insomnia was reported in a greater percentage of patients treated with [sertraline](#) compared with patients treated with placebo for [major depressive disorder](#) (16% vs 9%), [obsessive compulsive disorder](#) (28% vs 12%), [panic disorder](#) (25% vs 18%), [posttraumatic stress disorder](#) (20% vs 11%), [social anxiety disorder](#) (25% vs 10%), [premenstrual dysphoric disorder](#) (PMDD) with continuous daily dosing (17% vs 11%), and for PMDD with luteal-phase dosing only (12% vs 10%). All patients received between 50 and 200 mg/day of [sertraline](#) except for the PMDD populations, of which the continuous-dosing group received 50 to 150 mg/day and the luteal-phase dosing group received 50 to 100 mg/day during the luteal phase of their menstrual cycle [13].

c) Insomnia was the cause of therapy discontinuation in patients with [major depressive disorder](#) (1%, n=861), [obsessive compulsive disorder](#) (3%, n=533), [panic disorder](#) (2%, n=430), [social anxiety disorder](#) (3%, n=344), and [premenstrual dysphoric disorder](#) with luteal-phase dosing (1%, n=136) [13].

### 3.3.9.A.10] Paresthesia

a) Incidence: 2% [13]

b) During premarketing use of [sertraline](#) in clinical trials, paresthesia occurred in 2% of patients receiving [sertraline](#) compared with 1% of patients receiving placebo [13].

### 3.3.9.A.11] Parkinsonism

a) Two weeks after the dose of [sertraline](#) was increased to 150 mg daily, a 90-year-old man developed [parkinsonism](#) characterized by a pill-roll tremor, masked facies, bradykinesia, and festinating gait; he fell twice. The dose of [sertraline](#) was rapidly tapered to 50 mg/day, and within 2 weeks, all parkinsonian symptoms completely resolved. Before starting [sertraline](#), mental and neurologic examination was normal. The only other medical conditions were sinus node degeneration treated with a pacemaker, [cervical spondylosis](#), and [hypertension](#) treated with [furosemide](#) and [enalapril](#). In this case, other medical conditions and medications were not likely the cause of his [parkinsonism](#); therefore, the authors attribute the reaction to [sertraline](#), although rechallenge with the higher dose was not performed [73].

### 3.3.9.A.12] Restless legs syndrome

a) In a prospective, naturalistic study of patients (median age, 46 years; range, 18 to 87 years) treated with antidepressants, 24 of 271 (9%) subjects experienced new-onset [restless leg syndrome](#) (RLS) or worsening of preexisting RLS as a side effect related to treatment. Antidepressants included [fluoxetine](#), [paroxetine](#), [citalopram](#), [sertraline](#), [escitalopram](#), [venlafaxine](#), [duloxetine](#), [reboxetine](#), and [mirtazapine](#). [Mirtazapine](#) led to a marked decline of RLS in 28% of subjects compared with [reboxetine](#).



which had none. The other antidepressants showed RLS symptoms (newly occurred or deteriorated) at the rate of 5% to 10%. Subjects stated symptoms occurred early in treatment (median of 2.5 days, range 1 to 23 days) [66].

### 3.3.9.A.13] Seizure

a) Incidence: rare [13]

b) Seizure was reported in 4 out of approximately 1800 patients (220 patients less than 18 years of age) receiving [sertraline](#) for [obsessive-compulsive disorder](#) during premarketing trials. Three patients experiencing a seizure were adolescents, 2 with a history of seizures and 1 with a family history of seizure disorder, none of whom were on concomitant seizure medication. No seizures were observed in the approximately 3000 patients receiving [sertraline](#) for [major depressive disorder](#). Patients with seizure disorder were excluded from premarketing trials. [Sertraline](#) should be prescribed with caution in patients with seizure disorder [13].

c) A 34-year-old woman had a severe tonic-clonic seizure when her [sertraline](#) dose was increased from 150 mg to 200 mg per day for the treatment of depression. Initial [CT head scan](#) was unremarkable; however, a repeat EEG showed marked abnormalities which were consistent with a postictal disturbance rather than [epilepsy](#). [Sertraline](#) was switched to [citalopram](#), and [carbamazepine](#) was initiated. She remained seizure free. This patient had no predisposing risk factors for seizures, such as previous seizures or sedative or alcohol abuse. For most antidepressants, the risk of seizure increases with dose as was the case with this patient (Saraf & Schrader, 1999).

### 3.3.9.A.14] Sleep walking disorder

a) A 34-year-old HIV-positive woman developed [somnambulism](#) while being treated with [paroxetine](#), and later with [sertraline](#), for anxiety and depression. The initial 10-mg daily dose of [paroxetine](#) was gradually increased over 2 weeks to 20 mg daily. Three days after achieving 20 mg/day, the woman began to sleepwalk up to 3 times per night, according to witnesses. The [somnambulism](#) disappeared completely 1 week after the daily dose was reduced to 10 mg. However, at 10 mg/day, she had a [relapse](#) of depression. Upon again increasing the dose to 20 mg/day, the sleepwalking reappeared. [Paroxetine](#) was discontinued and [sertraline](#) 50 mg/day was substituted. Four days after the [sertraline](#) dose was increased to 100 mg/day, she again began to sleepwalk. Her symptoms of depression and anxiety improved at that dose. She therefore continued [sertraline](#) 100 mg/day despite continuing [somnambulism](#) [76].

### 3.3.9.A.15] Somnolence

a) Incidence: 2% to 15% [13]

b) Somnolence is one of the most frequently reported adverse effects of [sertraline](#). In placebo-controlled clinical trials of 5193 patients, somnolence was reported in a greater percentage of patients treated with [sertraline](#) compared with patients treated with placebo for [major depressive disorder](#) (13% vs 6%), [obsessive compulsive disorder](#) (15% vs 8%), [panic disorder](#) (15% vs 9%), [posttraumatic stress disorder](#) (13% vs 9%), [social anxiety disorder](#) (9% vs 6%), [premenstrual dysphoric disorder](#) (PMDD) with continuous daily dosing (7% vs less than 1%), and for PMDD with luteal-phase dosing only (2% vs 0%). All patients received between 50 and 200 mg/day of [sertraline](#) except for the PMDD populations, of which the continuous-dosing group received 50 to 150 mg/day and the luteal-phase dosing group received 50 to 100 mg/day during the luteal phase of their menstrual cycle [13].

c) Somnolence was the cause of therapy discontinuation in patients with [major depressive disorder](#) (1%, n=861), [obsessive compulsive disorder](#) (2%, n=533), and [panic disorder](#) (2%, n=430) [13].

d) Increases in objective measurements of alertness were observed with [sertraline](#) in doses of 50, 75, and 100 mg in a double-blind, placebo-controlled study. Cognitive function tests (critical flicker

fusion and choice reaction time tests) were performed on 10 patients after single doses. Measurement parameters were significantly improved compared with placebo from 3 to 7.5 hours post-dosing. However, subjective drowsiness was reported with these doses [77].

### 3.3.9.A.16] Tremor

a) Incidence: 5% to 11% [13]

b) Tremor is one of the most frequently reported adverse effects of [sertraline](#). In placebo-controlled clinical trials of 5193 patients, tremor was reported in a greater percentage of patients treated with [sertraline](#) compared with patients treated with placebo for [major depressive disorder](#) (11% vs 3%), [obsessive compulsive disorder](#) (8% vs 1%), [panic disorder](#) (5% vs 1%), [posttraumatic stress disorder](#) (5% vs 1%), and for [social anxiety disorder](#) (9% vs 3%). Tremor was observed in patients with [premenstrual dysphoric disorder](#) (PMDD) at incidences of 2% or less, and did not occur more often than with placebo. All patients received between 50 and 200 mg/day of [sertraline](#) except for the PMDD populations, of which the continuous-dosing group received 50 to 150 mg/day and the luteal-phase dosing group received 50 to 100 mg/day during the luteal phase of their menstrual cycle [13].

c) Tremor was the cause of therapy discontinuation in 2% of patients with [major depressive disorder](#) (n=861) [13].

## 3.3.10] Ophthalmic Effects

### 3.3.10.A] [Sertraline](#) Hydrochloride

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

a) General Information

1) Angle-closure attack has been reported with [sertraline](#) administration due to the mydriatic action of the drug [60].

2) Increased risk in patients with anatomically narrow angles who have not had a patent [iridectomy](#) [60].

b) Adult Case Reports

1) [Acute angle-closure glaucoma](#) was diagnosed within 5 days of [sertraline](#) 50 mg/day initiation in a 64-year-old woman. Ocular pain and blurred vision in the right eye began within hours of the first dose and the patient sought medical attention 4 days later. Urgent bilateral [iridectomy](#) and topical use of steroid and antiglaucoma agents, tapered over one month, returned intraocular pressure to normal and visual acuity to patient's baseline [96]

#### 3.3.10.A.2] Optic [neuritis](#)

a) Postmarketing

1) Has been temporally associated with use of [sertraline](#), although no causal relationship has been established [13]

#### 3.3.10.A.3] Raised intraocular pressure

a) General Information

1) Increased intraocular pressure and [angle-closure glaucoma](#) have occurred with [sertraline](#) administration due to the mydriatic action of the drug [13].

- 2)) Increased risk in patients with a history of [glaucoma](#) [13].

### 3.3.11] Otic Effects

#### 3.3.11.A] [Sertraline](#) Hydrochloride

##### 3.3.11.A.1] Tinnitus

- a)) Incidence: 1% or greater [13]  
b)) During premarketing use of [sertraline](#) in clinical trials of over 4000 patients, tinnitus occurred on one or more occasions in at least 1% of patients exposed to multiple doses of [sertraline](#) [13].

### 3.3.12] Psychiatric Effects

#### 3.3.12.A] [Sertraline](#) Hydrochloride

##### 3.3.12.A.1] Aggressive behavior

- a)) Incidence: Pediatric, 2% or greater [13]  
b)) Pediatric Clinical Trials
- 1)) Various indications (oral route): Significantly increased risk of aggressive behavior by 179% with antidepressant use ([duloxetine](#), [fluoxetine](#), [paroxetine](#), [sertraline](#), or [venlafaxine](#)) in a systematic review and meta-analysis of clinical study reports (11 trials in 1231 children and adolescents) [108].
- 2)) Various indications (oral route): 2% and occurred at a rate of at least twice that of placebo [13]

##### 3.3.12.A.2] Agitation

- a)) In placebo-controlled clinical trials of 5193 patients, agitation was reported in a greater percentage of patients treated with [sertraline](#) compared with patients treated with placebo for [major depressive disorder](#) (6% vs 4%), [obsessive compulsive disorder](#) (6% vs 3%), [panic disorder](#) (6% vs 2%), [social anxiety disorder](#) (4% vs 2%), [premenstrual dysphoric disorder](#) (PMDD) with continuous daily dosing (2% vs less than 1%), and for PMDD with luteal-phase dosing only (1% vs 0%). The incidence of agitation reported with [sertraline](#) was equal to that reported with placebo in patients with [posttraumatic stress disorder](#) (5%). All patients received between 50 and 200 mg/day of [sertraline](#) except for the PMDD populations, of which the continuous-dosing group received 50 to 150 mg/day and the luteal-phase dosing group received 50 to 100 mg/day during the luteal phase of their menstrual cycle [13].
- b)) Agitation was the cause of therapy discontinuation in 1% and 2% of patients with [major depressive disorder](#) (n=861) and [panic disorder](#) (n=430), respectively, but was not a cause for discontinuation in patients with [obsessive compulsive disorder](#), [posttraumatic stress disorder](#), [social anxiety disorder](#), and [premenstrual dysphoric disorder](#) [13].

##### 3.3.12.A.3] Depression, Exacerbation

- a)) While evidence exists from placebo-controlled, maintenance trials in adults with depression to substantiate a delay in the recurrence of depression with antidepressant use, clinical worsening of depression has been reported in patients receiving antidepressant therapy, particularly during the initial few months of treatment and during dose adjustments. It may persist until significant remission



occurs. All patients treated with antidepressants for any indication should be monitored for signs of clinical worsening [13].

**b)** 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 [111].

#### **3.3.12.A.4] Hallucinations**

**a)** Complex, colorful visual hallucinations have been reported less than 3 weeks after initiation of [sertraline](#) therapy in a 38-year-old man. Hallucinations were present daily for 30 to 40 seconds after awakening and resolved following discontinuation of [sertraline](#) [107].

#### **3.3.12.A.5] Hypomania**

**a)** Incidence: rare [13]

**b)** During clinical trials, [hypomania](#) or mania occurred in approximately 0.4% of sertraline-treated patients [13].

**c)** Two cases of [hypomania](#) were reported; one occurred after 5 weeks of [sertraline](#) 200 mg/day and one after 100 mg/day for 9 weeks. In both cases, symptoms resolved upon discontinuation of [sertraline](#) and treatment with short-term [clonazepam](#) or [lithium](#) [109].

#### **3.3.12.A.6] Mania**

**a)** Incidence: rare [13]

**b)** Mania or [hypomania](#) occurred in about 0.4% of patients during the premarketing use of [sertraline](#) [13].

#### **3.3.12.A.7] Psychotic disorder**

**a)** In postmarketing evaluation, [psychosis](#) has been temporally associated with use of [sertraline](#), although a causal relationship has not been established [13].

#### **3.3.12.A.8] Suicidal thoughts**

**a)** General Information

**1)** Most events were reported within the first 6 months after start of therapy [110].

**2)** The risk of suicidality varied among 11 antidepressant drugs studied in greater than 77,000 adults with [major depressive disorder](#) or other psychiatric disorders in pooled analysis of placebo-controlled trials. However, for almost all drugs studied, there was a tendency toward increased suicidality in younger patients. The risk difference (drug versus placebo in the number of cases of suicidality per 1000 patients treated) was 14 additional cases in patients less than 18 years of age, 5 additional cases in patients 18 to 24 years, 1 fewer case in patients 25 to 64 years, and 6 fewer cases in patients 65 years and older. No suicides occurred in the pediatric trials. Suicides did occur in the adult trials; however, the number of suicides was insufficient to determine causality [13].

**b)** Prevention and Management

1j) Patients should be observed for behavior changes especially during the initial few months of therapy, and at times of dosage increases or decreases [13].

c) Adult Clinical Trials

1j) Indications not specified (oral route): Suicide attempts, 4.7/1000 person-years with [sertraline](#) (n=36,135; 17,649 person-years) vs 4.25/1000 person-years with no treatment (n=20,941; 10,823 person-years) in a population-based cohort study of 287,534 adults receiving an antidepressant over a 9-year period [110].

d) Pediatric Clinical Trials

1j) Various indications (oral route): Significantly increased risk of suicidality by 139% and suicide events by 124% with antidepressant use ([duloxetine](#), [fluoxetine](#), [paroxetine](#), [sertraline](#), or [venlafaxine](#)) in a systematic review and meta-analysis of clinical study reports (11 trials in 1231 children and adolescents) [108].

### 3.3.12.A.9] Suicide

a) General Information

1j) Most events were reported within the first 6 months after start of therapy [110].

b) Adult Clinical Trials

1j) Indications not specified (oral route): Suicide occurred at an event rate of 0.62/1000 person-years and suicide attempts at a rate of 4.7/1000 person-years with [sertraline](#) (n=36,135; 17,649 person-years) vs 0.65/1000 person-years and 4.25/1000 person-years in treatment-naïve patients (n=20,941; 10,823 person-years) in a population-based cohort study of 287,534 adults receiving an antidepressant over a 9-year period. Additionally, there was no difference in risk compared with [fluoxetine](#) following extensive propensity score adjustment [110].

c) Pediatric Clinical Trials

1j) Various indications (oral route): Significantly increased risk of suicide events by 124% with antidepressant use ([duloxetine](#), [fluoxetine](#), [paroxetine](#), [sertraline](#), or [venlafaxine](#)) in a systematic review and meta-analysis of clinical study reports (11 trials in 1231 children and adolescents) [108].

### 3.3.13] Renal Effects

#### 3.3.13.A] [Sertraline Hydrochloride](#)

##### 3.3.13.A.1] [Renal failure](#)

a) [Acute renal failure](#) has been reported in temporal association with use of [sertraline](#), although a causal relationship has not been established [13].

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

a) Incidence: 2% or greater (pediatric) [13]

b) Among pediatric patients treated with [sertraline](#) in controlled clinical trials, [urinary incontinence](#) was reported at an incidence of at least 2% and occurred at a rate of at least twice that of placebo (n=281 treated with [sertraline](#)) [13].

##### 3.3.13.A.3] [Urinary tract infectious disease](#)

a) In placebo-controlled clinical trials with geriatric patients, the incidence of UTIs among patients taking [sertraline](#) was at least 2% and was greater than in patients taking placebo [83].

### 3.3.14] Reproductive Effects

#### 3.3.14.A] [Sertraline](#)

##### 3.3.14.A.1] Sexual dysfunction

See Drug Consult reference: Drug-Induced Sexual Dysfunction

#### 3.3.14.B] [Sertraline Hydrochloride](#)

##### 3.3.14.B.1] Abnormal ejaculation

a) Incidence: 7% to 19% [13]

b) In placebo-controlled clinical trials of 4687 patients, ejaculation failure (primarily ejaculatory delay) was reported in a greater percentage of male patients treated with [sertraline](#) compared with those treated with placebo for [major depressive disorder](#) (7% vs less than 1%), [obsessive compulsive disorder](#) (17% vs 2%), [panic disorder](#) (19% vs 1%), [posttraumatic stress disorder](#) (11% vs 1%), and [social anxiety disorder](#) (14% vs 0%). All patients received between 50 and 200 mg/day of [sertraline](#) [13].

c) Ejaculation failure was the cause of therapy discontinuation in 1% of male patients with [major depressive disorder](#) (n=271) and [obsessive compulsive disorder](#) (n=296), and in 2% of patients with [panic disorder](#) (n=216) and [social anxiety disorder](#) (n=205) [13].

##### 3.3.14.B.2] Disorder of menstruation

a) [Sertraline](#) may cause infrequent [dysmenorrhea](#), [intermenstrual bleeding](#), [amenorrhea](#), [leukorrhea](#), and [atrophic vaginitis](#) [13].

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

a) Incidence: 1% or greater [13]

b) During premarketing use of [sertraline](#) in clinical trials of over 4000 patients, impotence occurred on one or more occasions in at least 1% of patients exposed to multiple doses of [sertraline](#) [13].

##### 3.3.14.B.4] [Priapism](#)

a) Incidence: rare [13][112]

b) [Priapism](#) has occurred with all SSRIs [13].

c) Therapeutic use of [sertraline](#) has resulted in rare cases of [priapism](#). The Adverse Events Reporting System maintained by the US Food and Drug Administration has received 46 reports of [priapism](#) associated with [sertraline](#) [112].

d) A 47-year-old man treated with [sertraline](#) 200 mg/day and [dextroamphetamine](#) 10 mg/day for depression and [attention deficit disorder](#) developed [priapism](#). He reported several brief episodes over the past month. He came to the emergency department (ED) due to a 4-day history of intermittent [priapism](#) with moderate pain. Initially, intracorporeal injection of [methoxamine](#) appeared effective; however, he returned to the ED and was admitted due to poor response to repeat treatment with [methoxamine](#). A urologist treated him with injection of dilute [epinephrine](#) and a Winter's shunt procedure. At follow-up several weeks later, the [priapism](#) had completely resolved, and he was not impotent. After resolution, he was started on [nefazodone](#) [112].

### 3.3.14.B.5] Reduced libido

- a) Incidence: up to 11% [13]
- b) In placebo-controlled clinical trials of 5193 patients, decreased libido was reported in a greater percentage of patients treated with [sertraline](#) compared with patients treated with placebo for [major depressive disorder](#) (1% vs less than 1%), [obsessive compulsive disorder](#) (11% vs 2%), [panic disorder](#) (7% vs 1%), [posttraumatic stress disorder](#) (7% vs 2%), [social anxiety disorder](#) (9% vs 3%), [premenstrual dysphoric disorder](#) (PMDD) with continuous daily dosing (11% vs 2%), and for PMDD with luteal-phase dosing only (4% vs 2%). All patients received between 50 and 200 mg/day of [sertraline](#) except for the PMDD populations, of which the continuous-dosing group received 50 to 150 mg/day and the luteal-phase dosing group received 50 to 100 mg/day during the luteal phase of their menstrual cycle [13].

## 3.3.15] Respiratory Effects

### 3.3.15.A] [Sertraline](#) Hydrochloride

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

- a) Incidence: 0.1% to 1% (all patients); 2% or greater (pediatrics) [13]
- b) [Epistaxis](#) has been reported in 0.1% to 1% of patients receiving [sertraline](#) therapy in clinical trials [13].
- c) Among pediatric patients treated with [sertraline](#) in controlled clinical trials, [epistaxis](#) was reported at an incidence of at least 2% and occurred at a rate of at least twice that of placebo (n=281 treated with [sertraline](#)) [13].

#### 3.3.15.A.2] [Pulmonary hypertension](#)

- a) [Pulmonary hypertension](#) has been temporally associated with the use of [sertraline](#), although a causal relationship is unknown [97].

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

- a) Incidence: 1% or greater [13]
- b) During premarketing use of [sertraline](#) in clinical trials of over 4000 patients, [rhinitis](#) occurred on one or more occasions in at least 1% of patients exposed to multiple doses of [sertraline](#) [13].

#### 3.3.15.A.4] [Sinusitis](#)

- a) Incidence: 2% or greater (pediatrics) [13]
- b) Among pediatric patients treated with [sertraline](#) in controlled clinical trials, [sinusitis](#) was reported at an incidence of at least 2% and occurred at a rate of at least twice that of placebo (n=281 treated with [sertraline](#)) [13].

#### 3.3.15.A.5] [Yawning](#)

- a) Incidence: 1% or greater [13]
- b) During premarketing use of [sertraline](#) in clinical trials of over 4000 patients, increased yawning occurred on one or more occasions in at least 1% of patients exposed to multiple doses of [sertraline](#) [13].

## 3.3.16] Other

### 3.3.16.A] Sertraline Hydrochloride

#### 3.3.16.A.1] Drug withdrawal

a) Premarketing studies did not report a withdrawal reaction to [sertraline](#) [13]. However, a constellation of symptoms have been reported following discontinuation of [sertraline](#) therapy. Symptoms have included: [dysphoric mood](#), irritability, agitation, anxiety, confusion, emotional lability, [hypomania](#), fatigue, nausea, abdominal cramps, diarrhea, shortness of breath, [memory impairment](#), dizziness, insomnia, chills, headache, eye discomfort, tinnitus, ataxia, abnormal sensations ("electric shocks", skin tingling sensations, and involuntary movements). Symptoms typically resolve spontaneously, generally within 3 weeks, or with reinstatement of [sertraline](#) therapy [13][116][117][118][119]; (Frost & Lal, 1995).

b) On the fourth day, following the abrupt discontinuation of [sertraline](#) (200 mg per day), a 14-year-old girl experienced nausea, dizziness, poor concentration, fatigue, tremor, irritability, and insomnia. The patient was treated with [paroxetine](#) 20 mg/day ([sertraline](#) was not available) and her withdrawal symptoms lessened within 12 hours and completely resolved within 30 hours [120].

c) Withdrawal symptoms in a neonate after maternal [sertraline](#) therapy has been reported. Symptoms included: agitation, restlessness, poor feeding, constant crying, insomnia and an enhanced startle reaction. The child had been well until one day postpartum and symptoms resolved gradually over the course of a week. The mother remained asymptomatic (Kent & Laidlaw, 1995).

d) Patients should be monitored for these symptoms when discontinuing [sertraline](#), and the dose reduction should be gradual rather than abrupt. If symptoms are intolerable following a decrease in dose or discontinuation of [sertraline](#), resuming the previously prescribed dose may be considered, after which the dose should be decreased at a more gradual rate [13].

#### 3.3.16.A.2] Fatigue

a) Incidence: 10% to 16% [13]

b) Fatigue is one of the most frequently reported adverse effects of [sertraline](#). In placebo-controlled clinical trials of 5193 patients, fatigue was reported in a greater percentage of patients treated with [sertraline](#) compared with patients treated with placebo for [major depressive disorder](#) (11% vs 8%), [obsessive compulsive disorder](#) (14% vs 10%), [panic disorder](#) (11% vs 6%), [posttraumatic stress disorder](#) (10% vs 5%), [social anxiety disorder](#) (12% vs 6%), [premenstrual dysphoric disorder](#) (PMDD) with continuous daily dosing (16% vs 7%), and for PMDD with luteal-phase dosing only (10% vs less than 1%). All patients received between 50 and 200 mg/day of [sertraline](#) except for the PMDD populations, of which the continuous-dosing group received 50 to 150 mg/day and the luteal-phase dosing group received 50 to 100 mg/day during the luteal phase of their menstrual cycle [13].

c) Fatigue was the cause of therapy discontinuation in 2% of patients with [social anxiety disorder](#) (n=344) [13].

#### 3.3.16.A.3] Fever

a) Incidence: 2% or greater (pediatrics) [13]

b) Among pediatric patients treated with [sertraline](#) in controlled clinical trials, fever was reported at an incidence of at least 2%, and occurred at a rate of at least twice that of placebo (n=281 treated with [sertraline](#)) [13].

#### 3.3.16.A.4] Malaise

a) Incidence: 7% to 9% [13]

b) In placebo-controlled clinical trials of 5193 patients, malaise was reported in a greater percentage of patients treated with [sertraline](#) compared with patients treated with placebo in certain groups: [premenstrual dysphoric disorder](#) (PMDD) with continuous daily dosing (9% vs 5%), PMDD with luteal-phase dosing only (7% vs 5%) and in [social anxiety disorder](#) (8% vs 3%). The incidence of malaise reported with [sertraline](#) was equal to or less than that reported with placebo in patients with [major depressive disorder](#), [obsessive compulsive disorder](#), [panic disorder](#), and [posttraumatic stress disorder](#). All patients received between 50 and 200 mg/day of [sertraline](#) except for the PMDD populations, of which the continuous-dosing group received 50 to 150 mg/day and the luteal-phase dosing group received 50 to 100 mg/day during the luteal phase of their menstrual cycle [13].

#### 3.3.16.A.5] Pain

a) Incidence: 3% to 6% [13]

b) In placebo-controlled clinical trials of 5193 patients, pain was reported in a greater percentage of patients treated with [sertraline](#) compared with patients treated with placebo in certain groups: [premenstrual dysphoric disorder](#) (PMDD) with continuous daily dosing (6% vs less than 1%), PMDD with luteal-phase dosing only (3% vs 2%), and in [obsessive compulsive disorder](#) (3% vs 1%). The incidence of pain reported with [sertraline](#) was equal to or less than that reported with placebo in patients with [major depressive disorder](#), [panic disorder](#), [posttraumatic stress disorder](#), and [social anxiety disorder](#). All patients received between 50 and 200 mg/day of [sertraline](#) except for the PMDD populations, of which the continuous-dosing group received 50 to 150 mg/day and the luteal-phase dosing group received 50 to 100 mg/day during the luteal phase of their menstrual cycle [13].

#### 3.3.16.A.6] Serotonin syndrome

a) [Serotonin syndrome](#), including life-threatening cases, or [neuroleptic malignant syndrome](#) (NMS)-like reactions have been reported with the use of [sertraline](#) alone. Signs and symptoms of [serotonin syndrome](#) include mental status changes (eg, agitation, hallucination, coma), autonomic instability (eg, [tachycardia](#), labile blood pressure, [hyperthermia](#)), neuromuscular aberrations (eg, hyperreflexia, incoordination) and/or gastrointestinal symptoms (eg, nausea, vomiting, diarrhea). Severe [serotonin syndrome](#) can resemble NMS with symptoms including [hyperthermia](#), muscle rigidity, autonomic instability with possible rapid fluctuation of vital signs, and mental status changes. [Serotonin syndrome](#) occurs most commonly with the concomitant use of serotonergic drugs, including triptans, with drugs that impair metabolism of serotonin, including MAOIs, or with antipsychotics or other [dopamine](#) antagonists [103].

b) [Sertraline](#), an SSRI, is capable, as other drugs in this class, of inducing a [serotonin syndrome](#). Most often, this syndrome is induced by concurrent use of 2 or more drugs capable of enhancing CNS serotonin activity. Often, patients with [serotonin syndrome](#) will respond to discontinuation of [sertraline](#) and supportive care alone [113][114].

c) A 43-year-old woman with severe [mental retardation](#) experienced [serotonin syndrome](#) (palpitations, chest pain, [tachycardia](#), truncal and limb rigidity, tremulousness of fingers bilaterally, hypertonicity of the lower limbs, diffuse hyperreflexia, [hyperthermia](#), and [leukocytosis](#)) after taking 2 sub-therapeutic doses (25 mg/day) of [sertraline](#). Discontinuation of [sertraline](#) lead to sufficient recovery for hospital discharge on the second day [115].

#### 3.3.16.A.7] Transfusion reaction due to serum protein reaction

a) [Serum sickness](#) has been reported with [sertraline](#) therapy in postmarketing surveillance, although a causal relationship has not been established [106].

### 3.4] **Teratogenicity/Effects in Pregnancy/Breastfeeding**

#### A) **Teratogenicity/Effects in Pregnancy**

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

a) Either studies in animals have revealed adverse effects on the fetus (teratogenic or embryocidal or other) and there are no controlled studies in women or studies in women and animals are not available. Drugs should be given only if the potential benefit justifies the potential [risk to the fetus](#).

##### 2) Australian Drug Evaluation Committee's (ADEC) Category: C

a) Drugs which, owing to their pharmacological effects, have caused or may be suspected of causing harmful effects on the human fetus or neonate without causing malformations. These effects may be reversible. Accompanying texts should be consulted for further details.

See Drug Consult reference: PREGNANCY RISK CATEGORIES

##### 3) Crosses Placenta: Yes

##### 4) Clinical Management

a) Use [sertraline](#) cautiously during pregnancy, considering both the potential risk of taking [sertraline](#), along with the established benefits of treating depression [21].

##### 5) Literature Reports

a) In a population-wide cohort study, [sertraline](#) use during the first trimester of pregnancy was associated with an increased risk of infants developing atrial and/or ventricular defects and [craniosynostosis](#). When adjusted for potential confounders, [sertraline](#) use during the first trimester of pregnancy was not associated with a statistically significant overall risk of major [congenital malformations](#) compared with non-use of antidepressants; however, an increased risk of atrial and/or ventricular defects and [craniosynostosis](#) was associated with first trimester [sertraline](#) exposure. In addition, exposure to selective serotonin reuptake inhibitors other than [sertraline](#) during the first trimester of pregnancy was also associated with an increased risk of [craniosynostosis](#), as well as musculoskeletal defects suggesting an SSRI class effect [443].

b) In a clinical study of 831,234 infants born between 1997 and 2005 in Sweden, a significant 2.4-fold increased risk of [persistent pulmonary hypertension of the newborn](#) (PPHN) was clearly associated with maternal use of selective serotonin reuptake inhibitors (SSRIs) during early pregnancy. Maternal use of combination SSRIs during early pregnancy and antenatal use later in the pregnancy, was associated with a significant 3.6-fold increased risk of PPHN risk [78]. A case-control study found that the use of SSRIs ([fluoxetine](#), [paroxetine](#), and [sertraline](#)) after 20 weeks of gestation was associated with a significant 6.1-fold increased risk of [persistent pulmonary hypertension of the newborn](#) (PPHN) as compared with no use during the pregnancy. SSRI use before 20 weeks of gestation and non-SSRI antidepressants 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% [444].



c) A nested case-controlled study showed that [sertraline](#), [fluoxetine](#), [citalopram](#), [fluvoxamine](#), or combined use of 2 or more SSRIs during pregnancy did not correspond with a significantly increased risk of [spontaneous abortion](#). However, [paroxetine](#) use alone was associated with a significant 75% increased risk of [spontaneous abortion](#). The highest daily doses of [paroxetine](#) during pregnancy were associated with the greatest [spontaneous abortion](#) risk; of the women taking [paroxetine](#) (n=84) who spontaneously aborted, an adjusted analysis showed 25.5% averaged daily doses of more than 25 mg of [paroxetine](#) [445].

d) Data from the case-controlled National Birth Defects Prevention Study (NBDPS), which included data from 13,714 infants born between 1997 and 2002, indicated that early maternal exposure (defined as treatment with any SSRI from 1 month before to 3 months after conception) to SSRIs was associated with a significant 2.4-fold increased risk of [anencephaly](#) (occurring in 9 exposed infants out of 214), a significant 2.5-fold increased risk of [craniosynostosis](#) (occurring in 24 exposed infants out of 432), and a significant 2.8-fold increased risk of [omphalocele](#) (occurring in 11 exposed infants out of 181). However, early exposure did not significantly increase the risks of [congenital heart defects](#) or most other [birth defects](#). The most commonly used SSRIs reported by control mothers were [sertraline](#), [fluoxetine](#), [paroxetine](#), and [citalopram](#) [446].

e) A population-based study of 1782 pregnant women exposed to SSRIs found no increased risk of adverse perinatal outcome except for treatment in the neonatal intensive or special care unit, particularly with third trimester exposure. When compared to first trimester exposure, treatment in a special or intensive care unit was more common for the infants exposed during the third trimester (11.2% and 15.7%, respectively). Even after adjusting for confounding variables, the group exposed during the third trimester had a significant 60% increased risk compared with the first-trimester exposed group [447].

f) A cohort study of prospectively collected data demonstrated an increased risk of [autism](#) spectrum disorder (ASD) in children whose mothers used antidepressants during the second or third trimesters of pregnancy; the risk was even greater with second or third trimester exposure to SSRIs. Thirty-one infants who were exposed to antidepressants during the second or third trimester were diagnosed with ASD. After adjusting for potential confounders, second or third trimester exposure to antidepressants was associated with a significant 87% increased risk of ASD, while first trimester exposure or use of antidepressants in the year before pregnancy was not associated with any such risk. Use of SSRIs during the second or third trimester was associated with a significant more than 2-fold increased risk of ASD (22 exposed infants), while other classes of antidepressants were not associated with an increased risk. Even after restricting the sample size to those children whose mothers had a history of depression and used antidepressants during the second or third trimester, the risk of ASD still persisted. In addition, use of more than 1 class of antidepressants during the second or third trimester was associated with a significant more than 4-fold increased risk of ASD [448].

g) One small study indicated no long-term effects on cognitive ability were demonstrated but did show evidence of a significant 3-times increased risk for social-behavioral abnormalities at 2 to 6 years of age in children exposed to SSRIs or serotonin–norepinephrine reuptake inhibitors (SNRIs) in utero who developed [neonatal abstinence syndrome](#) (NAS) at birth [449].

h) In a prospective, multicenter, controlled cohort study of 267 pregnant women taking 3 different SSRIs, 147 women used [sertraline](#) at an average dose of 50 mg/day. When compared to the control group (267 pregnant women exposed only to nonteratogens) no differences between the 2 groups were reported with respect to occurrence of major fetal malformations, rate of miscarriage, stillbirth, prematurity, birth weight, and gestational age [450]. A prospective study through the California

Teratogen Information Service compared the outcomes of 112 pregnant women who took [sertraline](#) with 191 pregnant women not exposed to known teratogens. The rate of major anomalies in the two groups was similar (3.8% and 1.9%, respectively). Women taking [sertraline](#) during the third trimester more often delivered premature infants (16.3%) and their infants were more often admitted to the special care nursery [451].

i) SSRI administration lasting more than 30 days during the second or third lunar month of pregnancy was associated with a significant 80% increased risk of [clubfoot](#) occurrence in infants. Escitalopram administration had a significant 190% increased risk, [paroxetine](#) administration had a non-significant 820% increased risk, [sertraline](#) administration had a non-significant 60% increased risk, [fluoxetine](#) administration had a non-significant 30% increased risk, and [citalopram](#) administration had a non-significant 10% decreased risk. Because of small numbers of subjects exposed to these SSRIs, the estimated odds ratios were unstable for these agents, especially for [paroxetine](#) [452].

## B) Breastfeeding

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

2) Micromedex Lactation Rating: Infant risk is minimal.

a) The weight of an adequate body of evidence and/or expert consensus suggests this drug poses minimal risk to the infant when used during breastfeeding.

## 3) Clinical Management

a) Use caution when administering [sertraline](#) to nursing mothers [78]. The selective serotonin-reuptake inhibitors, including [sertraline](#), are lipid soluble and therefore excreted into breast milk [464]. However, because [sertraline](#) has a better safety profile compared to most other SSRIs, it should be considered when an SRI is clearly indicated in a nursing woman [463].

## 4) Literature Reports

a) Low or undetectable levels of [sertraline](#) in human breast milk have been reported. A study of 3 nursing infants exposed to [sertraline](#), low infant plasma concentrations (less than 2 ng/mL) of both [sertraline](#) and the metabolite nortriptyline were reported [454]. No adverse effects in the infants were reported. A case report describes a woman treated with [nortriptyline](#) and [sertraline](#); neither drug was detectable in the infant serum [455].

b) One study involved 12 nursing infants whose mothers used [sertraline](#) while breastfeeding [456]. Only 3 of the 12 infants had measurable serum levels of [sertraline](#) and no adverse effects were noted. Similarly, [sertraline](#) was not detectable in the serum of 6 nursing infants whose mothers were treated with the drug. There was no evidence of adverse effects in the infants as reported by the mothers. The authors suggest that breastfeeding should generally not be discouraged in mothers treated with serotonin reuptake inhibitor antidepressants [457]. Although the clinical data suggest that the absolute dose of [sertraline](#) and the metabolite N-desmethylertraline available to infants through breast milk is low and unlikely to cause significant adverse outcomes, the effects of perinatal infant exposure to [sertraline](#) on long-term cognitive development of the child cannot be evaluated at this point [458][459].

c) Non-quantifiable (0 ng/mL to 2 ng/mL) concentrations of [sertraline](#) were detected in 7 of 9 nursing infants; the other two had concentrations of 3 and 64 ng/mL. The infant with a [sertraline](#) concentration of 64 ng/mL had an N-desmethylertraline concentration of 68 ng/mL, about half of the concentration detected in the mother (taking 100 mg daily). The infant did not experience any adverse events related to the high concentrations. Two infants had non-quantifiable concentrations of N-desmethylertraline, 5 infants had low concentrations (2 ng/mL to 6 ng/mL), and 1 infant had a level of 24 ng/mL, despite a low serum [sertraline](#) level. Because N-desmethylertraline is a less potent inhibitor of serotonin reuptake, this was not a concern. Researchers could not conclude why the 1 infant had such high concentrations. Maternal doses of [sertraline](#) ranged from 50 to 200 mg daily [460].

d) Three and 6 infants of 12 infants total had detectable serum concentrations of [sertraline](#) and desmethylertraline, respectively, after breastfeeding from mothers taking [sertraline](#). Breast milk concentrations of [sertraline](#) and desmethylertraline were highest 7 to 8 hours and 5 to 11 hours, respectively, after the dose. Consequently, the infant dose can be reduced by about 25% by discarding 1 feeding of breast milk 7 to 8 hours after the maternal dose for an infant feeding every 3 hours. Breast milk concentrations, although variable, were generally higher than maternal serum concentrations and were higher with higher maternal doses. Maternal dose ranged from 25 to 150 mg daily [461].

e) Serotonergic overstimulation was reported in a breastfed [preterm infant](#) whose mother was taking [sertraline](#) during pregnancy and lactation. The infant developed [hyperthermia](#) and muscle tone regulation disorders such as muscular hypertonia, shivering, myoclonus, and tremor, as well as irritability and high-pitched crying. The symptoms were initially attributed to [neonatal abstinence syndrome](#); however after symptoms continued, the mother discontinued breastfeeding on day 9 and the infant began to thrive and developed normally [462].

f) According to a meta-analysis including studies of SRI use in lactating women, [paroxetine](#) and [sertraline](#) had better safety profiles than other SRIs. A daily dose of [sertraline](#) 25 to 300 mg resulted in a relative infant dose ranging from 0.54% to 2.2% (below the recommended safety limit). Detectable serum levels of [sertraline](#) (SR) were found in 10 out of 279 infants and norsertraline (NSR) was detected in 27 infants. Milk dosing concentrations were found in 62 infants (SER, 8.4 to 4640 ng/mL; NSER, 15 to 7897 mg/mL). The milk to plasma ratio for SER and NSER ranged from 0.42 to 4.81. [Sertraline](#) did not affect neurodevelopment and no long-term adverse effects were reported [463].

## 5) Drug Levels in Breastmilk

### a) Parent Drug

#### 1) Milk to Maternal Plasma Ratio

a) 1.0-3.6 [486]

### b) Active Metabolites

#### 1) Desmethylertraline [461]

### 3.5] Drug Interactions

#### 3.5.1] Drug-Drug Combinations

##### 3.5.1.A] [Abciximab](#)

- 1) Interaction Effect: increased risk of bleeding
- 2) Summary: Exercise caution when coadministering a SSRI and an antiplatelet agent as this may increase the risk of bleeding events[141][21][140].
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Concomitant use of [sertraline](#) and an antiplatelet agent should be undertaken with caution as this may increase the risk of bleeding events[21].
- 7) Probable Mechanism: unknown
- 8) Literature Reports

a) In a retrospective study of patients over 50 years of age with the diagnosis of acute [myocardial infarction](#) (N=27,058), SSRI use with any antiplatelet therapy significantly increased the risk of bleeding by 1.42-fold compared with [aspirin](#) use alone. Therapy with [aspirin](#), [clopidogrel](#), and an SSRI significantly increased risk by 2.35-fold compared with [aspirin](#) use alone and by 1.57-fold compared with [clopidogrel](#) and [aspirin](#) combination therapy [140].

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) [141].

##### 3.5.1.B] [Aceclofenac](#)

- 1) Interaction Effect: an increased risk of bleeding
- 2) Summary: Caution is recommended with the concomitant use of NSAIDs and antidepressants, including SSRIs due to an increased risk of [intracranial hemorrhage](#)[394] and [gastrointestinal bleeding](#) [398][399][395][396]. Bleeding events have included [epistaxis](#), ecchymosis, [hematoma](#), [petechiae](#), and life-threatening hemorrhages [401][400][402][403]. 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](#)[394] and [gastrointestinal bleeding](#) [395][396]. 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 [394].

**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 [397].

**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 [398] to 2.36 times [399], NSAIDs by 2.55 times [398], and the combination of SSRIs and NSAIDs by 4.02 [398] to 6.33 times [399].

**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 [400].

### 3.5.1.C] Acemetacin

**1)** Interaction Effect: an increased risk of bleeding

**2)** Summary: Caution is recommended with the concomitant use of NSAIDs and antidepressants, including SSRIs due to an increased risk of [intracranial hemorrhage](#)[394] and [gastrointestinal bleeding](#) [398][399][395][396]. Bleeding events have included [epistaxis](#), ecchymosis, [hematoma](#), [petechiae](#), and life-threatening hemorrhages [401][400][402][403]. 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](#)[394] and [gastrointestinal bleeding](#) [395][396]. 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 [394].

**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 [397].

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 [398] to 2.36 times [399], NSAIDs by 2.55 times [398], and the combination of SSRIs and NSAIDs by 4.02 [398] to 6.33 times [399].

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 [400].

### 3.5.1.D] Acenocoumarol

1) Interaction Effect: an increased risk of bleeding

2) Summary: The release of serotonin by [platelets](#) is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs (such as [sertraline](#)) and anticoagulants has been associated with an increased risk of bleeding[129][130][128]. Bleeding events reported have included [epistaxis](#), ecchymosis, [hematoma](#), [petechiae](#), and life-threatening hemorrhages. Altered anticoagulant effects (including increased bleeding) have been reported with the coadministration of SSRIs with [warfarin](#) [128]. Prothrombin time should be monitored in patients receiving both [warfarin](#) and [sertraline](#) [132].

3) Severity: major

4) Onset: delayed

5) Substantiation: probable

6) Clinical Management: When [sertraline](#) 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 [sertraline](#) therapy is initiated or discontinued[128].

7) Probable Mechanism: unknown

8) Literature Reports

a) According to a retrospective cohort study (n=234), there was an increased risk of clinically relevant bleeding (hospital admission due to bleeding) in patients receiving [warfarin](#) for [atrial fibrillation](#) during concomitant SSRI therapy or within 2 weeks following SSRI therapy termination. Patients with a mean age of 72 +/- 7 years receiving [warfarin](#) plus SSRI (n=117) were matched with randomly selected patients who received [warfarin](#) only (n=117). SSRI included [fluoxetine](#), [citalopram](#), [paroxetine](#), [sertraline](#), [fluvoxamine](#), or escitalopram. Nine patients experienced 11 bleeding episodes during 213.9 treatment years in the [warfarin](#) plus SSRI group, and 10 patients experienced 14 bleedings during 586.4 treatment years in the warfarin-only group. The corresponding total incidences of bleedings were 51.4 and 23.9 per 1000 treatment years, respectively. The hazard ratio for first bleedings during treatment with [warfarin](#) plus SSRI was 3.49 (95% CI; 1.37 to 8.91, p=0.009) compared with [warfarin](#) only. The SSRI implicated in patients experiencing bleeding at the time of concomitant administration were [sertraline](#) or [citalopram](#). The addition of an SSRI was not associated with a change in [warfarin](#) dose or INR (p=0.48 and p=0.31 respectively). The results of the study may be limited by earlier bleeding events, unknown patient adherence, and exclusion of [clopidogrel](#), dipyridamol, corticosteroids and anticoagulants other than [warfarin](#) in the model [129].

b) A population-based, case-controlled study of new coumarin users (acenocoumarol and phenprocoumon) with concomitant selective serotonin reuptake inhibitors (SSRIs) resulted in an increased risk of hospitalization due to non-gastrointestinal bleeding. Using national pharmacy and hospitalization records in the Netherlands, researchers identified 1848 cases that were



admitted for abnormal bleeding and compared them with 5818 control subjects who were also taking a coumarin. Median duration of treatment in patients was 220 days (range, 1 to 4690 days). Patients on SSRIs showed greater risk for hospitalization for nongastrointestinal bleeding (adjusted odds ratio (OR) 1.7, 95% confidence interval (CI), 1.1 to 2.5); however, the rate of [gastrointestinal bleeding](#) (adjusted OR 0.8, 95% CI, 0.4 to 1.5) was not significantly different [130].

c) [Sertraline](#) 50 mg to 200 mg daily for 21 days produced an 8% increase in prothrombin time in subjects who received a single dose of [warfarin](#) 0.75 mg/kg relative to the same [warfarin](#) dose given prior to [sertraline](#); this compared with a 1% decrease with placebo. Normalization of the prothrombin time was also delayed as compared with placebo. The clinical significance of these findings is unknown [128].

d) In a non-blinded, randomized, placebo-controlled trial involving 12 healthy volunteers, the effect of [sertraline](#) on the plasma protein binding of [warfarin](#) was assessed. On days 1 and 32 of the study, all participants received [warfarin](#) 0.75 mg/kg. Beginning on day 11, each volunteer was randomized to either the [sertraline](#) or placebo group; the [sertraline](#) was gradually increased from 50 mg/day to 200 mg/day. Prothrombin time was measured prior to each dose of [warfarin](#) and periodically thereafter. The researchers concluded that the anticoagulant effects of [warfarin](#) were not enhanced by [sertraline](#) to a clinically significant degree, despite the fact that [sertraline](#) was given in a higher-than-usual dose [131].

### 3.5.1.E] [Almotriptan](#)

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

2) Summary: Concomitant use of triptans and selective serotonin reuptake inhibitors (SSRI's) has been associated with [serotonin syndrome](#), some of which life-threatening[244]. 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](#) [220].

3) Severity: major

4) Onset: delayed

5) Substantiation: theoretical

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

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

8) Literature Reports

a) Concomitant administration of [fluoxetine](#) and [almotriptan](#) is well tolerated and [fluoxetine](#) has only a modest effect on [almotriptan](#) maximum plasma concentration (C<sub>max</sub>). 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<sub>max</sub> 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 [243].

### 3.5.1.F] [Alprazolam](#)

- 1) Interaction Effect: an increased risk of [psychomotor impairment](#) and sedation
- 2) Summary: To date, limited information is available related to the effects of coadministered [alprazolam](#) and [sertraline](#). One study found that [sertraline](#) was a moderate inhibitor in vitro of [alprazolam](#) metabolism[143]. It is theoretically possible that an interaction might occur because [alprazolam](#) is metabolized by the cytochrome P450 3A system and [sertraline](#) is thought to inhibit one or more P450 isoenzymes [144]. Current evidence indicates that [alprazolam](#) is metabolized at least in part by the CYP3A family of isoenzymes and [sertraline](#) is suspected of inhibiting the CYP3A4 isoenzyme. However, a study involving ten healthy volunteers failed to show an alteration in the pharmacokinetics or pharmacodynamics of [alprazolam](#) when given with [sertraline](#) [145].
- 3) Severity: moderate
- 4) Onset: rapid
- 5) Substantiation: probable
- 6) Clinical Management: Caution is warranted if [alprazolam](#) and [sertraline](#) are to be coadministered. Monitor patients for signs of [psychomotor impairment](#) or excessive sedation. [Alprazolam](#) doses may need to be reduced.
- 7) Probable Mechanism: inhibition of cytochrome P450 3A-mediated [alprazolam](#) metabolism
- 8) Literature Reports

a) Ten healthy white volunteers (eight women and two men) participated in a randomized, double-blind, placebo-controlled study to determine whether therapeutic doses of [sertraline](#) have the potential to impair [alprazolam](#) metabolism and to assess whether any potential impairment is dependent on [sertraline](#) dose. Study participants received [alprazolam](#) 1 mg orally or placebo and [sertraline](#) 50 mg, 100 mg, or 150 mg daily. The [alprazolam](#) maximum concentration (C<sub>max</sub>), time to maximum concentration (t<sub>max</sub>), half-life, and area under the concentration-time curve (AUC) were not clinically significantly altered in the presence of [sertraline](#). No pharmacodynamic interactions, as measured by sedation, digit-symbol substitution test, immediate recall, and delayed recall, were detected between [sertraline](#) and [alprazolam](#) at any dose of [sertraline](#). These in vivo findings are contrary to in vitro data which suggest that [sertraline](#) inhibits [alprazolam](#) metabolism via cytochrome P450 3A4 enzymes [142].

### 3.5.1.G] [Amitriptyline](#)

- 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[21].
- 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[21].
- 7) Probable Mechanism: inhibition of CYP2D6-mediated metabolism; additive serotonergic effects

### 3.5.1.H] [Amoxapine](#)

- 1) Interaction Effect: modest elevation in [amoxapine](#) serum levels or possible [serotonin syndrome](#) (hypertension, hyperthermia, myoclonus, mental status changes)
- 2) Summary: There is limited evidence suggesting that [sertraline](#) may inhibit tricyclic antidepressant (TCA) metabolism resulting in higher TCA serum concentrations. Sertraline inhibits cytochrome P450 2D6 enzyme activity and may increase the plasma concentrations of coadministered drugs that are metabolized by this pathway, including the tricyclic antidepressants[236][237][238]. Effects of the interaction may have little or no clinical impact, however. Increases in TCA serum levels associated with [sertraline](#) coadministration were modest compared with those found when [fluoxetine](#) (another selective serotonin reuptake inhibitor) was combined with [desipramine](#) [239]. Monitor patients on amoxapine-sertraline therapy for TCA toxicity (dry mouth, urinary retention, CNS depression). [Amoxapine](#) doses may need to be reduced.
- 3) Severity: major
- 4) Onset: delayed
- 5) Substantiation: probable
- 6) Clinical Management: The combined use of tricyclic antidepressants (TCAs) and selective serotonin reuptake inhibitors (SSRIs) may result in the inhibition of the TCA metabolism. A few cases of [serotonin syndrome](#) have also been reported with concurrent TCA and SSRI therapy. Caution should be observed when drugs in these two classes are used together.
- 7) Probable Mechanism: inhibition of [amoxapine](#) metabolism
- 8) Literature Reports

a) The pharmacokinetics of [desipramine](#) have been studied in 18 healthy male volunteers. Study subjects received only [desipramine](#) (50 mg daily) for seven days followed by [desipramine](#) with [sertraline](#) (50 mg daily) for 21 days. When [sertraline](#) was added to [desipramine](#) therapy, the mean maximum concentration of [desipramine](#) increased by 34% and the area under the concentration-time curve increased by 26%. Trough concentrations of [desipramine](#) were close to baseline one week after [sertraline](#) was discontinued. The changes in [desipramine](#) concentrations were modest and the interaction may not be clinically significant [235].

### 3.5.1.I] [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[393].
- 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[393].
- 7) Probable Mechanism: inhibition of CYP2D6-mediated metabolism of [amphetamine](#); additive serotonergic effects

### 3.5.1.J] 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](#)[394] and [gastrointestinal bleeding](#) [398][399][395][396]. Bleeding events have included [epistaxis](#), ecchymosis, [hematoma](#), [petechiae](#), and life-threatening hemorrhages [401][400][402][403]. 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](#)[394] and [gastrointestinal bleeding](#) [395][396]. 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 [394].

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 [397].

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 [398] to 2.36 times [399], NSAIDs by 2.55 times [398], and the combination of SSRIs and NSAIDs by 4.02 [398] to 6.33 times [399].

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 [400].

### 3.5.1.K] Anagrelide

- 1)) Interaction Effect: increased risk of bleeding
- 2)) Summary: Exercise caution when coadministering a SSRI and an antiplatelet agent as this may increase the risk of bleeding events[141][21][140].
- 3)) Severity: major
- 4)) Onset: unspecified
- 5)) Substantiation: theoretical
- 6)) Clinical Management: Concomitant use of [sertraline](#) and an antiplatelet agent should be undertaken with caution as this may increase the risk of bleeding events[21].
- 7)) Probable Mechanism: unknown
- 8)) Literature Reports

a)) In a retrospective study of patients over 50 years of age with the diagnosis of acute [myocardial infarction](#) (N=27,058), SSRI use with any antiplatelet therapy significantly increased the risk of bleeding by 1.42-fold compared with [aspirin](#) use alone. Therapy with [aspirin](#), [clopidogrel](#), and an SSRI significantly increased risk by 2.35-fold compared with [aspirin](#) use alone and by 1.57-fold compared with [clopidogrel](#) and [aspirin](#) combination therapy [140].

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) [141].

### 3.5.1.L] 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 (such as [sertraline](#)) and anticoagulants has been associated with an increased risk of bleeding[129][130][128]. Bleeding events reported have included [epistaxis](#), ecchymosis, [hematoma](#), [petechiae](#), and life-threatening hemorrhages. Altered anticoagulant effects (including increased bleeding) have been reported with the coadministration of SSRIs with [warfarin](#) [128]. Prothrombin time should be monitored in patients receiving both [warfarin](#) and [sertraline](#) [132].
- 3)) Severity: major
- 4)) Onset: delayed
- 5)) Substantiation: probable
- 6)) Clinical Management: When [sertraline](#) 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 [sertraline](#) therapy is initiated or discontinued[128].
- 7)) Probable Mechanism: unknown
- 8)) Literature Reports

a)) According to a retrospective cohort study (n=234), there was an increased risk of clinically relevant bleeding (hospital admission due to bleeding) in patients receiving [warfarin](#) for [atrial fibrillation](#) during concomitant SSRI therapy or within 2 weeks following SSRI therapy

termination. Patients with a mean age of 72 +/- 7 years receiving [warfarin](#) plus SSRI (n=117) were matched with randomly selected patients who received [warfarin](#) only (n=117). SSRI included [fluoxetine](#), [citalopram](#), [paroxetine](#), [sertraline](#), [fluvoxamine](#), or escitalopram. Nine patients experienced 11 bleeding episodes during 213.9 treatment years in the [warfarin](#) plus SSRI group, and 10 patients experienced 14 bleedings during 586.4 treatment years in the warfarin-only group. The corresponding total incidences of bleedings were 51.4 and 23.9 per 1000 treatment years, respectively. The hazard ratio for first bleedings during treatment with [warfarin](#) plus SSRI was 3.49 (95% CI; 1.37 to 8.91, p=0.009) compared with [warfarin](#) only. The SSRI implicated in patients experiencing bleeding at the time of concomitant administration were [sertraline](#) or [citalopram](#). The addition of an SSRI was not associated with a change in [warfarin](#) dose or INR (p=0.48 and p=0.31 respectively). The results of the study may be limited by earlier bleeding events, unknown patient adherence, and exclusion of [clopidogrel](#), dipyridamol, corticosteroids and anticoagulants other than [warfarin](#) in the model [129].

**b))** A population-based, case-controlled study of new coumarin users (acenocoumarol and phenprocoumon) with concomitant selective serotonin reuptake inhibitors (SSRIs) resulted in an increased risk of hospitalization due to non-gastrointestinal bleeding. Using national pharmacy and hospitalization records in the Netherlands, researchers identified 1848 cases that were admitted for abnormal bleeding and compared them with 5818 control subjects who were also taking a coumarin. Median duration of treatment in patients was 220 days (range, 1 to 4690 days). Patients on SSRIs showed greater risk for hospitalization for nongastrointestinal bleeding (adjusted odds ratio (OR) 1.7, 95% confidence interval (CI), 1.1 to 2.5); however, the rate of [gastrointestinal bleeding](#) (adjusted OR 0.8, 95% CI, 0.4 to 1.5) was not significantly different [130].

**c))** [Sertraline](#) 50 mg to 200 mg daily for 21 days produced an 8% increase in prothrombin time in subjects who received a single dose of [warfarin](#) 0.75 mg/kg relative to the same [warfarin](#) dose given prior to [sertraline](#); this compared with a 1% decrease with placebo. Normalization of the prothrombin time was also delayed as compared with placebo. The clinical significance of these findings is unknown [128].

**d))** In a non-blinded, randomized, placebo-controlled trial involving 12 healthy volunteers, the effect of [sertraline](#) on the plasma protein binding of [warfarin](#) was assessed. On days 1 and 32 of the study, all participants received [warfarin](#) 0.75 mg/kg. Beginning on day 11, each volunteer was randomized to either the [sertraline](#) or placebo group; the [sertraline](#) was gradually increased from 50 mg/day to 200 mg/day. Prothrombin time was measured prior to each dose of [warfarin](#) and periodically thereafter. The researchers concluded that the anticoagulant effects of [warfarin](#) were not enhanced by [sertraline](#) to a clinically significant degree, despite the fact that [sertraline](#) was given in a higher-than-usual dose [131].

### 3.5.1.M] [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 (such as [sertraline](#)) and anticoagulants has been associated with an increased risk of bleeding[129][130][128]. Bleeding events reported have included [epistaxis](#), ecchymosis, [hematoma](#), [petechiae](#), and life-threatening hemorrhages. Altered anticoagulant effects (including increased bleeding) have been reported with the coadministration of SSRIs with [warfarin](#) [128]. Prothrombin time should be monitored in patients receiving both [warfarin](#) and [sertraline](#) [132].

**3))** Severity: major

**4))** Onset: delayed

**5))** Substantiation: probable

**6j) Clinical Management:** When [sertraline](#) 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 [sertraline](#) therapy is initiated or discontinued[128].

**7j) Probable Mechanism:** unknown

**8j) Literature Reports**

**a)** According to a retrospective cohort study (n=234), there was an increased risk of clinically relevant bleeding (hospital admission due to bleeding) in patients receiving [warfarin](#) for [atrial fibrillation](#) during concomitant SSRI therapy or within 2 weeks following SSRI therapy termination. Patients with a mean age of 72 +/- 7 years receiving [warfarin](#) plus SSRI (n=117) were matched with randomly selected patients who received [warfarin](#) only (n=117). SSRI included [fluoxetine](#), [citalopram](#), [paroxetine](#), [sertraline](#), [fluvoxamine](#), or escitalopram. Nine patients experienced 11 bleeding episodes during 213.9 treatment years in the [warfarin](#) plus SSRI group, and 10 patients experienced 14 bleedings during 586.4 treatment years in the warfarin-only group. The corresponding total incidences of bleedings were 51.4 and 23.9 per 1000 treatment years, respectively. The hazard ratio for first bleedings during treatment with [warfarin](#) plus SSRI was 3.49 (95% CI; 1.37 to 8.91, p=0.009) compared with [warfarin](#) only. The SSRI implicated in patients experiencing bleeding at the time of concomitant administration were [sertraline](#) or [citalopram](#). The addition of an SSRI was not associated with a change in [warfarin](#) dose or INR (p=0.48 and p=0.31 respectively). The results of the study may be limited by earlier bleeding events, unknown patient adherence, and exclusion of [clopidogrel](#), dipyridamol, corticosteroids and anticoagulants other than [warfarin](#) in the model [129].

**b)** A population-based, case-controlled study of new coumarin users (acenocoumarol and phenprocoumon) with concomitant selective serotonin reuptake inhibitors (SSRIs) resulted in an increased risk of hospitalization due to non-gastrointestinal bleeding. Using national pharmacy and hospitalization records in the Netherlands, researchers identified 1848 cases that were admitted for abnormal bleeding and compared them with 5818 control subjects who were also taking a coumarin. Median duration of treatment in patients was 220 days (range, 1 to 4690 days). Patients on SSRIs showed greater risk for hospitalization for nongastrointestinal bleeding (adjusted odds ratio (OR) 1.7, 95% confidence interval (CI), 1.1 to 2.5); however, the rate of [gastrointestinal bleeding](#) (adjusted OR 0.8, 95% CI, 0.4 to 1.5) was not significantly different [130].

**c)** [Sertraline](#) 50 mg to 200 mg daily for 21 days produced an 8% increase in prothrombin time in subjects who received a single dose of [warfarin](#) 0.75 mg/kg relative to the same [warfarin](#) dose given prior to [sertraline](#); this compared with a 1% decrease with placebo. Normalization of the prothrombin time was also delayed as compared with placebo. The clinical significance of these findings is unknown [128].

**d)** In a non-blinded, randomized, placebo-controlled trial involving 12 healthy volunteers, the effect of [sertraline](#) on the plasma protein binding of [warfarin](#) was assessed. On days 1 and 32 of the study, all participants received [warfarin](#) 0.75 mg/kg. Beginning on day 11, each volunteer was randomized to either the [sertraline](#) or placebo group; the [sertraline](#) was gradually increased from 50 mg/day to 200 mg/day. Prothrombin time was measured prior to each dose of [warfarin](#) and periodically thereafter. The researchers concluded that the anticoagulant effects of [warfarin](#) were not enhanced by [sertraline](#) to a clinically significant degree, despite the fact that [sertraline](#) was given in a higher-than-usual dose [131].

### 3.5.1.N] 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 (such as [sertraline](#)) and anticoagulants has been associated with an increased risk of bleeding[129][130][128]. Bleeding events reported have included [epistaxis](#), ecchymosis, [hematoma](#), [petechiae](#), and life-threatening hemorrhages. Altered anticoagulant effects (including increased bleeding) have been reported with the coadministration of SSRIs with [warfarin](#) [128]. Prothrombin time should be monitored in patients receiving both [warfarin](#) and [sertraline](#) [132].
- 3) Severity: major
- 4) Onset: delayed
- 5) Substantiation: probable
- 6) Clinical Management: When [sertraline](#) 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 [sertraline](#) therapy is initiated or discontinued[128].
- 7) Probable Mechanism: unknown
- 8) Literature Reports

a) According to a retrospective cohort study (n=234), there was an increased risk of clinically relevant bleeding (hospital admission due to bleeding) in patients receiving [warfarin](#) for [atrial fibrillation](#) during concomitant SSRI therapy or within 2 weeks following SSRI therapy termination. Patients with a mean age of 72 +/- 7 years receiving [warfarin](#) plus SSRI (n=117) were matched with randomly selected patients who received [warfarin](#) only (n=117). SSRI included [fluoxetine](#), [citalopram](#), [paroxetine](#), [sertraline](#), [fluvoxamine](#), or escitalopram. Nine patients experienced 11 bleeding episodes during 213.9 treatment years in the [warfarin](#) plus SSRI group, and 10 patients experienced 14 bleedings during 586.4 treatment years in the warfarin-only group. The corresponding total incidences of bleedings were 51.4 and 23.9 per 1000 treatment years, respectively. The hazard ratio for first bleedings during treatment with [warfarin](#) plus SSRI was 3.49 (95% CI; 1.37 to 8.91, p=0.009) compared with [warfarin](#) only. The SSRI implicated in patients experiencing bleeding at the time of concomitant administration were [sertraline](#) or [citalopram](#). The addition of an SSRI was not associated with a change in [warfarin](#) dose or INR (p=0.48 and p=0.31 respectively). The results of the study may be limited by earlier bleeding events, unknown patient adherence, and exclusion of [clopidogrel](#), dipyridamol, corticosteroids and anticoagulants other than [warfarin](#) in the model [129].

b) A population-based, case-controlled study of new coumarin users (acenocoumarol and phenprocoumon) with concomitant selective serotonin reuptake inhibitors (SSRIs) resulted in an increased risk of hospitalization due to non-gastrointestinal bleeding. Using national pharmacy and hospitalization records in the Netherlands, researchers identified 1848 cases that were admitted for abnormal bleeding and compared them with 5818 control subjects who were also taking a coumarin. Median duration of treatment in patients was 220 days (range, 1 to 4690 days). Patients on SSRIs showed greater risk for hospitalization for nongastrointestinal bleeding (adjusted odds ratio (OR) 1.7, 95% confidence interval (CI), 1.1 to 2.5); however, the rate of [gastrointestinal bleeding](#) (adjusted OR 0.8, 95% CI, 0.4 to 1.5) was not significantly different [130].

c) [Sertraline](#) 50 mg to 200 mg daily for 21 days produced an 8% increase in prothrombin time in subjects who received a single dose of [warfarin](#) 0.75 mg/kg relative to the same [warfarin](#) dose given prior to [sertraline](#); this compared with a 1% decrease with placebo. Normalization of the prothrombin time was also delayed as compared with placebo. The clinical significance of these findings is unknown [128].



d)) In a non-blinded, randomized, placebo-controlled trial involving 12 healthy volunteers, the effect of [sertraline](#) on the plasma protein binding of [warfarin](#) was assessed. On days 1 and 32 of the study, all participants received [warfarin](#) 0.75 mg/kg. Beginning on day 11, each volunteer was randomized to either the [sertraline](#) or placebo group; the [sertraline](#) was gradually increased from 50 mg/day to 200 mg/day. Prothrombin time was measured prior to each dose of [warfarin](#) and periodically thereafter. The researchers concluded that the anticoagulant effects of [warfarin](#) were not enhanced by [sertraline](#) to a clinically significant degree, despite the fact that [sertraline](#) was given in a higher-than-usual dose [131].

### 3.5.1.O) Apixaban

- 1)) Interaction Effect: an increased risk of bleeding
- 2)) Summary: Coadministration of apixaban, a factor Xa inhibitor, and drugs that 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[295]. If concomitant apixaban and SSRI therapy is necessary, use caution and monitor the patient closely.
- 3)) Severity: major
- 4)) Onset: unspecified
- 5)) Substantiation: theoretical
- 6)) Clinical Management: Concomitant apixaban therapy with drugs that also affect hemostasis, such as an SSRI, increases the risk of bleeding. Discontinue apixaban if active pathological bleeding occurs. There is no established reversal therapy or antidote for apixaban-induced bleeding, and its [anticoagulation](#) effects usually persist for 24 hours after the last dose[295]. If concomitant apixaban and SSRI therapy is necessary, use caution and monitor the patient closely.
- 7)) Probable Mechanism: additive effects on hemostasis

### 3.5.1.P) Ardeparin

- 1)) Interaction Effect: an increased risk of bleeding
- 2)) Summary: The release of serotonin by [platelets](#) is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs (such as [sertraline](#)) and anticoagulants has been associated with an increased risk of bleeding[129][130][128]. Bleeding events reported have included [epistaxis](#), ecchymosis, [hematoma](#), [petechiae](#), and life-threatening hemorrhages. Altered anticoagulant effects (including increased bleeding) have been reported with the coadministration of SSRIs with [warfarin](#) [128]. Prothrombin time should be monitored in patients receiving both [warfarin](#) and [sertraline](#) [132].
- 3)) Severity: major
- 4)) Onset: delayed
- 5)) Substantiation: probable
- 6)) Clinical Management: When [sertraline](#) 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 [sertraline](#) therapy is initiated or discontinued[128].
- 7)) Probable Mechanism: unknown
- 8)) Literature Reports

a)) According to a retrospective cohort study (n=234), there was an increased risk of clinically relevant bleeding (hospital admission due to bleeding) in patients receiving [warfarin](#) for [atrial fibrillation](#) during concomitant SSRI therapy or within 2 weeks following SSRI therapy termination. Patients with a mean age of 72 +/- 7 years receiving [warfarin](#) plus SSRI (n=117)

were matched with randomly selected patients who received [warfarin](#) only (n=117). SSRI included [fluoxetine](#), [citalopram](#), [paroxetine](#), [sertraline](#), [fluvoxamine](#), or escitalopram. Nine patients experienced 11 bleeding episodes during 213.9 treatment years in the [warfarin](#) plus SSRI group, and 10 patients experienced 14 bleedings during 586.4 treatment years in the warfarin-only group. The corresponding total incidences of bleedings were 51.4 and 23.9 per 1000 treatment years, respectively. The hazard ratio for first bleedings during treatment with [warfarin](#) plus SSRI was 3.49 (95% CI; 1.37 to 8.91, p=0.009) compared with [warfarin](#) only. The SSRI implicated in patients experiencing bleeding at the time of concomitant administration were [sertraline](#) or [citalopram](#). The addition of an SSRI was not associated with a change in [warfarin](#) dose or INR (p=0.48 and p=0.31 respectively). The results of the study may be limited by earlier bleeding events, unknown patient adherence, and exclusion of [clopidogrel](#), dipyridamol, corticosteroids and anticoagulants other than [warfarin](#) in the model [129].

**b))** A population-based, case-controlled study of new coumarin users (acenocoumarol and phenprocoumon) with concomitant selective serotonin reuptake inhibitors (SSRIs) resulted in an increased risk of hospitalization due to non-gastrointestinal bleeding. Using national pharmacy and hospitalization records in the Netherlands, researchers identified 1848 cases that were admitted for abnormal bleeding and compared them with 5818 control subjects who were also taking a coumarin. Median duration of treatment in patients was 220 days (range, 1 to 4690 days). Patients on SSRIs showed greater risk for hospitalization for nongastrointestinal bleeding (adjusted odds ratio (OR) 1.7, 95% confidence interval (CI), 1.1 to 2.5); however, the rate of [gastrointestinal bleeding](#) (adjusted OR 0.8, 95% CI, 0.4 to 1.5) was not significantly different [130].

**c))** [Sertraline](#) 50 mg to 200 mg daily for 21 days produced an 8% increase in prothrombin time in subjects who received a single dose of [warfarin](#) 0.75 mg/kg relative to the same [warfarin](#) dose given prior to [sertraline](#); this compared with a 1% decrease with placebo. Normalization of the prothrombin time was also delayed as compared with placebo. The clinical significance of these findings is unknown [128].

**d))** In a non-blinded, randomized, placebo-controlled trial involving 12 healthy volunteers, the effect of [sertraline](#) on the plasma protein binding of [warfarin](#) was assessed. On days 1 and 32 of the study, all participants received [warfarin](#) 0.75 mg/kg. Beginning on day 11, each volunteer was randomized to either the [sertraline](#) or placebo group; the [sertraline](#) was gradually increased from 50 mg/day to 200 mg/day. Prothrombin time was measured prior to each dose of [warfarin](#) and periodically thereafter. The researchers concluded that the anticoagulant effects of [warfarin](#) were not enhanced by [sertraline](#) to a clinically significant degree, despite the fact that [sertraline](#) was given in a higher-than-usual dose [131].

### 3.5.1.Q) [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](#)[394] and [gastrointestinal bleeding](#) [398][399][395][396]. Bleeding events have included [epistaxis](#), ecchymosis, [hematoma](#), [petechiae](#), and life-threatening hemorrhages [401][400][402][403]. 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](#)[394] and [gastrointestinal](#)

[bleeding](#) [395][396]. 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 [394].

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 [397].

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 [398] to 2.36 times [399], NSAIDs by 2.55 times [398], and the combination of SSRIs and NSAIDs by 4.02 [398] to 6.33 times [399].

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 [400].

### 3.5.1.R] [Astemizole](#)

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

2) Summary: Coadministered [sertraline](#) may inhibit [astemizole](#) metabolism, thereby leading to increased [astemizole](#) serum concentrations and potential [astemizole](#) toxicity. Concomitant administration of [astemizole](#) and [sertraline](#) should be avoided[325].

3) Severity: major

4) Onset: rapid

5) Substantiation: probable

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

7) Probable Mechanism: inhibition of cytochrome P450-mediated metabolism of [astemizole](#)

### 3.5.1.S] [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 (such as [sertraline](#)) and anticoagulants has been associated with an increased risk of bleeding[129][130][128]. Bleeding events reported have included [epistaxis](#), ecchymosis, [hematoma](#), [petechiae](#), and life-threatening hemorrhages. Altered anticoagulant effects (including increased bleeding) have been reported with the coadministration of SSRIs with [warfarin](#) [128]. Prothrombin time should be monitored in patients receiving both [warfarin](#) and [sertraline](#) [132].

3)Severity: major

- 4) Onset: delayed
- 5) Substantiation: probable
- 6) Clinical Management: When [sertraline](#) 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 [sertraline](#) therapy is initiated or discontinued[128].
- 7) Probable Mechanism: unknown
- 8) Literature Reports

a) According to a retrospective cohort study (n=234), there was an increased risk of clinically relevant bleeding (hospital admission due to bleeding) in patients receiving [warfarin](#) for [atrial fibrillation](#) during concomitant SSRI therapy or within 2 weeks following SSRI therapy termination. Patients with a mean age of 72 +/- 7 years receiving [warfarin](#) plus SSRI (n=117) were matched with randomly selected patients who received [warfarin](#) only (n=117). SSRI included [fluoxetine](#), [citalopram](#), [paroxetine](#), [sertraline](#), [fluvoxamine](#), or [escitalopram](#). Nine patients experienced 11 bleeding episodes during 213.9 treatment years in the [warfarin](#) plus SSRI group, and 10 patients experienced 14 bleedings during 586.4 treatment years in the warfarin-only group. The corresponding total incidences of bleedings were 51.4 and 23.9 per 1000 treatment years, respectively. The hazard ratio for first bleedings during treatment with [warfarin](#) plus SSRI was 3.49 (95% CI; 1.37 to 8.91, p=0.009) compared with [warfarin](#) only. The SSRI implicated in patients experiencing bleeding at the time of concomitant administration were [sertraline](#) or [citalopram](#). The addition of an SSRI was not associated with a change in [warfarin](#) dose or INR (p=0.48 and p=0.31 respectively). The results of the study may be limited by earlier bleeding events, unknown patient adherence, and exclusion of [clopidogrel](#), dipyridamol, corticosteroids and anticoagulants other than [warfarin](#) in the model [129].

b) A population-based, case-controlled study of new coumarin users (acenocoumarol and phenprocoumon) with concomitant selective serotonin reuptake inhibitors (SSRIs) resulted in an increased risk of hospitalization due to non-gastrointestinal bleeding. Using national pharmacy and hospitalization records in the Netherlands, researchers identified 1848 cases that were admitted for abnormal bleeding and compared them with 5818 control subjects who were also taking a coumarin. Median duration of treatment in patients was 220 days (range, 1 to 4690 days). Patients on SSRIs showed greater risk for hospitalization for nongastrointestinal bleeding (adjusted odds ratio (OR) 1.7, 95% confidence interval (CI), 1.1 to 2.5); however, the rate of [gastrointestinal bleeding](#) (adjusted OR 0.8, 95% CI, 0.4 to 1.5) was not significantly different [130].

c) [Sertraline](#) 50 mg to 200 mg daily for 21 days produced an 8% increase in prothrombin time in subjects who received a single dose of [warfarin](#) 0.75 mg/kg relative to the same [warfarin](#) dose given prior to [sertraline](#); this compared with a 1% decrease with placebo. Normalization of the prothrombin time was also delayed as compared with placebo. The clinical significance of these findings is unknown [128].

d) In a non-blinded, randomized, placebo-controlled trial involving 12 healthy volunteers, the effect of [sertraline](#) on the plasma protein binding of [warfarin](#) was assessed. On days 1 and 32 of the study, all participants received [warfarin](#) 0.75 mg/kg. Beginning on day 11, each volunteer was randomized to either the [sertraline](#) or placebo group; the [sertraline](#) was gradually increased from 50 mg/day to 200 mg/day. Prothrombin time was measured prior to each dose of [warfarin](#) and periodically thereafter. The researchers concluded that the anticoagulant effects of [warfarin](#) were not enhanced by [sertraline](#) to a clinically significant degree, despite the fact that [sertraline](#) was given in a higher-than-usual dose [131].

### 3.5.1.T] Benzphetamine

- 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[393].
- 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[393].
- 7J) Probable Mechanism: inhibition of CYP2D6-mediated metabolism of [amphetamine](#); additive serotonergic effects

### 3.5.1.U] Bivalirudin

- 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 (such as [sertraline](#)) and anticoagulants has been associated with an increased risk of bleeding[129][130][128]. Bleeding events reported have included [epistaxis](#), ecchymosis, [hematoma](#), [petechiae](#), and life-threatening hemorrhages. Altered anticoagulant effects (including increased bleeding) have been reported with the coadministration of SSRIs with [warfarin](#) [128]. Prothrombin time should be monitored in patients receiving both [warfarin](#) and [sertraline](#) [132].
- 3J) Severity: major
- 4J) Onset: delayed
- 5J) Substantiation: probable
- 6J) Clinical Management: When [sertraline](#) 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 [sertraline](#) therapy is initiated or discontinued[128].
- 7J) Probable Mechanism: unknown
- 8J) Literature Reports

aJ) According to a retrospective cohort study (n=234), there was an increased risk of clinically relevant bleeding (hospital admission due to bleeding) in patients receiving [warfarin](#) for [atrial fibrillation](#) during concomitant SSRI therapy or within 2 weeks following SSRI therapy termination. Patients with a mean age of 72 +/- 7 years receiving [warfarin](#) plus SSRI (n=117) were matched with randomly selected patients who received [warfarin](#) only (n=117). SSRI included [fluoxetine](#), [citalopram](#), [paroxetine](#), [sertraline](#), [fluvoxamine](#), or escitalopram. Nine patients experienced 11 bleeding episodes during 213.9 treatment years in the [warfarin](#) plus SSRI group, and 10 patients experienced 14 bleedings during 586.4 treatment years in the warfarin-only group. The corresponding total incidences of bleedings were 51.4 and 23.9 per 1000 treatment



years, respectively. The hazard ratio for first bleedings during treatment with [warfarin](#) plus SSRI was 3.49 (95% CI; 1.37 to 8.91,  $p=0.009$ ) compared with [warfarin](#) only. The SSRI implicated in patients experiencing bleeding at the time of concomitant administration were [sertraline](#) or [citalopram](#). The addition of an SSRI was not associated with a change in [warfarin](#) dose or INR ( $p=0.48$  and  $p=0.31$  respectively). The results of the study may be limited by earlier bleeding events, unknown patient adherence, and exclusion of [clopidogrel](#), dipyridamol, corticosteroids and anticoagulants other than [warfarin](#) in the model [129].

**b)** A population-based, case-controlled study of new coumarin users (acenocoumarol and phenprocoumon) with concomitant selective serotonin reuptake inhibitors (SSRIs) resulted in an increased risk of hospitalization due to non-gastrointestinal bleeding. Using national pharmacy and hospitalization records in the Netherlands, researchers identified 1848 cases that were admitted for abnormal bleeding and compared them with 5818 control subjects who were also taking a coumarin. Median duration of treatment in patients was 220 days (range, 1 to 4690 days). Patients on SSRIs showed greater risk for hospitalization for nongastrointestinal bleeding (adjusted odds ratio (OR) 1.7, 95% confidence interval (CI), 1.1 to 2.5); however, the rate of [gastrointestinal bleeding](#) (adjusted OR 0.8, 95% CI, 0.4 to 1.5) was not significantly different [130].

**c)** [Sertraline](#) 50 mg to 200 mg daily for 21 days produced an 8% increase in prothrombin time in subjects who received a single dose of [warfarin](#) 0.75 mg/kg relative to the same [warfarin](#) dose given prior to [sertraline](#); this compared with a 1% decrease with placebo. Normalization of the prothrombin time was also delayed as compared with placebo. The clinical significance of these findings is unknown [128].

**d)** In a non-blinded, randomized, placebo-controlled trial involving 12 healthy volunteers, the effect of [sertraline](#) on the plasma protein binding of [warfarin](#) was assessed. On days 1 and 32 of the study, all participants received [warfarin](#) 0.75 mg/kg. Beginning on day 11, each volunteer was randomized to either the [sertraline](#) or placebo group; the [sertraline](#) was gradually increased from 50 mg/day to 200 mg/day. Prothrombin time was measured prior to each dose of [warfarin](#) and periodically thereafter. The researchers concluded that the anticoagulant effects of [warfarin](#) were not enhanced by [sertraline](#) to a clinically significant degree, despite the fact that [sertraline](#) was given in a higher-than-usual dose [131].

### 3.5.1.V] [Bromfenac](#)

**1)** Interaction Effect: an increased risk of bleeding

**2)** Summary: Caution is recommended with the concomitant use of NSAIDs and antidepressants, including SSRIs due to an increased risk of [intracranial hemorrhage](#)[394] and [gastrointestinal bleeding](#) [398][399][395][396]. Bleeding events have included [epistaxis](#), ecchymosis, [hematoma](#), [petechiae](#), and life-threatening hemorrhages [401][400][402][403]. 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](#)[394] and [gastrointestinal bleeding](#) [395][396]. 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 [394].

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 [397].

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 [398] to 2.36 times [399], NSAIDs by 2.55 times [398], and the combination of SSRIs and NSAIDs by 4.02 [398] to 6.33 times [399].

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 [400].

### 3.5.1.W) 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[122].
- 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[122].
- 7) Probable Mechanism: additive extrapyramidal side effects

### 3.5.1.X) Bufexamac

- 1) Interaction Effect: an increased risk of bleeding
- 2) Summary: Caution is recommended with the concomitant use of NSAIDs and antidepressants, including SSRIs due to an increased risk of [intracranial hemorrhage](#)[394] and [gastrointestinal bleeding](#) [398][399][395][396]. Bleeding events have included [epistaxis](#), ecchymosis, [hematoma](#), [petechiae](#), and life-threatening hemorrhages [401][400][402][403]. 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](#)[394] and [gastrointestinal](#)



bleeding [395][396]. 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 [394].

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 [397].

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 [398] to 2.36 times [399], NSAIDs by 2.55 times [398], and the combination of SSRIs and NSAIDs by 4.02 [398] to 6.33 times [399].

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 [400].

### 3.5.1.Y] 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[207]

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[207]

7) Probable Mechanism: additive serotonergic effects

### 3.5.1.Z] Bupropion

1) Interaction Effect: lower seizure threshold

2) Summary: Use extreme caution when prescribing bupropion with drugs that lower seizure threshold (eg, antipsychotics, antidepressants, theophylline, systemic corticosteroids). Begin treatment with a low initial dose and increase dose gradually[390].

- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Use extreme caution when prescribing [bupropion](#) with drugs that lower seizure threshold (eg, antipsychotics, antidepressants, [theophylline](#), systemic corticosteroids). Begin treatment with a low initial dose and increase dose gradually[390].
- 7) Probable Mechanism: unknown

### 3.5.1.AA] Cangrelor

- 1) Interaction Effect: increased risk of bleeding
- 2) Summary: Exercise caution when coadministering a SSRI and an antiplatelet agent as this may increase the risk of bleeding events[141][21][140].
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Concomitant use of [sertraline](#) and an antiplatelet agent should be undertaken with caution as this may increase the risk of bleeding events[21].
- 7) Probable Mechanism: unknown
- 8) Literature Reports

a) In a retrospective study of patients over 50 years of age with the diagnosis of acute [myocardial infarction](#) (N=27,058), SSRI use with any antiplatelet therapy significantly increased the risk of bleeding by 1.42-fold compared with [aspirin](#) use alone. Therapy with [aspirin](#), [clopidogrel](#), and an SSRI significantly increased risk by 2.35-fold compared with [aspirin](#) use alone and by 1.57-fold compared with [clopidogrel](#) and [aspirin](#) combination therapy [140].

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) [141].

### 3.5.1.AB] Cannabis

- 1) Interaction Effect: manic symptoms
- 2) Summary: One case of mania following use of marijuana with [fluoxetine](#) therapy has been reported[153]. 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 [152].

### 3.5.1.AC] Carbamazepine

1) Interaction Effect: an increased risk of carbamazepine toxicity (ataxia, nystagmus, diplopia, headache, vomiting, apnea, seizures, coma)

2) Summary: Coadministration of sertraline and carbamazepine may cause reduced carbamazepine clearance leading to carbamazepine toxicity manifesting in blurred vision, dizziness, tremor, and possibly blood dyscrasias[280]. Similar interactions have been reported between carbamazepine and two other selective serotonin reuptake inhibitors (SSRIs), fluoxetine and fluvoxamine [281][282]. However, in two separate in vivo studies, coadministration of sertraline and carbamazepine under steady-state conditions did not increase the plasma concentrations of carbamazepine [283]. Two case reports of coadministration of carbamazepine and sertraline resulted in lower-than-expected levels as well as lack of efficacy of sertraline [284].

3) Severity: moderate

4) Onset: delayed

5) Substantiation: probable

6) Clinical Management: Due to the potential for elevated carbamazepine levels, patients should be closely followed for evidence of carbamazepine toxicity when sertraline is added to therapy. Consider measuring carbamazepine serum concentrations within two to three weeks of adding or discontinuing sertraline, with dosage adjustments as needed. Due to cytochrome P450 3A4-mediated metabolism of sertraline, sertraline levels may be lower than expected, which may result in lack of efficacy of sertraline when carbamazepine is coadministered.

7) Probable Mechanism: inhibition of carbamazepine metabolism, increase in sertraline CYP3A4-mediated metabolism

8) Literature Reports

a) A 24-year-old woman received maintenance carbamazepine 600 mg daily and flecainide 100 mg daily. Four weeks after beginning sertraline 100 mg daily, her carbamazepine trough level increased from 4.7 to 8.5 mg/L (normal range, 4 to 10 mg/L), and her blood counts were normal. Two months later, in routine testing before elective surgery, her hemoglobin, platelet, and red and white blood cell counts were abnormally low. Postoperatively her blood counts remained low, despite blood transfusions, and on day 3 her trough carbamazepine was 11.9 mg/L, although she had missed one or more doses. On bone marrow examination, erythroid hyperplasia with megaloblastic characteristics and reduced megakaryocyte numbers were observed. Her hematologic counts began to improve five days after withdrawal of sertraline and carbamazepine; she was not rechallenged. Suggested mechanisms of action were reduced carbamazepine metabolism due to inhibition of cytochrome P450 isoenzymes and carbamazepine protein binding displacement [276].

b) Sertraline is suspected of inhibiting cytochrome P450III A4 (CYP3A4) enzyme activity [277]. Because carbamazepine is known to be a CYP3A4 substrate, carbamazepine might have a potentially significant interaction with sertraline. Conversely, carbamazepine is also a known potent inducer of CYP3A4 and may stimulate the metabolism of sertraline, resulting in decreased sertraline concentrations [278].

c) Two cases have been reported in which concomitant use of [sertraline](#) and [carbamazepine](#) resulted in lack of [sertraline](#) efficacy. The first such case describes a 33-year-old female with [schizoaffective disorder](#) who had been successfully treated with [haloperidol](#) and [carbamazepine](#) for 3 years. After a [depressive episode](#), [sertraline](#) had been initiated and titrated slowly to 300 mg/day. A plasma level for [carbamazepine](#) and [sertraline](#) was obtained after [sertraline](#) initiation. [Sertraline](#) was undetectable with levels below 10 ng/ml. Another case describes a 25-year-old male diagnosed with [posttraumatic stress disorder](#) who had been successfully treated with [carbamazepine](#) for 13 years. [Sertraline](#) was initiated after the patient developed [major depressive disorder](#). Plasma levels were obtained for [sertraline](#) and [carbamazepine](#) during therapy. [Sertraline](#) levels were undetectable with [carbamazepine](#) doses of 400 mg/day and [sertraline](#) doses of 100 mg/day [279].

### 3.5.1.AD] 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](#)[394] and [gastrointestinal bleeding](#) [398][399][395][396]. Bleeding events have included [epistaxis](#), ecchymosis, [hematoma](#), [petechiae](#), and life-threatening hemorrhages [401][400][402][403]. 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](#)[394] and [gastrointestinal bleeding](#) [395][396]. 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 [394].

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 [397].

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 [398] to 2.36 times [399], NSAIDs by 2.55 times [398], and the combination of SSRIs and NSAIDs by 4.02 [398] to 6.33 times [399].

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 [400].

### 3.5.1.AE] 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 (such as [sertraline](#)) and anticoagulants has been associated with an increased risk of bleeding[129][130][128]. Bleeding events reported have included [epistaxis](#), ecchymosis, [hematoma](#), [petechiae](#), and life-threatening hemorrhages. Altered anticoagulant effects (including increased bleeding) have been reported with the coadministration of SSRIs with [warfarin](#) [128]. Prothrombin time should be monitored in patients receiving both [warfarin](#) and [sertraline](#) [132].

3)] Severity: major

4)] Onset: delayed

5)] Substantiation: probable

6)] Clinical Management: When [sertraline](#) 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 [sertraline](#) therapy is initiated or discontinued[128].

7)] Probable Mechanism: unknown

8)] Literature Reports

a)] According to a retrospective cohort study (n=234), there was an increased risk of clinically relevant bleeding (hospital admission due to bleeding) in patients receiving [warfarin](#) for [atrial fibrillation](#) during concomitant SSRI therapy or within 2 weeks following SSRI therapy termination. Patients with a mean age of 72 +/- 7 years receiving [warfarin](#) plus SSRI (n=117) were matched with randomly selected patients who received [warfarin](#) only (n=117). SSRI included [fluoxetine](#), [citalopram](#), [paroxetine](#), [sertraline](#), [fluvoxamine](#), or escitalopram. Nine patients experienced 11 bleeding episodes during 213.9 treatment years in the [warfarin](#) plus SSRI group, and 10 patients experienced 14 bleedings during 586.4 treatment years in the warfarin-only group. The corresponding total incidences of bleedings were 51.4 and 23.9 per 1000 treatment years, respectively. The hazard ratio for first bleedings during treatment with [warfarin](#) plus SSRI was 3.49 (95% CI; 1.37 to 8.91, p=0.009) compared with [warfarin](#) only. The SSRI implicated in patients experiencing bleeding at the time of concomitant administration were [sertraline](#) or [citalopram](#). The addition of an SSRI was not associated with a change in [warfarin](#) dose or INR (p=0.48 and p=0.31 respectively). The results of the study may be limited by earlier bleeding events, unknown patient adherence, and exclusion of [clopidogrel](#), dipyridamol, corticosteroids and anticoagulants other than [warfarin](#) in the model [129].

b)] A population-based, case-controlled study of new coumarin users (acenocoumarol and phenprocoumon) with concomitant selective serotonin reuptake inhibitors (SSRIs) resulted in an increased risk of hospitalization due to non-gastrointestinal bleeding. Using national pharmacy and hospitalization records in the Netherlands, researchers identified 1848 cases that were admitted for abnormal bleeding and compared them with 5818 control subjects who were also taking a coumarin. Median duration of treatment in patients was 220 days (range, 1 to 4690 days). Patients on SSRIs showed greater risk for hospitalization for nongastrointestinal bleeding (adjusted odds ratio (OR) 1.7, 95% confidence interval (CI), 1.1 to 2.5); however, the rate of [gastrointestinal bleeding](#) (adjusted OR 0.8, 95% CI, 0.4 to 1.5) was not significantly different [130].

c) **Sertraline** 50 mg to 200 mg daily for 21 days produced an 8% increase in prothrombin time in subjects who received a single dose of **warfarin** 0.75 mg/kg relative to the same **warfarin** dose given prior to **sertraline**; this compared with a 1% decrease with placebo. Normalization of the prothrombin time was also delayed as compared with placebo. The clinical significance of these findings is unknown [128].

d) In a non-blinded, randomized, placebo-controlled trial involving 12 healthy volunteers, the effect of **sertraline** on the plasma protein binding of **warfarin** was assessed. On days 1 and 32 of the study, all participants received **warfarin** 0.75 mg/kg. Beginning on day 11, each volunteer was randomized to either the **sertraline** or placebo group; the **sertraline** was gradually increased from 50 mg/day to 200 mg/day. Prothrombin time was measured prior to each dose of **warfarin** and periodically thereafter. The researchers concluded that the anticoagulant effects of **warfarin** were not enhanced by **sertraline** to a clinically significant degree, despite the fact that **sertraline** was given in a higher-than-usual dose [131].

### 3.5.1.AF] **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**[394] and **gastrointestinal bleeding** [398][399][395][396]. Bleeding events have included **epistaxis**, ecchymosis, **hematoma**, **petechiae**, and life-threatening hemorrhages [401][400][402][403]. 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**[394] and **gastrointestinal bleeding** [395][396]. 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 [394].

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 [397].



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 [398] to 2.36 times [399], NSAIDs by 2.55 times [398], and the combination of SSRIs and NSAIDs by 4.02 [398] to 6.33 times [399].

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 [400].

### 3.5.1.AG| [Cilostazol](#)

1) Interaction Effect: increased risk of bleeding

2) Summary: Exercise caution when coadministering a SSRI and an antiplatelet agent as this may increase the risk of bleeding events[141][21][140].

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Concomitant use of [sertraline](#) and an antiplatelet agent should be undertaken with caution as this may increase the risk of bleeding events[21].

7) Probable Mechanism: unknown

8) Literature Reports

a) In a retrospective study of patients over 50 years of age with the diagnosis of acute [myocardial infarction](#) (N=27,058), SSRI use with any antiplatelet therapy significantly increased the risk of bleeding by 1.42-fold compared with [aspirin](#) use alone. Therapy with [aspirin](#), [clopidogrel](#), and an SSRI significantly increased risk by 2.35-fold compared with [aspirin](#) use alone and by 1.57-fold compared with [clopidogrel](#) and [aspirin](#) combination therapy [140].

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) [141].

### 3.5.1.AH| [Cimetidine](#)

1) Interaction Effect: elevated [sertraline](#) serum concentrations and increased risk of adverse side effects

2) Summary: Coadministration of [cimetidine](#) with [sertraline](#) may result in inhibition of [sertraline](#) metabolism, leading to increased serum concentrations of [sertraline](#)[136]. The clinical significance of this effect is as yet undefined. Adjustments in [sertraline](#) doses may be required when [cimetidine](#) is added to or withdrawn from therapy.

3) Severity: moderate

4) Onset: rapid

5) Substantiation: probable

6) Clinical Management: Closely follow patients for signs of [sertraline](#) toxicity (nausea, diarrhea, tremor, dizziness). Doses of [sertraline](#) may need to be reduced in patients receiving concomitant [cimetidine](#).

7) Probable Mechanism: inhibited cytochrome P450 metabolism of [sertraline](#)

8) Literature Reports

a) When [sertraline](#) 100 mg was given on the second day of an 8-day regimen of [cimetidine](#) 800 mg daily, there was a 50% increase in the [sertraline](#) mean area under the concentration-time curve (AUC), a 24% in the maximum concentration (C<sub>max</sub>), and a 26% increased in the half-life as compared to the placebo group [135]. The clinical significance of this interaction is unknown.



**3.5.1.AI] Citalopram**

- 1) Interaction Effect: increased risk of [serotonin syndrome](#)
- 2) Summary: The concomitant use of 2 SSRIs, such as [citalopram](#) and [sertraline](#), increases the risk of [serotonin syndrome](#). The risk of [serotonin syndrome](#) is greater during treatment initiation and dose increases. Discontinue any concomitant serotonergic agents immediately and initiate supportive treatment if [serotonin syndrome](#) is suspected. Patients should be monitored closely for [serotonin syndrome](#), especially during treatment initiation and dose increases. Symptoms of [serotonin syndrome](#) include neuromuscular abnormalities (eg, hyperreflexia, tremor, and ataxia), autonomic instability (eg, [tachycardia](#), diaphoresis, and [hyperthermia](#)), gastrointestinal symptoms (eg, nausea, vomiting, diarrhea), or mental status changes (eg, agitation and confusion)[21][164].
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: The concomitant use of 2 SSRIs, such as [citalopram](#) and [sertraline](#), increases the risk of [serotonin syndrome](#). The risk of [serotonin syndrome](#) is greater during treatment initiation and dose increases. Discontinue any concomitant serotonergic agents immediately and initiate supportive treatment if [serotonin syndrome](#) is suspected. Monitor patients closely for [serotonin syndrome](#), especially during treatment initiation and dose increases. Symptoms of [serotonin syndrome](#) include neuromuscular abnormalities (eg, hyperreflexia, tremor, and ataxia), autonomic instability (eg, [tachycardia](#), diaphoresis, and [hyperthermia](#)), gastrointestinal symptoms (eg, nausea, vomiting, diarrhea), or mental status changes (eg, agitation and confusion)[21][164].
- 7) Probable Mechanism: additive serotonergic effects

**3.5.1.AJ] Clomipramine**

- 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[21].
- 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[21].
- 7) Probable Mechanism: inhibition of CYP2D6-mediated metabolism; additive serotonergic effects

**3.5.1.AK] Clonixin**

- 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](#)[394] and [gastrointestinal bleeding](#) [398][399][395][396]. Bleeding events have included [epistaxis](#), ecchymosis, [hematoma](#), [petechiae](#), and life-threatening hemorrhages [401][400][402][403]. 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](#)[394] and [gastrointestinal bleeding](#) [395][396]. 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 [394].

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 [397].

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 [398] to 2.36 times [399], NSAIDs by 2.55 times [398], and the combination of SSRIs and NSAIDs by 4.02 [398] to 6.33 times [399].

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 [400].

### 3.5.1.AL] [Clopidogrel](#)

1j) Interaction Effect: increased risk of bleeding

2j) Summary: Exercise caution when coadministering a SSRI and an antiplatelet agent as this may increase the risk of bleeding events[141][21][140].

3j) Severity: major

4j) Onset: unspecified

5j) Substantiation: theoretical

6j) Clinical Management: Concomitant use of [sertraline](#) and an antiplatelet agent should be undertaken with caution as this may increase the risk of bleeding events[21].

7j) Probable Mechanism: unknown

8j) 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 [140].

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) [141].

### 3.5.1.AM] Clorgyline

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

2) Summary: Concurrent administration or overlapping therapy with [sertraline](#) 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[382][383][384][385] [386]. Concomitant use is contraindicated.

3) Severity: contraindicated

4) Onset: rapid

5) Substantiation: probable

6) Clinical Management: Concurrent use of [sertraline](#) and a MAO inhibitor is contraindicated. Wait at least 14 days after discontinuing a MAO inhibitor before initiating therapy with [sertraline](#). Wait at least 14 days after discontinuing [sertraline](#) 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](#) [378]. [Serotonin syndrome](#) is a condition of serotonergic hyperstimulation and manifests as restlessness, myoclonus, changes in mental status, hyperreflexia, diaphoresis, shivering, and tremor. If the syndrome is not recognized and correctly treated, death can result.

b) A 26-year old woman who had been taking [isocarboxazid](#) for eight weeks stopped taking the drug for 11 days before beginning therapy with [sertraline](#). After a single 100 mg [sertraline](#) dose, the patient became restless and developed leg twitches. The patient was later admitted to the emergency room with diaphoresis, [tachycardia](#), hyperreflexia, and various neuromuscular disturbances. The patient did not improve after treatment with [diazepam](#) and [propranolol](#). The patient was then given two 4 mg doses of [cyproheptadine](#) an hour apart, with notable improvement in symptoms after the second dose [379].

c) A drug interaction was reported in a 61-year old woman in which [sertraline](#) 100 mg twice daily was added to a regimen of [lithium](#), [phenelzine](#), [thioridazine](#), and [doxepin](#). Three hours after taking the first [sertraline](#) dose, the patient was found in a semicomatose state, with elevated body temperature, increased pulse, increased respiration rate, and a blood pressure of 140/110 mmHg. After transportation to the hospital, the patient was misdiagnosed as having [neuroleptic malignant syndrome](#) (NMS) which was later changed to [serotonin syndrome](#) due to a reaction between [sertraline](#) and [phenelzine](#). The authors suggest that MAO inhibitor therapy should be discontinued

for at least two weeks before initiation of therapy with a selective serotonin reuptake inhibitor (SSRI) and that before starting a MAOI, SSRI therapy should be discontinued for at least 5 half-lives of the parent drug and any active metabolites [380].

d)) Two cases reports suggested a possible interaction between [fluoxetine](#) and [selegiline](#) [381]. One case involved a first episode of mania being observed approximately one month after adding [selegiline](#) to [fluoxetine](#) therapy. The patient improved 2 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.AN] Clozapine

- 1)) Interaction Effect: increased [clozapine](#) exposure and risk for QT interval prolongation
- 2)) Summary: Caution is advised with the concomitant use of [sertraline](#) (CYP2D6 inhibitor) and drugs that are known to prolong the QT interval and are CYP2D6 substrates, such as [clozapine](#), due to the possibility of increased [clozapine](#) exposure and risk for QT interval prolongation[21][296]. If concurrent use is required, monitor for adverse reactions, including QT interval prolongation, and consider reducing the [clozapine](#) dose. Cardiac evaluation and treatment discontinuation are warranted if the patient develops symptoms of [torsade de pointes](#) or other [arrhythmias](#) [296].
- 3)) Severity: major
- 4)) Onset: unspecified
- 5)) Substantiation: theoretical
- 6)) Clinical Management: Concomitant use of [sertraline](#) (CYP2D6 inhibitor) with CYP2D6 substrates, such as [clozapine](#), should be undertaken with caution due to the possibility of increased [clozapine](#) exposure and risk for QT interval prolongation[21][296]. If concurrent use is required, monitor for adverse reactions, including QT interval prolongation, and consider reducing the [clozapine](#) dose. Cardiac evaluation and treatment discontinuation are warranted if the patient develops symptoms of [torsade de pointes](#) or other [arrhythmias](#) [296].
- 7)) Probable Mechanism: inhibition of CYP2D6-mediated [clozapine](#) metabolism by [sertraline](#)

### 3.5.1.AO] Cyclobenzaprine

- 1)) Interaction Effect: increased risk of [serotonin syndrome](#)
- 2)) Summary: [Sertraline](#) is a serotonergic drug. Avoid concurrent use with [cyclobenzaprine](#) as coadministration may result in additive [serotonin syndrome](#). The risk of [serotonin syndrome](#) is greater during treatment initiation and dose increases. Discontinue [sertraline](#) and any concomitant serotonergic agents immediately and initiate supportive treatment if [serotonin syndrome](#) is suspected. If concurrent use is necessary, patients should be monitored closely for [serotonin syndrome](#), especially during treatment initiation and dose increases. Symptoms of [serotonin syndrome](#) include neuromuscular abnormalities (eg, hyperreflexia, tremor, and ataxia), autonomic instability (eg, [tachycardia](#), diaphoresis, and [hyperthermia](#)), gastrointestinal symptoms (eg, nausea, vomiting, diarrhea), or mental status changes (eg, agitation and confusion). Discontinue both drugs immediately if these symptoms occur and initiate supportive therapy[21][297].
- 3)) Severity: major
- 4)) Onset: unspecified
- 5)) Substantiation: theoretical
- 6)) Clinical Management: [Sertraline](#) is a serotonergic drug . Avoid concurrent use with [cyclobenzaprine](#) as coadministration may result in additive [serotonin syndrome](#). The risk of [serotonin syndrome](#) is greater during treatment initiation and dose increases. Discontinue [sertraline](#) and any concomitant

serotonergic agents immediately and initiate supportive treatment if [serotonin syndrome](#) is suspected. 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[21][297].

7) Probable Mechanism: additive serotonergic effects

### 3.5.1.AP] [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 (such as [sertraline](#)) and anticoagulants has been associated with an increased risk of bleeding[129][130][128]. Bleeding events reported have included [epistaxis](#), ecchymosis, [hematoma](#), [petechiae](#), and life-threatening hemorrhages. Altered anticoagulant effects (including increased bleeding) have been reported with the coadministration of SSRIs with [warfarin](#) [128]. Prothrombin time should be monitored in patients receiving both [warfarin](#) and [sertraline](#) [132].

3) Severity: major

4) Onset: delayed

5) Substantiation: probable

6) Clinical Management: When [sertraline](#) 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 [sertraline](#) therapy is initiated or discontinued[128].

7) Probable Mechanism: unknown

8) Literature Reports

a) According to a retrospective cohort study (n=234), there was an increased risk of clinically relevant bleeding (hospital admission due to bleeding) in patients receiving [warfarin](#) for [atrial fibrillation](#) during concomitant SSRI therapy or within 2 weeks following SSRI therapy termination. Patients with a mean age of 72 +/- 7 years receiving [warfarin](#) plus SSRI (n=117) were matched with randomly selected patients who received [warfarin](#) only (n=117). SSRI included [fluoxetine](#), [citalopram](#), [paroxetine](#), [sertraline](#), [fluvoxamine](#), or escitalopram. Nine patients experienced 11 bleeding episodes during 213.9 treatment years in the [warfarin](#) plus SSRI group, and 10 patients experienced 14 bleedings during 586.4 treatment years in the warfarin-only group. The corresponding total incidences of bleedings were 51.4 and 23.9 per 1000 treatment years, respectively. The hazard ratio for first bleedings during treatment with [warfarin](#) plus SSRI was 3.49 (95% CI; 1.37 to 8.91, p=0.009) compared with [warfarin](#) only. The SSRI implicated in patients experiencing bleeding at the time of concomitant administration were [sertraline](#) or [citalopram](#). The addition of an SSRI was not associated with a change in [warfarin](#) dose or INR (p=0.48 and p=0.31 respectively). The results of the study may be limited by earlier bleeding events, unknown patient adherence, and exclusion of [clopidogrel](#), dipyridamol, corticosteroids and anticoagulants other than [warfarin](#) in the model [129].

b) A population-based, case-controlled study of new coumarin users (acenocoumarol and phenprocoumon) with concomitant selective serotonin reuptake inhibitors (SSRIs) resulted in an increased risk of hospitalization due to non-gastrointestinal bleeding. Using national pharmacy and hospitalization records in the Netherlands, researchers identified 1848 cases that were admitted for abnormal bleeding and compared them with 5818 control subjects who were also

taking a coumarin. Median duration of treatment in patients was 220 days (range, 1 to 4690 days). Patients on SSRIs showed greater risk for hospitalization for nongastrointestinal bleeding (adjusted odds ratio (OR) 1.7, 95% confidence interval (CI), 1.1 to 2.5); however, the rate of [gastrointestinal bleeding](#) (adjusted OR 0.8, 95% CI, 0.4 to 1.5) was not significantly different [130].

c) [Sertraline](#) 50 mg to 200 mg daily for 21 days produced an 8% increase in prothrombin time in subjects who received a single dose of [warfarin](#) 0.75 mg/kg relative to the same [warfarin](#) dose given prior to [sertraline](#); this compared with a 1% decrease with placebo. Normalization of the prothrombin time was also delayed as compared with placebo. The clinical significance of these findings is unknown [128].

d) In a non-blinded, randomized, placebo-controlled trial involving 12 healthy volunteers, the effect of [sertraline](#) on the plasma protein binding of [warfarin](#) was assessed. On days 1 and 32 of the study, all participants received [warfarin](#) 0.75 mg/kg. Beginning on day 11, each volunteer was randomized to either the [sertraline](#) or placebo group; the [sertraline](#) was gradually increased from 50 mg/day to 200 mg/day. Prothrombin time was measured prior to each dose of [warfarin](#) and periodically thereafter. The researchers concluded that the anticoagulant effects of [warfarin](#) were not enhanced by [sertraline](#) to a clinically significant degree, despite the fact that [sertraline](#) was given in a higher-than-usual dose [131].

### 3.5.1.AQ] [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 (such as [sertraline](#)) and anticoagulants has been associated with an increased risk of bleeding[129][130][128]. Bleeding events reported have included [epistaxis](#), ecchymosis, [hematoma](#), [petechiae](#), and life-threatening hemorrhages. Altered anticoagulant effects (including increased bleeding) have been reported with the coadministration of SSRIs with [warfarin](#) [128]. Prothrombin time should be monitored in patients receiving both [warfarin](#) and [sertraline](#) [132].

3) Severity: major

4) Onset: delayed

5) Substantiation: probable

6) Clinical Management: When [sertraline](#) 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 [sertraline](#) therapy is initiated or discontinued[128].

7) Probable Mechanism: unknown

8) Literature Reports

a) According to a retrospective cohort study (n=234), there was an increased risk of clinically relevant bleeding (hospital admission due to bleeding) in patients receiving [warfarin](#) for [atrial fibrillation](#) during concomitant SSRI therapy or within 2 weeks following SSRI therapy termination. Patients with a mean age of 72 +/- 7 years receiving [warfarin](#) plus SSRI (n=117) were matched with randomly selected patients who received [warfarin](#) only (n=117). SSRI included [fluoxetine](#), [citalopram](#), [paroxetine](#), [sertraline](#), [fluvoxamine](#), or [escitalopram](#). Nine patients experienced 11 bleeding episodes during 213.9 treatment years in the [warfarin](#) plus SSRI group, and 10 patients experienced 14 bleedings during 586.4 treatment years in the warfarin-only group. The corresponding total incidences of bleedings were 51.4 and 23.9 per 1000 treatment years, respectively. The hazard ratio for first bleedings during treatment with [warfarin](#) plus SSRI was 3.49 (95% CI; 1.37 to 8.91, p=0.009) compared with [warfarin](#) only. The SSRI implicated in patients experiencing bleeding at the time of concomitant administration were [sertraline](#) or



**citalopram.** The addition of an SSRI was not associated with a change in **warfarin** dose or INR ( $p=0.48$  and  $p=0.31$  respectively). The results of the study may be limited by earlier bleeding events, unknown patient adherence, and exclusion of **clopidogrel**, dipyridamol, corticosteroids and anticoagulants other than **warfarin** in the model [129].

**b))** A population-based, case-controlled study of new coumarin users (acenocoumarol and phenprocoumon) with concomitant selective serotonin reuptake inhibitors (SSRIs) resulted in an increased risk of hospitalization due to non-gastrointestinal bleeding. Using national pharmacy and hospitalization records in the Netherlands, researchers identified 1848 cases that were admitted for abnormal bleeding and compared them with 5818 control subjects who were also taking a coumarin. Median duration of treatment in patients was 220 days (range, 1 to 4690 days). Patients on SSRIs showed greater risk for hospitalization for nongastrointestinal bleeding (adjusted odds ratio (OR) 1.7, 95% confidence interval (CI), 1.1 to 2.5); however, the rate of **gastrointestinal bleeding** (adjusted OR 0.8, 95% CI, 0.4 to 1.5) was not significantly different [130].

**c))** **Sertraline** 50 mg to 200 mg daily for 21 days produced an 8% increase in prothrombin time in subjects who received a single dose of **warfarin** 0.75 mg/kg relative to the same **warfarin** dose given prior to **sertraline**; this compared with a 1% decrease with placebo. Normalization of the prothrombin time was also delayed as compared with placebo. The clinical significance of these findings is unknown [128].

**d))** In a non-blinded, randomized, placebo-controlled trial involving 12 healthy volunteers, the effect of **sertraline** on the plasma protein binding of **warfarin** was assessed. On days 1 and 32 of the study, all participants received **warfarin** 0.75 mg/kg. Beginning on day 11, each volunteer was randomized to either the **sertraline** or placebo group; the **sertraline** was gradually increased from 50 mg/day to 200 mg/day. Prothrombin time was measured prior to each dose of **warfarin** and periodically thereafter. The researchers concluded that the anticoagulant effects of **warfarin** were not enhanced by **sertraline** to a clinically significant degree, despite the fact that **sertraline** was given in a higher-than-usual dose [131].

### 3.5.1.AR] 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 (such as **sertraline**) and anticoagulants has been associated with an increased risk of bleeding[129][130][128]. Bleeding events reported have included **epistaxis**, ecchymosis, **hematoma**, **petechiae**, and life-threatening hemorrhages. Altered anticoagulant effects (including increased bleeding) have been reported with the coadministration of SSRIs with **warfarin** [128]. Prothrombin time should be monitored in patients receiving both **warfarin** and **sertraline** [132].

**3))** Severity: major

**4))** Onset: delayed

**5))** Substantiation: probable

**6))** Clinical Management: When **sertraline** 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 **sertraline** therapy is initiated or discontinued[128].

**7))** Probable Mechanism: unknown

**8))** Literature Reports

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

fibrillation during concomitant SSRI therapy or within 2 weeks following SSRI therapy termination. Patients with a mean age of 72 +/- 7 years receiving warfarin plus SSRI (n=117) were matched with randomly selected patients who received warfarin only (n=117). SSRI included fluoxetine, citalopram, paroxetine, sertraline, fluvoxamine, or escitalopram. Nine patients experienced 11 bleeding episodes during 213.9 treatment years in the warfarin plus SSRI group, and 10 patients experienced 14 bleedings during 586.4 treatment years in the warfarin-only group. The corresponding total incidences of bleedings were 51.4 and 23.9 per 1000 treatment years, respectively. The hazard ratio for first bleedings during treatment with warfarin plus SSRI was 3.49 (95% CI; 1.37 to 8.91, p=0.009) compared with warfarin only. The SSRI implicated in patients experiencing bleeding at the time of concomitant administration were sertraline or citalopram. The addition of an SSRI was not associated with a change in warfarin dose or INR (p=0.48 and p=0.31 respectively). The results of the study may be limited by earlier bleeding events, unknown patient adherence, and exclusion of clopidogrel, dipyridamol, corticosteroids and anticoagulants other than warfarin in the model [129].

b) A population-based, case-controlled study of new coumarin users (acenocoumarol and phenprocoumon) with concomitant selective serotonin reuptake inhibitors (SSRIs) resulted in an increased risk of hospitalization due to non-gastrointestinal bleeding. Using national pharmacy and hospitalization records in the Netherlands, researchers identified 1848 cases that were admitted for abnormal bleeding and compared them with 5818 control subjects who were also taking a coumarin. Median duration of treatment in patients was 220 days (range, 1 to 4690 days). Patients on SSRIs showed greater risk for hospitalization for nongastrointestinal bleeding (adjusted odds ratio (OR) 1.7, 95% confidence interval (CI), 1.1 to 2.5); however, the rate of gastrointestinal bleeding (adjusted OR 0.8, 95% CI, 0.4 to 1.5) was not significantly different [130].

c) Sertraline 50 mg to 200 mg daily for 21 days produced an 8% increase in prothrombin time in subjects who received a single dose of warfarin 0.75 mg/kg relative to the same warfarin dose given prior to sertraline; this compared with a 1% decrease with placebo. Normalization of the prothrombin time was also delayed as compared with placebo. The clinical significance of these findings is unknown [128].

d) In a non-blinded, randomized, placebo-controlled trial involving 12 healthy volunteers, the effect of sertraline on the plasma protein binding of warfarin was assessed. On days 1 and 32 of the study, all participants received warfarin 0.75 mg/kg. Beginning on day 11, each volunteer was randomized to either the sertraline or placebo group; the sertraline was gradually increased from 50 mg/day to 200 mg/day. Prothrombin time was measured prior to each dose of warfarin and periodically thereafter. The researchers concluded that the anticoagulant effects of warfarin were not enhanced by sertraline to a clinically significant degree, despite the fact that sertraline was given in a higher-than-usual dose [131].

### 3.5.1.AS] 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 [268]. DHEA was also noted to cause mania in a patient with no previous personal or family history of bipolar disorder [269]. Elevated DHEA levels have been found in patients with mental disorders; DHEA suppression has led to improvement in psychotic symptoms [270]. DHEA possesses proserotonergic activity which may predispose patients to manic episodes [271]. DHEA is a precursor to androgenic steroids, which in high doses may precipitate mania [269]. 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](#) [267].

### 3.5.1.AT] 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 (such as [sertraline](#)) and anticoagulants has been associated with an increased risk of bleeding[129][130][128]. Bleeding events reported have included [epistaxis](#), ecchymosis, [hematoma](#), [petechiae](#), and life-threatening hemorrhages. Altered anticoagulant effects (including increased bleeding) have been reported with the coadministration of SSRIs with [warfarin](#) [128]. Prothrombin time should be monitored in patients receiving both [warfarin](#) and [sertraline](#) [132].

3) Severity: major

4) Onset: delayed

5) Substantiation: probable

6) Clinical Management: When [sertraline](#) 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 [sertraline](#) therapy is initiated or discontinued[128].

7) Probable Mechanism: unknown

8) Literature Reports

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

patients experienced 11 bleeding episodes during 213.9 treatment years in the [warfarin](#) plus SSRI group, and 10 patients experienced 14 bleedings during 586.4 treatment years in the warfarin-only group. The corresponding total incidences of bleedings were 51.4 and 23.9 per 1000 treatment years, respectively. The hazard ratio for first bleedings during treatment with [warfarin](#) plus SSRI was 3.49 (95% CI; 1.37 to 8.91,  $p=0.009$ ) compared with [warfarin](#) only. The SSRI implicated in patients experiencing bleeding at the time of concomitant administration were [sertraline](#) or [citalopram](#). The addition of an SSRI was not associated with a change in [warfarin](#) dose or INR ( $p=0.48$  and  $p=0.31$  respectively). The results of the study may be limited by earlier bleeding events, unknown patient adherence, and exclusion of [clopidogrel](#), dipyridamol, corticosteroids and anticoagulants other than [warfarin](#) in the model [129].

**b))** A population-based, case-controlled study of new coumarin users (acenocoumarol and phenprocoumon) with concomitant selective serotonin reuptake inhibitors (SSRIs) resulted in an increased risk of hospitalization due to non-gastrointestinal bleeding. Using national pharmacy and hospitalization records in the Netherlands, researchers identified 1848 cases that were admitted for abnormal bleeding and compared them with 5818 control subjects who were also taking a coumarin. Median duration of treatment in patients was 220 days (range, 1 to 4690 days). Patients on SSRIs showed greater risk for hospitalization for nongastrointestinal bleeding (adjusted odds ratio (OR) 1.7, 95% confidence interval (CI), 1.1 to 2.5); however, the rate of [gastrointestinal bleeding](#) (adjusted OR 0.8, 95% CI, 0.4 to 1.5) was not significantly different [130].

**c))** [Sertraline](#) 50 mg to 200 mg daily for 21 days produced an 8% increase in prothrombin time in subjects who received a single dose of [warfarin](#) 0.75 mg/kg relative to the same [warfarin](#) dose given prior to [sertraline](#); this compared with a 1% decrease with placebo. Normalization of the prothrombin time was also delayed as compared with placebo. The clinical significance of these findings is unknown [128].

**d))** In a non-blinded, randomized, placebo-controlled trial involving 12 healthy volunteers, the effect of [sertraline](#) on the plasma protein binding of [warfarin](#) was assessed. On days 1 and 32 of the study, all participants received [warfarin](#) 0.75 mg/kg. Beginning on day 11, each volunteer was randomized to either the [sertraline](#) or placebo group; the [sertraline](#) was gradually increased from 50 mg/day to 200 mg/day. Prothrombin time was measured prior to each dose of [warfarin](#) and periodically thereafter. The researchers concluded that the anticoagulant effects of [warfarin](#) were not enhanced by [sertraline](#) to a clinically significant degree, despite the fact that [sertraline](#) was given in a higher-than-usual dose [131].

### 3.5.1.AU] [Desipramine](#)

**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[21].

**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[21].

7J) Probable Mechanism: inhibition of CYP2D6-mediated metabolism; additive serotonergic effects

### 3.5.1.AV] Desirudin

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 (such as [sertraline](#)) and anticoagulants has been associated with an increased risk of bleeding[129][130][128]. Bleeding events reported have included [epistaxis](#), ecchymosis, [hematoma](#), [petechiae](#), and life-threatening hemorrhages. Altered anticoagulant effects (including increased bleeding) have been reported with the coadministration of SSRIs with [warfarin](#) [128]. Prothrombin time should be monitored in patients receiving both [warfarin](#) and [sertraline](#) [132].

3J) Severity: major

4J) Onset: delayed

5J) Substantiation: probable

6J) Clinical Management: When [sertraline](#) 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 [sertraline](#) therapy is initiated or discontinued[128].

7J) Probable Mechanism: unknown

8J) Literature Reports

aJ) According to a retrospective cohort study (n=234), there was an increased risk of clinically relevant bleeding (hospital admission due to bleeding) in patients receiving [warfarin](#) for [atrial fibrillation](#) during concomitant SSRI therapy or within 2 weeks following SSRI therapy termination. Patients with a mean age of 72 +/- 7 years receiving [warfarin](#) plus SSRI (n=117) were matched with randomly selected patients who received [warfarin](#) only (n=117). SSRI included [fluoxetine](#), [citalopram](#), [paroxetine](#), [sertraline](#), [fluvoxamine](#), or escitalopram. Nine patients experienced 11 bleeding episodes during 213.9 treatment years in the [warfarin](#) plus SSRI group, and 10 patients experienced 14 bleedings during 586.4 treatment years in the warfarin-only group. The corresponding total incidences of bleedings were 51.4 and 23.9 per 1000 treatment years, respectively. The hazard ratio for first bleedings during treatment with [warfarin](#) plus SSRI was 3.49 (95% CI; 1.37 to 8.91, p=0.009) compared with [warfarin](#) only. The SSRI implicated in patients experiencing bleeding at the time of concomitant administration were [sertraline](#) or [citalopram](#). The addition of an SSRI was not associated with a change in [warfarin](#) dose or INR (p=0.48 and p=0.31 respectively). The results of the study may be limited by earlier bleeding events, unknown patient adherence, and exclusion of [clopidogrel](#), dipyridamol, corticosteroids and anticoagulants other than [warfarin](#) in the model [129].

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



(adjusted odds ratio (OR) 1.7, 95% confidence interval (CI), 1.1 to 2.5); however, the rate of [gastrointestinal bleeding](#) (adjusted OR 0.8, 95% CI, 0.4 to 1.5) was not significantly different [130].

c) [Sertraline](#) 50 mg to 200 mg daily for 21 days produced an 8% increase in prothrombin time in subjects who received a single dose of [warfarin](#) 0.75 mg/kg relative to the same [warfarin](#) dose given prior to [sertraline](#); this compared with a 1% decrease with placebo. Normalization of the prothrombin time was also delayed as compared with placebo. The clinical significance of these findings is unknown [128].

d) In a non-blinded, randomized, placebo-controlled trial involving 12 healthy volunteers, the effect of [sertraline](#) on the plasma protein binding of [warfarin](#) was assessed. On days 1 and 32 of the study, all participants received [warfarin](#) 0.75 mg/kg. Beginning on day 11, each volunteer was randomized to either the [sertraline](#) or placebo group; the [sertraline](#) was gradually increased from 50 mg/day to 200 mg/day. Prothrombin time was measured prior to each dose of [warfarin](#) and periodically thereafter. The researchers concluded that the anticoagulant effects of [warfarin](#) were not enhanced by [sertraline](#) to a clinically significant degree, despite the fact that [sertraline](#) was given in a higher-than-usual dose [131].

### 3.5.1.AW] Desvenlafaxine

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

2) Summary: Desvenlafaxine is a serotonergic drug; concomitant use with another agent that affects the serotonergic neurotransmitter system may result in an increased risk of [serotonin syndrome](#) and should be approached with extreme caution. [Serotonin syndrome](#) may be life-threatening. Symptoms may include mental status changes (eg, agitation, hallucinations, coma), autonomic instability (eg, [tachycardia](#), labile blood pressure, [hyperthermia](#)), neuromuscular aberrations (eg, hyperreflexia, incoordination), and/or gastrointestinal symptoms (eg, nausea, vomiting, diarrhea). If coadministration is required, monitor closely for signs and symptoms of [serotonin syndrome](#), especially during treatment initiation and dose increases of either drug. If [serotonin syndrome](#) develops, discontinue both agents and initiate supportive symptomatic therapy[226].

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Use extreme caution with coadministration of desvenlafaxine and another serotonergic drug, such as an SSRI, serotonin-norepinephrine reuptake inhibitor, or tricyclic antidepressant, as this may result in additive serotonergic effects and may increase the risk of [serotonin syndrome](#). If coadministration is required, careful monitoring is recommended, especially during treatment initiation and dose increases. Immediate discontinuation of both agents and supportive symptomatic treatment is warranted if [serotonin syndrome](#) develops[226].

7) Probable Mechanism: additive serotonergic effect

### 3.5.1.AX] Dexfenfluramine

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

2) Summary: Dexfenfluramine is a nonspecific serotonin agonist that both enhances the release of serotonin and inhibits serotonin reuptake. Combination therapy with dexfenfluramine and another selective serotonin reuptake inhibitor, such as [sertraline](#), has the potential to cause [serotonin syndrome](#)[312]. [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 [313]. Dexfenfluramine should not be used in combination with [sertraline](#) [314].

3) Severity: major

4) Onset: rapid

5) Substantiation: theoretical

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

7) Probable Mechanism: additive serotonergic effects

### 3.5.1.AY] Dexibuprofen

1) Interaction Effect: an increased risk of bleeding

2) Summary: Caution is recommended with the concomitant use of NSAIDs and antidepressants, including SSRIs due to an increased risk of [intracranial hemorrhage](#)[394] and [gastrointestinal bleeding](#) [398][399][395][396]. Bleeding events have included [epistaxis](#), ecchymosis, [hematoma](#), [petechiae](#), and life-threatening hemorrhages [401][400][402][403]. 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](#)[394] and [gastrointestinal bleeding](#) [395][396]. 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 [394].

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 [397].

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 [398] to 2.36 times [399], NSAIDs by 2.55 times [398], and the combination of SSRIs and NSAIDs by 4.02 [398] to 6.33 times [399].

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 [400].

### 3.5.1.AZ] 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](#)[394] and [gastrointestinal bleeding](#) [398][399][395][396]. Bleeding events have included [epistaxis](#), ecchymosis, [hematoma](#), [petechiae](#), and life-threatening hemorrhages [401][400][402][403]. 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](#)[394] and [gastrointestinal bleeding](#) [395][396]. 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 [394].

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 [397].

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 [398] to 2.36 times [399], NSAIDs by 2.55 times [398], and the combination of SSRIs and NSAIDs by 4.02 [398] to 6.33 times [399].

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 [400].

### 3.5.1.BA] 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[393].

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[393].

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

### 3.5.1.BB| [Dextromethorphan](#)

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

2) Summary: [Sertraline](#) is a moderate CYP2D6 inhibitor[13] and [dextromethorphan](#) is a CYP2D6 substrate. While not specifically studied with [sertraline](#), the concomitant use of [paroxetine](#) (another SSRI) with the combination of [dextromethorphan/quinidine](#) in one study resulted in increased AUC and Cmax of [paroxetine](#), [dextromethorphan](#), and [quinidine](#). As the concomitant use of [dextromethorphan](#) with [sertraline](#) may increase the risk of [serotonin syndrome](#), initial dose reductions of [dextromethorphan](#) may be warranted [437] along with monitoring for signs/symptoms of [serotonin syndrome](#) (eg, altered mental status, [hypertension](#), restlessness, myoclonus, [hyperthermia](#), hyperreflexia, diaphoresis, shivering, and tremor).

3) Severity: major

4) Onset: delayed

5) Substantiation: theoretical

6) Clinical Management: Use caution when prescribing [dextromethorphan](#) to patients who are taking an SSRI (such as [sertraline](#)), as concomitant use may result in an increased risk of [serotonin syndrome](#). Initial dose reductions of [dextromethorphan](#) may be warranted when administered with CYP2D6 inhibitors, such as [sertraline](#)[437][13].

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

8) Literature Reports

a) In a group of 14 healthy subjects, the administration of [paroxetine](#) (20 mg once daily for 12 days) followed by a combination of [dextromethorphan](#) 30 mg/[quinidine](#) 30 mg (twice daily for 8 days) resulted in an increase in [paroxetine](#) AUC and Cmax (1.7- and 1.5-fold, respectively) and a decrease in dextromethorphan AUC and Cmax (34% and 33%, respectively). The [dextromethorphan/quinidine](#) exposure did not change significantly. In a second group of 13 healthy subjects, the administration of [dextromethorphan](#) 30 mg/[quinidine](#) 30 mg (twice daily for 8 days) followed by [paroxetine](#) (20 mg once daily for 12 days) resulted in an increase in [dextromethorphan](#) AUC and Cmax (1.5- and 1.4-fold, respectively), a decrease in dextromethorphan AUC and Cmax (14% and 18%, respectively) an increase in [quinidine](#) AUC and Cmax (1.4- and 1.3-fold, respectively), and an increase in [paroxetine](#) AUC and Cmax (2.3- and 2-fold, respectively) [437].

**3.5.1.BC] 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](#)[394] and [gastrointestinal bleeding](#) [398][399][395][396]. Bleeding events have included [epistaxis](#), ecchymosis, [hematoma](#), [petechiae](#), and life-threatening hemorrhages [401][400][402][403]. 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](#)[394] and [gastrointestinal bleeding](#) [395][396]. 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 [394].

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 [397].

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 [398] to 2.36 times [399], NSAIDs by 2.55 times [398], and the combination of SSRIs and NSAIDs by 4.02 [398] to 6.33 times [399].

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 [400].

**3.5.1.BD] 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 (such as [sertraline](#)) and anticoagulants has been associated with an increased risk of bleeding[129][130][128]. Bleeding events reported have included [epistaxis](#), ecchymosis, [hematoma](#), [petechiae](#), and life-threatening hemorrhages. Altered anticoagulant

effects (including increased bleeding) have been reported with the coadministration of SSRIs with [warfarin](#) [128]. Prothrombin time should be monitored in patients receiving both [warfarin](#) and [sertraline](#) [132].

3) Severity: major

4) Onset: delayed

5) Substantiation: probable

6) Clinical Management: When [sertraline](#) 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 [sertraline](#) therapy is initiated or discontinued[128].

7) Probable Mechanism: unknown

8) Literature Reports

a) According to a retrospective cohort study (n=234), there was an increased risk of clinically relevant bleeding (hospital admission due to bleeding) in patients receiving [warfarin](#) for [atrial fibrillation](#) during concomitant SSRI therapy or within 2 weeks following SSRI therapy termination. Patients with a mean age of 72 +/- 7 years receiving [warfarin](#) plus SSRI (n=117) were matched with randomly selected patients who received [warfarin](#) only (n=117). SSRI included [fluoxetine](#), [citalopram](#), [paroxetine](#), [sertraline](#), [fluvoxamine](#), or [escitalopram](#). Nine patients experienced 11 bleeding episodes during 213.9 treatment years in the [warfarin](#) plus SSRI group, and 10 patients experienced 14 bleedings during 586.4 treatment years in the warfarin-only group. The corresponding total incidences of bleedings were 51.4 and 23.9 per 1000 treatment years, respectively. The hazard ratio for first bleedings during treatment with [warfarin](#) plus SSRI was 3.49 (95% CI; 1.37 to 8.91, p=0.009) compared with [warfarin](#) only. The SSRI implicated in patients experiencing bleeding at the time of concomitant administration were [sertraline](#) or [citalopram](#). The addition of an SSRI was not associated with a change in [warfarin](#) dose or INR (p=0.48 and p=0.31 respectively). The results of the study may be limited by earlier bleeding events, unknown patient adherence, and exclusion of [clopidogrel](#), dipyridamol, corticosteroids and anticoagulants other than [warfarin](#) in the model [129].

b) A population-based, case-controlled study of new coumarin users (acenocoumarol and phenprocoumon) with concomitant selective serotonin reuptake inhibitors (SSRIs) resulted in an increased risk of hospitalization due to non-gastrointestinal bleeding. Using national pharmacy and hospitalization records in the Netherlands, researchers identified 1848 cases that were admitted for abnormal bleeding and compared them with 5818 control subjects who were also taking a coumarin. Median duration of treatment in patients was 220 days (range, 1 to 4690 days). Patients on SSRIs showed greater risk for hospitalization for nongastrointestinal bleeding (adjusted odds ratio (OR) 1.7, 95% confidence interval (CI), 1.1 to 2.5); however, the rate of [gastrointestinal bleeding](#) (adjusted OR 0.8, 95% CI, 0.4 to 1.5) was not significantly different [130].

c) [Sertraline](#) 50 mg to 200 mg daily for 21 days produced an 8% increase in prothrombin time in subjects who received a single dose of [warfarin](#) 0.75 mg/kg relative to the same [warfarin](#) dose given prior to [sertraline](#); this compared with a 1% decrease with placebo. Normalization of the prothrombin time was also delayed as compared with placebo. The clinical significance of these findings is unknown [128].

d) In a non-blinded, randomized, placebo-controlled trial involving 12 healthy volunteers, the effect of [sertraline](#) on the plasma protein binding of [warfarin](#) was assessed. On days 1 and 32 of the study, all participants received [warfarin](#) 0.75 mg/kg. Beginning on day 11, each volunteer was randomized to either the [sertraline](#) or placebo group; the [sertraline](#) was gradually increased from 50 mg/day to 200 mg/day. Prothrombin time was measured prior to each dose of [warfarin](#) and

periodically thereafter. The researchers concluded that the anticoagulant effects of [warfarin](#) were not enhanced by [sertraline](#) to a clinically significant degree, despite the fact that [sertraline](#) was given in a higher-than-usual dose [131].

### 3.5.1.BE] [Diflunisal](#)

- 1) Interaction Effect: an increased risk of bleeding
- 2) Summary: Caution is recommended with the concomitant use of NSAIDs and antidepressants, including SSRIs due to an increased risk of [intracranial hemorrhage](#)[394] and [gastrointestinal bleeding](#) [398][399][395][396]. Bleeding events have included [epistaxis](#), ecchymosis, [hematoma](#), [petechiae](#), and life-threatening hemorrhages [401][400][402][403]. 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](#)[394] and [gastrointestinal bleeding](#) [395][396]. 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 [394].

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 [397].

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 [398] to 2.36 times [399], NSAIDs by 2.55 times [398], and the combination of SSRIs and NSAIDs by 4.02 [398] to 6.33 times [399].

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 [400].

### 3.5.1.BF] [Dipyridamole](#)

- 1) Interaction Effect: increased risk of bleeding
- 2) Summary: Exercise caution when coadministering a SSRI and an antiplatelet agent as this may increase the risk of bleeding events[141][21][140].



- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Concomitant use of [sertraline](#) and an antiplatelet agent should be undertaken with caution as this may increase the risk of bleeding events[21].
- 7) Probable Mechanism: unknown
- 8) Literature Reports

a) In a retrospective study of patients over 50 years of age with the diagnosis of acute [myocardial infarction](#) (N=27,058), SSRI use with any antiplatelet therapy significantly increased the risk of bleeding by 1.42-fold compared with [aspirin](#) use alone. Therapy with [aspirin](#), [clopidogrel](#), and an SSRI significantly increased risk by 2.35-fold compared with [aspirin](#) use alone and by 1.57-fold compared with [clopidogrel](#) and [aspirin](#) combination therapy [140].

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) [141].

### 3.5.1.BG] Dipyrrone

- 1) Interaction Effect: an increased risk of bleeding
- 2) Summary: Caution is recommended with the concomitant use of NSAIDs and antidepressants, including SSRIs due to an increased risk of [intracranial hemorrhage](#)[394] and [gastrointestinal bleeding](#) [398][399][395][396]. Bleeding events have included [epistaxis](#), ecchymosis, [hematoma](#), [petechiae](#), and life-threatening hemorrhages [401][400][402][403]. 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](#)[394] and [gastrointestinal bleeding](#) [395][396]. 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 [394].

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 [397].

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 [398] to 2.36 times [399], NSAIDs by 2.55 times [398], and the combination of SSRIs and NSAIDs by 4.02 [398] to 6.33 times [399].

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 [400].

### 3.5.1.BH] [Dolasetron](#)

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

2) Summary: Concomitant use of [dolasetron](#) with a serotonergic agent may increase the risk of [serotonin syndrome](#). Monitor for the emergence of [serotonin syndrome](#). Discontinue treatment with [dolasetron](#) and institute supportive therapy if symptoms of [serotonin syndrome](#) occur[157][158].

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Concomitant use of [dolasetron](#) with a serotonergic agent may increase the risk of [serotonin syndrome](#). Monitor for the emergence of [serotonin syndrome](#). Discontinue treatment with [dolasetron](#) and institute supportive therapy if symptoms of [serotonin syndrome](#) occur[157][158].

7) Probable Mechanism: unknown

### 3.5.1.BI] [Donepezil](#)

1) Interaction Effect: reduced seizure threshold

2) Summary: Seizure threshold lowering effects have been associated with [donepezil](#)[151]. Use extreme caution when prescribing [donepezil](#) with drugs that lower seizure threshold (eg, antipsychotics, antidepressants, [theophylline](#), systemic corticosteroids). Begin treatment with a low initial dose and increase dose gradually.

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Seizure threshold lowering effects have been associated with [donepezil](#)[151]. Use extreme caution when prescribing [donepezil](#) with drugs that lower seizure threshold (eg, antipsychotics, antidepressants, [theophylline](#), systemic corticosteroids). Begin treatment with a low initial dose and increase dose gradually.

7) Probable Mechanism: unknown

### 3.5.1.BJ] [Dothiepin](#)

1) Interaction Effect: modest elevations in dothiepin serum levels or possible [serotonin syndrome](#) ([hypertension](#), [hyperthermia](#), myoclonus, mental status changes)

2) Summary: There is limited evidence suggesting that [sertraline](#) may inhibit tricyclic antidepressant (TCA) metabolism resulting in higher TCA serum concentrations. Sertraline inhibits cytochrome P450 2D6 enzyme activity and may increase the plasma concentrations of coadministered drugs that are metabolized by this pathway, including the tricyclic antidepressants[228][229][230]. Effects of the interaction may have little or no clinical impact, however. Increases in TCA serum levels associated with [sertraline](#) coadministration were modest compared with those found when [fluoxetine](#) (another selective

serotonin reuptake inhibitor) was combined with [desipramine](#) [231]. Monitor patients on dothiepin-sertraline therapy for TCA toxicity (dry mouth, urinary retention, CNS depression). Dothiepin doses may need to be reduced.

3) Severity: major

4) Onset: delayed

5) Substantiation: probable

6) Clinical Management: The combined use of tricyclic antidepressants (TCAs) and selective serotonin reuptake inhibitors (SSRIs) may result in the inhibition of the TCA metabolism. A few cases of [serotonin syndrome](#) have also been reported with concurrent TCA and SSRI therapy. Caution should be observed when drugs in these two classes are used together.

7) Probable Mechanism: inhibition of dothiepin metabolism

8) Literature Reports

a) [Desipramine](#) pharmacokinetics were studied in 18 healthy male volunteers. Study subjects received only [desipramine](#) (50 mg daily) for 7 days followed by [desipramine](#) with [sertraline](#) (50 mg daily) for 21 days. When [sertraline](#) was added to [desipramine](#) therapy, the mean maximum concentration of [desipramine](#) increased by 34% and the area under the concentration-time curve increased by 26%. Trough concentrations of [desipramine](#) were close to baseline one week after [sertraline](#) was discontinued. The changes in [desipramine](#) concentrations were modest and the interaction may not be clinically significant [227].

### 3.5.1.BK] [Doxepin](#)

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[21].

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[21].

7) Probable Mechanism: inhibition of CYP2D6-mediated metabolism; additive serotonergic effects

### 3.5.1.BL] [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](#)[394] and [gastrointestinal bleeding](#) [398][399][395][396]. Bleeding events have included [epistaxis](#), ecchymosis, [hematoma](#), [petechiae](#), and life-threatening hemorrhages [401][400][402][403]. 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](#)[394] and [gastrointestinal bleeding](#) [395][396]. 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 [394].

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 [397].

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 [398] to 2.36 times [399], NSAIDs by 2.55 times [398], and the combination of SSRIs and NSAIDs by 4.02 [398] to 6.33 times [399].

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 [400].

### 3.5.1.BM] [Duloxetine](#)

- 1) Interaction Effect: an increased risk of [serotonin syndrome](#)
- 2) Summary: [Duloxetine](#) is a selective serotonin and [norepinephrine](#) reuptake inhibitor. The concomitant use of [duloxetine](#) with [sertraline](#), a selective serotonin reuptake inhibitor, is not recommended due to the potential for [serotonin syndrome](#)[154].
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: The concomitant use of [duloxetine](#) and [sertraline](#) is not recommended due to the potential for development of [serotonin syndrome](#)[154].
- 7) Probable Mechanism: additive serotonergic effects

### 3.5.1.BN] [Edoxaban](#)

- 1) Interaction Effect: increased risk of bleeding

- 2) Summary: Concomitant use of edoxaban and SSRIs may increase the risk of bleeding. If coadministration is necessary, promptly evaluate any signs or symptoms of blood loss[202].
- 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[202].
- 7) Probable Mechanism: unknown

### 3.5.1.BO| Efavirenz

- 1) Interaction Effect: decreased [sertraline](#) plasma concentrations
- 2) Summary: Coadministration of [efavirenz](#) and [sertraline](#) resulted in significantly decreased concentrations of [sertraline](#). Therefore, use caution when these two drugs are coadministered and adjust [sertraline](#) doses based on clinical response[121].
- 3) Severity: moderate
- 4) Onset: unspecified
- 5) Substantiation: established
- 6) Clinical Management: The concomitant use of [efavirenz](#) and [sertraline](#) resulted in significantly reduced exposure and plasma concentrations of [sertraline](#). Therefore, use caution if [efavirenz](#) and [sertraline](#) are coadministered. [Sertraline](#) doses may need to be increased based on clinical response[121].
- 7) Probable Mechanism: induction of CYP3A4-mediated [sertraline](#) metabolism by [efavirenz](#)
- 8) Literature Reports

a) In a [pharmacokinetics study](#), concurrent administration of [efavirenz](#) and [sertraline](#) significantly decreased [sertraline](#) exposure and plasma concentrations. Thirteen subjects were administered [sertraline](#) 50 mg orally once daily concurrently with [efavirenz](#) 600 mg orally once daily for 14 days. Results indicated a 29% decrease in [sertraline](#) C<sub>max</sub> (90% confidence interval (CI), 15% to 40%), a 39% decrease in [sertraline](#) AUC (90% CI, 27% to 50%), and a 46% decrease in [sertraline](#) C<sub>min</sub> (90% CI, 31% to 58%). [Efavirenz](#) pharmacokinetics were not significantly altered; there was a mean 11% (90% CI, 6% to 16%) increase in [efavirenz](#) C<sub>max</sub> [121].

### 3.5.1.BP| 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[438].
- 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[438].
- 7) Probable Mechanism: additive serotonergic effects

**3.5.1.BQ| 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 (such as [sertraline](#)) and anticoagulants has been associated with an increased risk of bleeding[129][130][128]. Bleeding events reported have included [epistaxis](#), ecchymosis, [hematoma](#), [petechiae](#), and life-threatening hemorrhages. Altered anticoagulant effects (including increased bleeding) have been reported with the coadministration of SSRIs with [warfarin](#) [128]. Prothrombin time should be monitored in patients receiving both [warfarin](#) and [sertraline](#) [132].

**3)** Severity: major

**4)** Onset: delayed

**5)** Substantiation: probable

**6)** Clinical Management: When [sertraline](#) 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 [sertraline](#) therapy is initiated or discontinued[128].

**7)** Probable Mechanism: unknown

**8)** Literature Reports

**a)** According to a retrospective cohort study (n=234), there was an increased risk of clinically relevant bleeding (hospital admission due to bleeding) in patients receiving [warfarin](#) for [atrial fibrillation](#) during concomitant SSRI therapy or within 2 weeks following SSRI therapy termination. Patients with a mean age of 72 +/- 7 years receiving [warfarin](#) plus SSRI (n=117) were matched with randomly selected patients who received [warfarin](#) only (n=117). SSRI included [fluoxetine](#), [citalopram](#), [paroxetine](#), [sertraline](#), [fluvoxamine](#), or escitalopram. Nine patients experienced 11 bleeding episodes during 213.9 treatment years in the [warfarin](#) plus SSRI group, and 10 patients experienced 14 bleedings during 586.4 treatment years in the warfarin-only group. The corresponding total incidences of bleedings were 51.4 and 23.9 per 1000 treatment years, respectively. The hazard ratio for first bleedings during treatment with [warfarin](#) plus SSRI was 3.49 (95% CI; 1.37 to 8.91, p=0.009) compared with [warfarin](#) only. The SSRI implicated in patients experiencing bleeding at the time of concomitant administration were [sertraline](#) or [citalopram](#). The addition of an SSRI was not associated with a change in [warfarin](#) dose or INR (p=0.48 and p=0.31 respectively). The results of the study may be limited by earlier bleeding events, unknown patient adherence, and exclusion of [clopidogrel](#), dipyridamol, corticosteroids and anticoagulants other than [warfarin](#) in the model [129].

**b)** A population-based, case-controlled study of new coumarin users (acenocoumarol and phenprocoumon) with concomitant selective serotonin reuptake inhibitors (SSRIs) resulted in an increased risk of hospitalization due to non-gastrointestinal bleeding. Using national pharmacy and hospitalization records in the Netherlands, researchers identified 1848 cases that were admitted for abnormal bleeding and compared them with 5818 control subjects who were also taking a coumarin. Median duration of treatment in patients was 220 days (range, 1 to 4690 days). Patients on SSRIs showed greater risk for hospitalization for nongastrointestinal bleeding (adjusted odds ratio (OR) 1.7, 95% confidence interval (CI), 1.1 to 2.5); however, the rate of [gastrointestinal bleeding](#) (adjusted OR 0.8, 95% CI, 0.4 to 1.5) was not significantly different [130].

**c)** [Sertraline](#) 50 mg to 200 mg daily for 21 days produced an 8% increase in prothrombin time in subjects who received a single dose of [warfarin](#) 0.75 mg/kg relative to the same [warfarin](#) dose given prior to [sertraline](#); this compared with a 1% decrease with placebo. Normalization of the



prothrombin time was also delayed as compared with placebo. The clinical significance of these findings is unknown [128].

**d))** In a non-blinded, randomized, placebo-controlled trial involving 12 healthy volunteers, the effect of [sertraline](#) on the plasma protein binding of [warfarin](#) was assessed. On days 1 and 32 of the study, all participants received [warfarin](#) 0.75 mg/kg. Beginning on day 11, each volunteer was randomized to either the [sertraline](#) or placebo group; the [sertraline](#) was gradually increased from 50 mg/day to 200 mg/day. Prothrombin time was measured prior to each dose of [warfarin](#) and periodically thereafter. The researchers concluded that the anticoagulant effects of [warfarin](#) were not enhanced by [sertraline](#) to a clinically significant degree, despite the fact that [sertraline](#) was given in a higher-than-usual dose [131].

### 3.5.1.BR] [Epoprostenol](#)

- 1))** Interaction Effect: increased risk of bleeding
- 2))** Summary: Exercise caution when coadministering a SSRI and an antiplatelet agent as this may increase the risk of bleeding events[141][21][140].
- 3))** Severity: major
- 4))** Onset: unspecified
- 5))** Substantiation: theoretical
- 6))** Clinical Management: Concomitant use of [sertraline](#) and an antiplatelet agent should be undertaken with caution as this may increase the risk of bleeding events[21].
- 7))** Probable Mechanism: unknown
- 8))** Literature Reports

**a))** In a retrospective study of patients over 50 years of age with the diagnosis of acute [myocardial infarction](#) (N=27,058), SSRI use with any antiplatelet therapy significantly increased the risk of bleeding by 1.42-fold compared with [aspirin](#) use alone. Therapy with [aspirin](#), [clopidogrel](#), and an SSRI significantly increased risk by 2.35-fold compared with [aspirin](#) use alone and by 1.57-fold compared with [clopidogrel](#) and [aspirin](#) combination therapy [140].

**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) [141].

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

- 1))** Interaction Effect: increased risk of bleeding
- 2))** Summary: Exercise caution when coadministering a SSRI and an antiplatelet agent as this may increase the risk of bleeding events[141][21][140].
- 3))** Severity: major
- 4))** Onset: unspecified
- 5))** Substantiation: theoretical
- 6))** Clinical Management: Concomitant use of [sertraline](#) and an antiplatelet agent should be undertaken with caution as this may increase the risk of bleeding events[21].
- 7))** Probable Mechanism: unknown
- 8))** Literature Reports

**a))** In a retrospective study of patients over 50 years of age with the diagnosis of acute [myocardial infarction](#) (N=27,058), SSRI use with any antiplatelet therapy significantly increased the risk of

bleeding by 1.42-fold compared with [aspirin](#) use alone. Therapy with [aspirin](#), [clopidogrel](#), and an SSRI significantly increased risk by 2.35-fold compared with [aspirin](#) use alone and by 1.57-fold compared with [clopidogrel](#) and [aspirin](#) combination therapy [140].

**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) [141].

### 3.5.1.BT] Escitalopram

- 1)) Interaction Effect: increased risk of [serotonin syndrome](#)
- 2)) Summary: Escitalopram and [sertraline](#) are serotonergic drugs that may result in additive [serotonin syndrome](#) if used concomitantly. The risk of [serotonin syndrome](#) is greater during treatment initiation and dose increases. Escitalopram and [sertraline](#) should be discontinued immediately and supportive treatment initiated if [serotonin syndrome](#) is suspected[21][422].
- 3)) Severity: major
- 4)) Onset: unspecified
- 5)) Substantiation: theoretical
- 6)) Clinical Management: Escitalopram and [sertraline](#) are both serotonergic drugs. Use caution if concurrent use is necessary, as coadministration may result in additive [serotonin syndrome](#). The risk of [serotonin syndrome](#) is greater during treatment initiation and dose increases. Discontinue escitalopram and [sertraline](#) immediately and initiate supportive treatment if [serotonin syndrome](#) is suspected[21][422].
- 7)) Probable Mechanism: additive serotonergic effects

### 3.5.1.BU] 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](#)[394] and [gastrointestinal bleeding](#) [398][399][395][396]. Bleeding events have included [epistaxis](#), ecchymosis, [hematoma](#), [petechiae](#), and life-threatening hemorrhages [401][400][402][403]. 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](#)[394] and [gastrointestinal bleeding](#) [395][396]. 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 [394].

**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 [397].

**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 [398] to 2.36 times [399], NSAIDs by 2.55 times [398], and the combination of SSRIs and NSAIDs by 4.02 [398] to 6.33 times [399].

**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 [400].

### 3.5.1.BV] 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](#)[394] and [gastrointestinal bleeding](#) [398][399][395][396]. Bleeding events have included [epistaxis](#), ecchymosis, [hematoma](#), [petechiae](#), and life-threatening hemorrhages [401][400][402][403]. 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](#)[394] and [gastrointestinal bleeding](#) [395][396]. 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 [394].

**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 [397].

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 [398] to 2.36 times [399], NSAIDs by 2.55 times [398], and the combination of SSRIs and NSAIDs by 4.02 [398] to 6.33 times [399].

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 [400].

### 3.5.1.BW] 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](#)[394] and [gastrointestinal bleeding](#) [398][399][395][396]. Bleeding events have included [epistaxis](#), ecchymosis, [hematoma](#), [petechiae](#), and life-threatening hemorrhages [401][400][402][403]. 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](#)[394] and [gastrointestinal bleeding](#) [395][396]. 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 [394].

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 [397].

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 [398] to 2.36 times [399], NSAIDs by 2.55 times [398], and the combination of SSRIs and NSAIDs by 4.02 [398] to 6.33 times [399].

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 [400].

**3.5.1.BX] 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](#)[394] and [gastrointestinal bleeding](#) [398][399][395][396]. Bleeding events have included [epistaxis](#), ecchymosis, [hematoma](#), [petechiae](#), and life-threatening hemorrhages [401][400][402][403]. 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](#)[394] and [gastrointestinal bleeding](#) [395][396]. 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 [394].

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 [397].

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 [398] to 2.36 times [399], NSAIDs by 2.55 times [398], and the combination of SSRIs and NSAIDs by 4.02 [398] to 6.33 times [399].

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 [400].

**3.5.1.BY] 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 [sertraline](#), has the potential to cause [serotonin syndrome](#)[310]. [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 [311]. Until more data are available, [fenfluramine](#) should not be used in combination with [sertraline](#).

3) Severity: major

4) Onset: rapid

5) Substantiation: theoretical

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

7) Probable Mechanism: additive serotonergic effects

### 3.5.1.BZ] [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](#)[394] and [gastrointestinal bleeding](#) [398][399][395][396]. Bleeding events have included [epistaxis](#), ecchymosis, [hematoma](#), [petechiae](#), and life-threatening hemorrhages [401][400][402][403]. 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](#)[394] and [gastrointestinal bleeding](#) [395][396]. 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 [394].

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 [397].

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 [398] to 2.36 times [399], NSAIDs by 2.55 times [398], and the combination of SSRIs and NSAIDs by 4.02 [398] to 6.33 times [399].



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 [400].

### 3.5.1.CA] [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[159], including SSRIs [406][405][407]. [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 [159]. 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 [148].

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](#)) [159]. 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 [148].

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 [405].

b) **Serotonin syndrome** following the administration of IV **fentanyl** during surgical procedures was reported in 2 patients also taking SSRIs (**sertraline** and escitalopram). The first patient received IV **fentanyl** (50 micrograms), **midazolam** (2 mg), and 2 doses **propofol** (60 mg and 40 mg) in an **outpatient surgery** center prior to a **carpal tunnel release** procedure. Postoperatively the patient began shivering and became increasingly agitated for which she was transferred to the emergency department. On presentation the patient was combative, diaphoretic, confused, was unable to follow commands, tachycardic, hypertensive, had hyperreflexia, and ankle clonus. Baseline **creatinine** kinase rose to 613 units/L on day 2 of hospitalization. The toxicology service treated her with escalating doses of benzodiazepines with no improvement. The patient was subsequently intubated and sedated with a continuous **propofol** infusion. After 2 days the patient was extubated and by day 3 all symptoms had resolved and the patient was discharged home. The second patient was a 59-year-old woman admitted for an **omentectomy** for which she received IV **fentanyl** 250 micrograms, **etomidate**, vecuronium, **morphine** and cephazolin. Following **extubation** the patient became hypoxic and acidotic and was reintubated and transferred to the ICU. On postoperative day 1 she was extubated and later became tachycardic and was unable to follow commands. On examination the patient was agitated and diaphoretic, had patellar hyperreflexia and a bilateral 3 to 4 beat ankle clonus. Laboratory evaluation was remarkable for a peak **creatinine kinase** of 1161 units/L on postoperative day 2. The patient was treated with **lorazepam** and **cycloheptadine** with resolution of symptoms after 3 days [406].

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 [407].

### 3.5.1.CB] 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**[394] and **gastrointestinal bleeding** [398][399][395][396]. Bleeding events have included **epistaxis**, ecchymosis, **hematoma**, **petechiae**, and life-threatening hemorrhages [401][400][402][403]. 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](#)[394] and [gastrointestinal bleeding](#) [395][396]. 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 [394].

**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 [397].

**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 [398] to 2.36 times [399], NSAIDs by 2.55 times [398], and the combination of SSRIs and NSAIDs by 4.02 [398] to 6.33 times [399].

**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 [400].

### 3.5.1.CC] Feprazone

**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](#)[394] and [gastrointestinal bleeding](#) [398][399][395][396]. Bleeding events have included [epistaxis](#), ecchymosis, [hematoma](#), [petechiae](#), and life-threatening hemorrhages [401][400][402][403]. 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](#)[394] and [gastrointestinal bleeding](#) [395][396]. 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 [394].

**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 [397].

**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 [398] to 2.36 times [399], NSAIDs by 2.55 times [398], and the combination of SSRIs and NSAIDs by 4.02 [398] to 6.33 times [399].

**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 [400].

### 3.5.1.CD] [Flecainide](#)

- 1)) Interaction Effect: increased [flecainide](#) exposure and risk for toxicity ([cardiac arrhythmia](#))
- 2)) Summary: Concomitant use of [flecainide](#) (a CYP2D6 substrate)[134] and [sertraline](#) (a CYP2D6 inhibitor) may increase exposure of the CYP2D6 substrate and risk for toxicity [21], including QT prolongation. If QT prolongation occurs, dosage adjustment should be considered [133].
- 3)) Severity: major
- 4)) Onset: rapid
- 5)) Substantiation: theoretical
- 6)) Clinical Management: Use caution with coadministration of [sertraline](#) and CYP2D6 substrates, such as [flecainide](#), as concomitant use may increase exposure to the CYP2D6 substrate and risk for toxicity[21], including QT prolongation. If QT prolongation occurs, consider dosage adjustment [133].
- 7)) Probable Mechanism: inhibition of CYP2D6-mediated [flecainide](#) metabolism by [sertraline](#)

### 3.5.1.CE] [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](#)[394] and [gastrointestinal bleeding](#) [398][399][395][396]. Bleeding events have included [epistaxis](#), ecchymosis, [hematoma](#), [petechiae](#), and life-threatening hemorrhages [401][400][402][403]. 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](#)[394] and [gastrointestinal bleeding](#) [395][396]. 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 [394].

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 [397].

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 [398] to 2.36 times [399], NSAIDs by 2.55 times [398], and the combination of SSRIs and NSAIDs by 4.02 [398] to 6.33 times [399].

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 [400].

### 3.5.1.CF] Flufenamic Acid

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](#)[394] and [gastrointestinal bleeding](#) [398][399][395][396]. Bleeding events have included [epistaxis](#), ecchymosis, [hematoma](#), [petechiae](#), and life-threatening hemorrhages [401][400][402][403]. 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](#)[394] and [gastrointestinal bleeding](#) [395][396]. 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 [394].



**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 [397].

**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 [398] to 2.36 times [399], NSAIDs by 2.55 times [398], and the combination of SSRIs and NSAIDs by 4.02 [398] to 6.33 times [399].

**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 [400].

### 3.5.1.CG| [Fluoxetine](#)

**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[21].

**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[21].

**7)** Probable Mechanism: inhibition of CYP2D6-mediated metabolism; additive serotonergic effects

### 3.5.1.CH| [Fluphenazine](#)

**1)** Interaction Effect: an increased risk of developing acute [parkinsonism](#)

**2)** Summary: The development of acute, severe [parkinsonism](#) has been observed in a patient receiving [fluphenazine](#) for [Tourette's syndrome](#) and [sertraline](#) for depression. Upon discontinuation of [sertraline](#), the [parkinsonism](#) resolved. A similar interaction has been observed when [fluphenazine](#) was given in combination with [fluoxetine](#) or [paroxetine](#)[260].

**3)** Severity: moderate

**4)** Onset: delayed

**5)** Substantiation: probable



6) Clinical Management: Patients receiving concurrent therapy with fluphenazine and sertraline should be monitored for the development of drug-induced parkinsonism. Therapy with sertraline may need to be discontinued.

7) Probable Mechanism: inhibition of cytochrome P450-mediated fluphenazine metabolism by sertraline

8) Literature Reports

a) A 45-year-old male with chronic, multiple motor and vocal tics since childhood was successfully controlled with haloperidol, but symptoms of depression emerged. Haloperidol was discontinued, and fluphenazine was instituted without an improvement in the patient's mood. Sertraline 125 mg daily was added incrementally, and the patient developed acute, severe parkinsonism after eight weeks. When fluphenazine was discontinued, the parkinsonism resolved, but the tics returned to their baseline level of severity within three weeks [259].

### 3.5.1.CI) 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[394] and gastrointestinal bleeding [398][399][395][396]. Bleeding events have included epistaxis, ecchymosis, hematoma, petechiae, and life-threatening hemorrhages [401][400][402][403]. 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[394] and gastrointestinal bleeding [395][396]. 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 [394].

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 [397].

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 [398] to 2.36 times [399], NSAIDs by 2.55 times [398], and the combination of SSRIs and NSAIDs by 4.02 [398] to 6.33 times [399].

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 [400].

### 3.5.1.CJ] [Fluvoxamine](#)

- 1)) Interaction Effect: increased risk of [serotonin syndrome](#)
- 2)) Summary: Coadministration 2 SSRIs may result in an increased risk of [serotonin syndrome](#). Monitor patients closely for [serotonin syndrome](#), especially during treatment initiation and dose increases. Symptoms of [serotonin syndrome](#) include neuromuscular abnormalities (eg, hyperreflexia, tremor, and ataxia), autonomic instability (eg, [tachycardia](#), diaphoresis, and [hyperthermia](#)), gastrointestinal symptoms (eg, nausea, vomiting, diarrhea), or mental status changes (eg, agitation and confusion). Discontinue both drugs immediately if these symptoms occur and initiate supportive therapy[60].
- 3)) Severity: major
- 4)) Onset: unspecified
- 5)) Substantiation: theoretical
- 6)) Clinical Management: Coadministration 2 SSRIs may result in an increased risk of [serotonin syndrome](#). Monitor patients closely for [serotonin syndrome](#), especially during treatment initiation and dose increases. Symptoms of [serotonin syndrome](#) include neuromuscular abnormalities (eg, hyperreflexia, tremor, and ataxia), autonomic instability (eg, [tachycardia](#), diaphoresis, and [hyperthermia](#)), gastrointestinal symptoms (eg, nausea, vomiting, diarrhea), or mental status changes (eg, agitation and confusion). Discontinue both drugs immediately if these symptoms occur and initiate supportive therapy[60].
- 7)) Probable Mechanism: additive serotonergic effects

### 3.5.1.CK] [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 (such as [sertraline](#)) and anticoagulants has been associated with an increased risk of bleeding[129][130][128]. Bleeding events reported have included [epistaxis](#), ecchymosis, [hematoma](#), [petechiae](#), and life-threatening hemorrhages. Altered anticoagulant effects (including increased bleeding) have been reported with the coadministration of SSRIs with [warfarin](#) [128]. Prothrombin time should be monitored in patients receiving both [warfarin](#) and [sertraline](#) [132].
- 3)) Severity: major
- 4)) Onset: delayed
- 5)) Substantiation: probable
- 6)) Clinical Management: When [sertraline](#) 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 [sertraline](#) therapy is initiated or discontinued[128].
- 7)) Probable Mechanism: unknown
- 8)) Literature Reports

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

group, and 10 patients experienced 14 bleedings during 586.4 treatment years in the warfarin-only group. The corresponding total incidences of bleedings were 51.4 and 23.9 per 1000 treatment years, respectively. The hazard ratio for first bleedings during treatment with [warfarin](#) plus SSRI was 3.49 (95% CI; 1.37 to 8.91,  $p=0.009$ ) compared with [warfarin](#) only. The SSRI implicated in patients experiencing bleeding at the time of concomitant administration were [sertraline](#) or [citalopram](#). The addition of an SSRI was not associated with a change in [warfarin](#) dose or INR ( $p=0.48$  and  $p=0.31$  respectively). The results of the study may be limited by earlier bleeding events, unknown patient adherence, and exclusion of [clopidogrel](#), dipyridamol, corticosteroids and anticoagulants other than [warfarin](#) in the model [129].

**b))** A population-based, case-controlled study of new coumarin users (acenocoumarol and phenprocoumon) with concomitant selective serotonin reuptake inhibitors (SSRIs) resulted in an increased risk of hospitalization due to non-gastrointestinal bleeding. Using national pharmacy and hospitalization records in the Netherlands, researchers identified 1848 cases that were admitted for abnormal bleeding and compared them with 5818 control subjects who were also taking a coumarin. Median duration of treatment in patients was 220 days (range, 1 to 4690 days). Patients on SSRIs showed greater risk for hospitalization for nongastrointestinal bleeding (adjusted odds ratio (OR) 1.7, 95% confidence interval (CI), 1.1 to 2.5); however, the rate of [gastrointestinal bleeding](#) (adjusted OR 0.8, 95% CI, 0.4 to 1.5) was not significantly different [130].

**c))** [Sertraline](#) 50 mg to 200 mg daily for 21 days produced an 8% increase in prothrombin time in subjects who received a single dose of [warfarin](#) 0.75 mg/kg relative to the same [warfarin](#) dose given prior to [sertraline](#); this compared with a 1% decrease with placebo. Normalization of the prothrombin time was also delayed as compared with placebo. The clinical significance of these findings is unknown [128].

**d))** In a non-blinded, randomized, placebo-controlled trial involving 12 healthy volunteers, the effect of [sertraline](#) on the plasma protein binding of [warfarin](#) was assessed. On days 0 and 32 of the study, all participants received [warfarin](#) 0.75 mg/kg. Beginning on day 11, each volunteer was randomized to either the [sertraline](#) or placebo group; the [sertraline](#) was gradually increased from 50 mg/day to 200 mg/day. Prothrombin time was measured prior to each dose of [warfarin](#) and periodically thereafter. The researchers concluded that the anticoagulant effects of [warfarin](#) were not enhanced by [sertraline](#) to a clinically significant degree, despite the fact that [sertraline](#) was given in a higher-than-usual dose [131].

### 3.5.1.CL] [Fosphenytoin](#)

**1))** Interaction Effect: increased risk of [phenytoin](#) toxicity and decreased efficacy of [sertraline](#)

**2))** Summary: The concomitant use of [phenytoin](#), a CYP2C9 and CYP2C19 substrate and potent CYP-enzyme inducer, and [sertraline](#) may increase the risk of [phenytoin](#) toxicity and reduce [sertraline](#) efficacy[285][286]. Coadministration of [phenytoin](#) with [sertraline](#) has resulted in elevated serum [phenytoin](#) levels in 2 elderly patients [291]. To achieve optimal clinical outcomes, consider [phenytoin](#) and [sertraline](#) dose adjustments when [phenytoin](#) is added to or withdrawn from a patient's regimen. [Phenytoin](#) serum drug level monitoring is suggested during concurrent use of [phenytoin](#) and [sertraline](#) [285][286].

**3))** Severity: major

**4))** Onset: unspecified

**5))** Substantiation: probable

**6))** Clinical Management: Use caution with coadministration of [phenytoin](#) and [sertraline](#), as concurrent use may increase the risk of [phenytoin](#) toxicity and reduce [sertraline](#) efficacy. Consider [phenytoin](#) and [sertraline](#) dose adjustments when [phenytoin](#) is added to or withdrawn from a patient's regimen. [Phenytoin](#) serum drug level monitoring is suggested during concurrent use of [phenytoin](#) and [sertraline](#)[285][286].

- 7j) Probable Mechanism: inhibition of CYP-mediated [phenytoin](#) metabolism by [sertraline](#); induction of CYP-mediated [sertraline](#) metabolism by [phenytoin](#)
- 8j) Literature Reports

a) Two elderly patients developed elevated serum [phenytoin](#) concentrations during coadministration with [sertraline](#). Patient 1, a 78-year old man, was taking [phenytoin](#) 300 mg per day in addition to several other medications. After [sertraline](#) 25 mg every night was added to his regimen for depression, serum [phenytoin](#) levels increased from 5.2 mcg/mL to 12.3 mcg/mL. After serial increases in the [sertraline](#) dose to 75 mg per day, the patient's serum [phenytoin](#) level rose to 30.9 mcg/mL. [Phenytoin](#) was discontinued but was later successfully restarted at a dose of 200 mg per day. [Sertraline](#) 100 mg per day was also administered without further adverse effects. Patient 2, an 85-year old man, developed increased serum [phenytoin](#) levels (from 15.6 mcg/mL to 20 mcg/mL) after the addition of [sertraline](#) 25 mg every other day to [phenytoin](#) 260 mg per day. The authors recommend checking serum [phenytoin](#) concentrations within one week after starting [sertraline](#) therapy or initiating a change in [sertraline](#) dose [287].

b) [Sertraline](#) is known to be a moderate to weak inhibitor of the CYP2D6 isoenzyme and is suspected of inhibiting the CYP2C9 and CYP3A4 hepatic isoenzymes. The metabolism of [phenytoin](#) may involve the CYP2D6 [288] and CYP2C9 hepatic isoenzymes [289][290]. Given this overlap of hepatic enzyme activity and pathways, it seems theoretically possible that concurrent [sertraline](#) may act to inhibit metabolic clearance of [phenytoin](#), thereby producing higher [phenytoin](#) serum concentrations.

### 3.5.1.CM| [Frovatriptan](#)

- 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](#), a 5-hydroxytryptamine-1 (5HT-1) agonist, and a serotonin specific reuptake inhibitor (SSRI)[435]. Because [frovatriptan](#) is a 5HT 1B/1D agonist, a similar interaction between SSRIs and [frovatriptan](#) may occur [436]. 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](#) [220].
- 3j) Severity: major
- 4j) Onset: delayed
- 5j) Substantiation: probable
- 6j) Clinical Management: Coadministration of a triptan, such as [frovatriptan](#), and an SSRI may result in a life-threatening condition called [serotonin syndrome](#). Be aware that triptans may be commonly used intermittently and that either the triptan or the SSRI may be prescribed by a different physician. If these agents are used together, discuss the risks of [serotonin syndrome](#) with the patient and monitor closely for symptoms of [serotonin syndrome](#) (restlessness, [hyperthermia](#), hyperreflexia, incoordination).
- 7j) Probable Mechanism: additive pharmacologic effects resulting in excessive serotonergic stimulation

### 3.5.1.CN| [Furazolidone](#)

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

2) Summary: Although not its primary mechanism of action, [furazolidone](#) has MAOI activity. Cases of serious and sometimes fatal reactions have been reported in patients receiving SSRIs in combination with MAOIs. [Hyperthermia](#), rigidity, myoclonus, autonomic instability with possible rapid fluctuations of vital signs, and mental status changes, that include extreme agitation progressing to [delirium](#) and coma, have been reported. [Furazolidone](#) should not be used in combination with an SSRI or within a minimum of 14 days of discontinuing therapy with an MAOI[139].

3) Severity: contraindicated

4) Onset: delayed

5) Substantiation: theoretical

6) Clinical Management: If concurrent therapy with [furazolidone](#) and an SSRI is deemed to be necessary, closely monitor the patient for signs of serotonergic excess (eg, mental status changes, diaphoresis, fever, weakness, hyperreflexia, incoordination).

7) Probable Mechanism: additive serotonergic effects

### 3.5.1.CO| 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[253]. 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 [254][255], and has demonstrated serotonergic activity in animals [256] 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 [257]. Ginkgo biloba extract inhibited MAO-A/MAO-B in the rat brain in vitro [254][255] and MAO-B in human [platelets](#) in vitro [255]. No significant MAO inhibition was found in mice following oral consumption [258].

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 [252].

### 3.5.1.CP| [Granisetron](#)



- 1) Interaction Effect: increased risk of [serotonin syndrome](#)
- 2) Summary: Concomitant use of [granisetron](#) with a serotonergic agent may increase the risk of [serotonin syndrome](#). Instruct patients of the increased risk of [serotonin syndrome](#) with concurrent use of these drugs. Monitor for the emergence of [serotonin syndrome](#) and discontinue treatment with [granisetron](#) and institute supportive therapy if symptoms of [serotonin syndrome](#) occur[155].
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Concomitant use of [granisetron](#) with a serotonergic agent may increase the risk of [serotonin syndrome](#). Instruct patients of the increased risk of [serotonin syndrome](#) with concurrent use of these drugs. Monitor for the emergence of [serotonin syndrome](#) and discontinue treatment with [granisetron](#) and institute supportive therapy if symptoms of [serotonin syndrome](#) occur[155].
- 7) Probable Mechanism: unknown

### 3.5.1.CQ| [Haloperidol](#)

- 1) Interaction Effect: increased [haloperidol](#) concentrations
- 2) Summary: Concurrent administration of [haloperidol](#) (a CYP2D6 substrate) and CYP2D6 inhibitors, such as [sertraline](#)[21], may increase [haloperidol](#) exposure and risk for toxicity, including QT prolongation. Regardless of formulation or predisposing factors, use of [haloperidol](#) doses greater than recommended has been associated with QT prolongation and [torsades de pointes](#). Although the increase in [haloperidol](#) exposure may range from mild to moderate, it is advisable to use additional caution upon coadministration [209].
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Concurrent administration of [haloperidol](#) (a CYP2D6 substrate) and CYP2D6 inhibitors, such as [sertraline](#)[21], may increase [haloperidol](#) exposure and risk for toxicity, including QT prolongation. Regardless of formulation or predisposing factors, use of [haloperidol](#) doses greater than recommended has been associated with QT prolongation and [torsades de pointes](#). Although the increase in [haloperidol](#) exposure may range from mild to moderate, additional caution upon coadministration is advised [209].
- 7) Probable Mechanism: inhibition of CYP2D6-mediated [haloperidol](#) metabolism by [sertraline](#)

### 3.5.1.CR| [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 (such as [sertraline](#)) and anticoagulants has been associated with an increased risk of bleeding[129][130][128]. Bleeding events reported have included [epistaxis](#), ecchymosis, [hematoma](#), [petechiae](#), and life-threatening hemorrhages. Altered anticoagulant effects (including increased bleeding) have been reported with the coadministration of SSRIs with [warfarin](#) [128]. Prothrombin time should be monitored in patients receiving both [warfarin](#) and [sertraline](#) [132].
- 3) Severity: major
- 4) Onset: delayed
- 5) Substantiation: probable
- 6) Clinical Management: When [sertraline](#) 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 [sertraline](#) therapy is initiated or discontinued[128].



## 7J) Probable Mechanism: unknown

## 8J) Literature Reports

aJ) According to a retrospective cohort study (n=234), there was an increased risk of clinically relevant bleeding (hospital admission due to bleeding) in patients receiving [warfarin](#) for [atrial fibrillation](#) during concomitant SSRI therapy or within 2 weeks following SSRI therapy termination. Patients with a mean age of 72 +/- 7 years receiving [warfarin](#) plus SSRI (n=117) were matched with randomly selected patients who received [warfarin](#) only (n=117). SSRI included [fluoxetine](#), [citalopram](#), [paroxetine](#), [sertraline](#), [fluvoxamine](#), or escitalopram. Nine patients experienced 11 bleeding episodes during 213.9 treatment years in the [warfarin](#) plus SSRI group, and 10 patients experienced 14 bleedings during 586.4 treatment years in the warfarin-only group. The corresponding total incidences of bleedings were 51.4 and 23.9 per 1000 treatment years, respectively. The hazard ratio for first bleedings during treatment with [warfarin](#) plus SSRI was 3.49 (95% CI; 1.37 to 8.91, p=0.009) compared with [warfarin](#) only. The SSRI implicated in patients experiencing bleeding at the time of concomitant administration were [sertraline](#) or [citalopram](#). The addition of an SSRI was not associated with a change in [warfarin](#) dose or INR (p=0.48 and p=0.31 respectively). The results of the study may be limited by earlier bleeding events, unknown patient adherence, and exclusion of [clopidogrel](#), dipyridamol, corticosteroids and anticoagulants other than [warfarin](#) in the model [129].

bJ) A population-based, case-controlled study of new coumarin users (acenocoumarol and phenprocoumon) with concomitant selective serotonin reuptake inhibitors (SSRIs) resulted in an increased risk of hospitalization due to non-gastrointestinal bleeding. Using national pharmacy and hospitalization records in the Netherlands, researchers identified 1848 cases that were admitted for abnormal bleeding and compared them with 5818 control subjects who were also taking a coumarin. Median duration of treatment in patients was 220 days (range, 1 to 4690 days). Patients on SSRIs showed greater risk for hospitalization for nongastrointestinal bleeding (adjusted odds ratio (OR) 1.7, 95% confidence interval (CI), 1.1 to 2.5); however, the rate of [gastrointestinal bleeding](#) (adjusted OR 0.8, 95% CI, 0.4 to 1.5) was not significantly different [130].

cJ) [Sertraline](#) 50 mg to 200 mg daily for 21 days produced an 8% increase in prothrombin time in subjects who received a single dose of [warfarin](#) 0.75 mg/kg relative to the same [warfarin](#) dose given prior to [sertraline](#); this compared with a 1% decrease with placebo. Normalization of the prothrombin time was also delayed as compared with placebo. The clinical significance of these findings is unknown [128].

dJ) In a non-blinded, randomized, placebo-controlled trial involving 12 healthy volunteers, the effect of [sertraline](#) on the plasma protein binding of [warfarin](#) was assessed. On days 1 and 32 of the study, all participants received [warfarin](#) 0.75 mg/kg. Beginning on day 11, each volunteer was randomized to either the [sertraline](#) or placebo group; the [sertraline](#) was gradually increased from 50 mg/day to 200 mg/day. Prothrombin time was measured prior to each dose of [warfarin](#) and periodically thereafter. The researchers concluded that the anticoagulant effects of [warfarin](#) were not enhanced by [sertraline](#) to a clinically significant degree, despite the fact that [sertraline](#) was given in a higher-than-usual dose [131].

## 3.5.1.CSJ Hydroxytryptophan

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

2J) Summary: Potentially life-threatening [serotonin syndrome](#) has been reported with SSRIs when used concomitantly with other serotonergic drugs, such as hydroxytryptophan or tryptophan. If

coadministration is clinically warranted, monitor for the development of [serotonin syndrome](#), especially during treatment initiation and dose increases[149].

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[149].

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 [150].

### 3.5.1.CT] [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](#)[394] and [gastrointestinal bleeding](#) [398][399][395][396]. Bleeding events have included [epistaxis](#), ecchymosis, [hematoma](#), [petechiae](#), and life-threatening hemorrhages [401][400][402][403]. 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](#)[394] and [gastrointestinal bleeding](#) [395][396]. 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 [394].

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 [397].

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 [398] to 2.36 times [399], NSAIDs by 2.55 times [398], and the combination of SSRIs and NSAIDs by 4.02 [398] to 6.33 times [399].

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 [400].

### 3.5.1.CU] [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](#)[394] and [gastrointestinal bleeding](#) [398][399][395][396]. Bleeding events have included [epistaxis](#), ecchymosis, [hematoma](#), [petechiae](#), and life-threatening hemorrhages [401][400][402][403]. 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](#)[394] and [gastrointestinal bleeding](#) [395][396]. 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 [394].

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 [397].

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 [398] to 2.36 times [399], NSAIDs by 2.55 times [398], and the combination of SSRIs and NSAIDs by 4.02 [398] to 6.33 times [399].

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 [400].

**3.5.1.CV] Iloprost**

- 1) Interaction Effect: increased risk of bleeding
- 2) Summary: Exercise caution when coadministering a SSRI and an antiplatelet agent as this may increase the risk of bleeding events[141][21][140].
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Concomitant use of [sertraline](#) and an antiplatelet agent should be undertaken with caution as this may increase the risk of bleeding events[21].
- 7) Probable Mechanism: unknown
- 8) Literature Reports

a) In a retrospective study of patients over 50 years of age with the diagnosis of acute [myocardial infarction](#) (N=27,058), SSRI use with any antiplatelet therapy significantly increased the risk of bleeding by 1.42-fold compared with [aspirin](#) use alone. Therapy with [aspirin](#), [clopidogrel](#), and an SSRI significantly increased risk by 2.35-fold compared with [aspirin](#) use alone and by 1.57-fold compared with [clopidogrel](#) and [aspirin](#) combination therapy [140].

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) [141].

**3.5.1.CW] Imipramine**

- 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[21].
- 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[21].
- 7) Probable Mechanism: inhibition of CYP2D6-mediated metabolism; additive serotonergic effects

**3.5.1.CX] Indomethacin**

- 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](#)[394] and [gastrointestinal bleeding](#) [398][399][395][396]. Bleeding events have included [epistaxis](#), ecchymosis, [hematoma](#), [petechiae](#), and life-threatening hemorrhages [401][400][402][403]. 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](#)[394] and [gastrointestinal bleeding](#) [395][396]. 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 [394].

**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 [397].

**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 [398] to 2.36 times [399], NSAIDs by 2.55 times [398], and the combination of SSRIs and NSAIDs by 4.02 [398] to 6.33 times [399].

**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 [400].

### 3.5.1.CY| [Iobenguane I 123](#)

**1j) Interaction Effect:** potential for false negative imaging results

**2j) 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[240].

**3j) 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[240].
- 7) Probable Mechanism: inhibition of [norepinephrine](#) transporter function by antidepressants

### 3.5.1.CZ| Ioflupane I 123

- 1) Interaction Effect: interference with ioflupane I 123 imaging
- 2) Summary: The ioflupane component of ioflupane I 123 binds to the [dopamine](#) transporter allowing for striatal [dopamine](#) transport visualization using [single photon emission computed tomography](#) (SPECT) [brain imaging](#). Because [sertraline](#) binds with high affinity to the [dopamine](#) transporter, there is the potential for interference with ioflupane I 123 imaging. It is unknown whether discontinuing [sertraline](#) prior to ioflupane I 123 administration may minimize this interference[201]. The potential for imaging interference should be considered when administering ioflupane I 123 to patients who are already receiving [sertraline](#).
- 3) Severity: moderate
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Concomitant use of ioflupane I 123 and [sertraline](#) may result in interference with ioflupane I 123 imaging. It is unknown whether discontinuing [sertraline](#) prior to ioflupane I 123 administration may minimize the interference[201]. Consider the potential for imaging interference when administering ioflupane I 123 to patients who are already receiving [sertraline](#).
- 7) Probable Mechanism: unknown

### 3.5.1.DA| Iproniazid

- 1) Interaction Effect: CNS toxicity or [serotonin syndrome](#) ([hypertension](#), [hyperthermia](#), myoclonus, mental status changes)
- 2) Summary: Concurrent administration or overlapping therapy with [sertraline](#) and a monoamine oxidase (MAO) inhibitor may result in CNS toxicity or [serotonin syndrome](#), a hyperserotonergic state characterized by symptoms such as restlessness, myoclonus, changes in mental status, hyperreflexia, diaphoresis, shivering, and tremor. Serious, even fatal, reactions have been reported with concomitant use of serotonin specific reuptake inhibitors and MAO inhibitors[214][215][216][217][218]. Concomitant use is contraindicated.
- 3) Severity: contraindicated
- 4) Onset: rapid
- 5) Substantiation: probable
- 6) Clinical Management: Concurrent use of [sertraline](#) and a MAO inhibitor is contraindicated. Wait at least 14 days after discontinuing a MAO inhibitor before initiating therapy with [sertraline](#). Wait at least 14 days after discontinuing [sertraline](#) before initiating therapy with a MAO inhibitor.
- 7) Probable Mechanism: inhibition of serotonin metabolism by monoamine oxidase
- 8) Literature Reports

- a) Concomitant use of SSRIs and monoamine oxidase inhibitors can produce a toxic reaction known as [serotonin syndrome](#) [210]. [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, fatality can result.

**b))** A 26-year old woman who had been taking [isocarboxazid](#) for eight weeks stopped taking the drug for 11 days before beginning therapy with [sertraline](#). After a single 100 mg [sertraline](#) dose, the patient became restless and developed leg twitches. The patient was later admitted to the emergency room with diaphoresis, [tachycardia](#), hyperreflexia, and various neuromuscular disturbances. After treatment with [diazepam](#) and [propranolol](#) the patient did not improve. The patient was then given two 4 mg doses of [cyproheptadine](#) an hour apart, with notable improvement in symptoms after the second dose [211].

**c))** A drug interaction was reported in a 61-year old woman in which [sertraline](#) 100 mg twice daily was added to a regimen of [lithium](#), [phenelzine](#), [thioridazine](#), and [doxepin](#). Three hours after taking the first [sertraline](#) dose, the patient was found in a semicomatose state, with elevated body temperature, increased pulse, increased respiration rate, and a blood pressure of 140/110 mm Hg. After transportation to the hospital, the patient was misdiagnosed as having [neuroleptic malignant syndrome](#) (NMS) which was later changed to [serotonin syndrome](#) due to a reaction between [sertraline](#) and [phenelzine](#). The authors suggest that monoamine oxidase inhibitor (MAOI) therapy should be discontinued for at least two weeks before initiation of therapy with a selective serotonin reuptake inhibitor (SSRI) and that before starting a MAOI, SSRI therapy should be discontinued for at least five half-lives of the parent drug and any active metabolites [212].

**d))** Two cases reports suggested a possible interaction between [fluoxetine](#) and [selegiline](#) [213]. One case involved a first episode of mania being observed approximately one month after adding [selegiline](#) to [fluoxetine](#). 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](#) to [selegiline](#). Both drugs were discontinued, with relatively quick resolution of symptoms. Rechallenge with [fluoxetine](#) alone occurred without incident.

### 3.5.1.DB| [Isocarboxazid](#)

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

**2))** Summary: Concurrent administration or overlapping therapy with [sertraline](#) 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[349][350][351][352][353]. Concomitant use is contraindicated [354].

**3))** Severity: contraindicated

**4))** Onset: rapid

**5))** Substantiation: probable

**6))** Clinical Management: Concurrent use of [sertraline](#) and a MAO inhibitor is contraindicated. Wait at least 14 days after discontinuing a MAO inhibitor before initiating therapy with [sertraline](#). Wait at least 14 days after discontinuing [sertraline](#) 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](#) [345]. [Serotonin syndrome](#) is a condition of serotonergic hyperstimulation and manifests as restlessness, myoclonus, changes in

mental status, hyperreflexia, diaphoresis, shivering, and tremor. If the syndrome is not recognized and correctly treated, death can result.

**b))** A 26-year old woman who had been taking [isocarboxazid](#) for eight weeks stopped taking the drug for 11 days before beginning therapy with [sertraline](#). After a single 100 mg [sertraline](#) dose, the patient became restless and developed leg twitches. The patient was later admitted to the emergency room with diaphoresis, [tachycardia](#), hyperreflexia, and various neuromuscular disturbances. The patient did not improve after treatment with [diazepam](#) and [propranolol](#). The patient was then given two 4 mg doses of [cyproheptadine](#) an hour apart, with notable improvement in symptoms after the second dose [346].

**c))** A drug interaction was reported in a 61-year old woman in which [sertraline](#) 100 mg twice daily was added to a regimen of [lithium](#), [phenelzine](#), [thioridazine](#), and [doxepin](#). Three hours after taking the first [sertraline](#) dose, the patient was found in a semicomatose state, with elevated body temperature, increased pulse, increased respiration rate, and a blood pressure of 140/110 mmHg. After transportation to the hospital, the patient was misdiagnosed as having [neuroleptic malignant syndrome](#) (NMS) which was later changed to [serotonin syndrome](#) due to a reaction between [sertraline](#) and [phenelzine](#). The authors suggest that MAO inhibitor therapy should be discontinued for at least two weeks before initiation of therapy with a selective serotonin reuptake inhibitor (SSRI) and that before starting a MAOI, SSRI therapy should be discontinued for at least 5 half-lives of the parent drug and any active metabolites [347].

**d))** Two case reports suggested a possible interaction between [fluoxetine](#) and [selegiline](#) [348]. One case involved a first episode of mania being observed approximately 1 month after adding [selegiline](#) to [fluoxetine](#) therapy. The patient improved 2 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.DC| [Ketoprofen](#)

**1))** Interaction Effect: an increased risk of bleeding

**2))** Summary: Caution is recommended with the concomitant use of NSAIDs and antidepressants, including SSRIs due to an increased risk of [intracranial hemorrhage](#)[394] and [gastrointestinal bleeding](#) [398][399][395][396]. Bleeding events have included [epistaxis](#), ecchymosis, [hematoma](#), [petechiae](#), and life-threatening hemorrhages [401][400][402][403]. 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](#)[394] and [gastrointestinal bleeding](#) [395][396]. 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 [394].

**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 [397].

**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 [398] to 2.36 times [399], NSAIDs by 2.55 times [398], and the combination of SSRIs and NSAIDs by 4.02 [398] to 6.33 times [399].

**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 [400].

### 3.5.1.DD) 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](#)[394] and [gastrointestinal bleeding](#) [398][399][395][396]. Bleeding events have included [epistaxis](#), ecchymosis, [hematoma](#), [petechiae](#), and life-threatening hemorrhages [401][400][402][403]. 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](#)[394] and [gastrointestinal bleeding](#) [395][396]. 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 [394].

**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 [397].

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 [398] to 2.36 times [399], NSAIDs by 2.55 times [398], and the combination of SSRIs and NSAIDs by 4.02 [398] to 6.33 times [399].

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 [400].

### 3.5.1.DE] Lamotrigine

1) Interaction Effect: an increased risk of lamotrigine toxicity (fatigue, sedation, confusion, decreased cognition)

2) Summary: Two case reports describe epileptic patients who experienced lamotrigine toxicity when sertraline therapy was initiated. Lamotrigine is metabolized primarily via glucuronidation, while sertraline relies on N-demethylation, hydroxylation, oxidative deamination, and glucuronidation. It is hypothesized that sertraline decreases lamotrigine metabolism through competitive inhibition of glucuronidation [242].

3) Severity: moderate

4) Onset: delayed

5) Substantiation: probable

6) Clinical Management: Caution should be exercised when combining sertraline and lamotrigine therapy. Lamotrigine blood levels should be closely monitored and dosages adjusted accordingly.

7) Probable Mechanism: inhibition of lamotrigine glucuronidation

8) Literature Reports

a) A 39-year-old female with epilepsy was maintained on lamotrigine 200 mg daily with a baseline lamotrigine blood level of 2.5 mcg/mL (9.8 mcmol/L). Because of an intermittent explosive disorder, sertraline 25 mg daily was initiated. Six weeks later, the lamotrigine level was 5.1 mcg/mL (20 mcmol/L) and the patient complained of confusion and cognitive impairment. Sertraline was increased to 50 mg daily while lamotrigine was decreased to 100 mg daily. This lower lamotrigine dose eliminated the patient's confusion and impaired cognition, and the blood level of lamotrigine stabilized at 3.1 mcg/mL (12.1 mcmol/L) [241].

b) Lamotrigine 450 mg daily was not controlling seizures in a 17-year-old female with mixed epileptic disorder and explosivity. Sertraline therapy was initiated and titrated to 75 mg daily without any side effects. Lamotrigine was also increased to 600 mg daily, and six weeks later, the patient complained of sedation, fatigue, and decreased cognition. The lamotrigine blood level was 19.3 mcg/mL (75.4 mcmol/L) at this time. The sertraline dose was decreased to 50 mg daily while the lamotrigine level was increased to 800 mg daily, resulting in a new steady-state lamotrigine level of 9.8 mcg/mL (38.3 mcmol/L). In this case report, the lamotrigine blood level decreased to approximately 50% with a 33% decrease in the sertraline daily dose, even though the lamotrigine dose had been increased by 33% [241].

### 3.5.1.DF] 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[434].

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[434].

7) Probable Mechanism: additive serotonergic effects

### 3.5.1.DG| [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[408].

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[408].

7) Probable Mechanism: unknown

### 3.5.1.DH| [Linezolid](#)

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

2) Summary: Concurrent use of [sertraline](#) and an MAOI, such as [linezolid](#), is contraindicated. If urgent treatment with [linezolid](#) is necessary in a patient receiving [sertraline](#) and alternatives are not available, promptly discontinue [sertraline](#) and then administer [linezolid](#), if risk/benefit has been evaluated. Monitor for [serotonin syndrome](#) for 2 weeks or until 24 hours after the last dose of [linezolid](#), whichever comes first. [Sertraline](#) can be resumed 24 hours after the last dose of [linezolid](#)[106].

3) Severity: contraindicated

4) Onset: unspecified

5) Substantiation: probable

6) Clinical Management: Concurrent use of [sertraline](#) and an MAOI, such as [linezolid](#), is contraindicated. If urgent treatment with [linezolid](#) is necessary in a patient receiving [sertraline](#) and alternatives are not available, promptly discontinue [sertraline](#) and then administer [linezolid](#), if risk/benefit has been evaluated. Monitor for [serotonin syndrome](#) for 2 weeks or until 24 hours after the last dose of [linezolid](#), whichever comes first. [Sertraline](#) can be resumed 24 hours after the last dose of [linezolid](#)[106].

7) Probable Mechanism: additive serotonergic effects

8) Literature Reports



a) A case of [serotonin syndrome](#) occurred in a patient who was prescribed [linezolid](#) and [sertraline](#). A 45-year-old man with a history of [schizoaffective disorder](#) was admitted to the trauma service after an acute suicide attempt that resulted in a T6 level [spinal cord injury](#) and [paraplegia](#). Pharmacotherapy with [sertraline](#) (200 mg daily) and [risperidone](#) (1 mg twice daily) was initiated after the patient was diagnosed with acute depression and [psychosis](#). [Bupropion](#) 75 mg twice daily, [trazodone](#) 50 mg every evening, and [lithium](#) 300 mg twice daily were added to his therapy. The patient underwent sacral flap closure with a bilateral gluteal myocutaneous flap and then developed a deep sacral [decubitus ulcer](#). His temperature and WBC count remained elevated for several days. Culture of the ulcer revealed a vancomycin-resistant *Enterococcus faecalis*. He was started on [linezolid](#) 600 mg IV every 12 hours and [metronidazole](#) 500 mg every 6 hours. [Lithium](#) was discontinued after the patient's [lithium](#) level was found to be elevated at 1.1 mEq/L. Ten days after [linezolid](#) therapy was initiated, the patient complained of increasing tremor, nausea, vomiting, diarrhea, and dry mouth. [Sertraline](#), [bupropion](#), and [trazodone](#) were discontinued. His concurrent medications included [baclofen](#), [promethazine](#), [docusate](#) sodium, [bisacodyl](#), [megestrol](#), [lansoprazole](#), and [risperidone](#). The following day, the patient became delirious marked by acute confusion, visual hallucinations, and delusions. His temperature was elevated to 100.1 degrees F, pulse 101, respirations 20/min, and blood pressure 100/71 mmHg. He displayed coarse tremor and myoclonus. His pupils were dilated to 6 mm and minimally reactive. A diagnosis of [serotonin syndrome](#) was considered. Symptoms of [serotonin syndrome](#) resolved with [cyproheptadine](#) treatment [292].

b) A retrospective chart review identified one highly probable case of [serotonin syndrome](#) in a patient who received concomitant therapy with [linezolid](#) and [venlafaxine](#), followed by [citalopram](#). Charts of 72 inpatients who received [linezolid](#) and an SSRI or [venlafaxine](#) within 14 days of each other were reviewed for a diagnosis of [serotonin syndrome](#) (SS) using the Sternbach and the Hunter serotonin toxicity criteria. Of these patients, 52 (72%) were treated concomitantly with [linezolid](#) and an SSRI or [venlafaxine](#). Four patients met the criteria for having either high or low probability of SS. Of these, one case involved an 81-year-old woman who was determined to have high probability of having 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 [293].

c) In one case report, a 36-year-old man experienced symptoms of [serotonin syndrome](#) after concomitant treatment with [linezolid](#) and [sertraline](#). The patient underwent an allogeneic stem cell transplant after receiving high-dose [cyclophosphamide](#), [total body irradiation](#), and antithymocyte globulin. His recovery was hindered by severe [hemorrhagic cystitis](#), steroid-refractory [graft-versus-host disease](#), thrombotic thrombocytopenic [purpura](#), [renal failure](#), and multiple [pulmonary infections](#). On day 137, the patient received [linezolid](#) 600 mg IV every 12 hours. Current medications included [tacrolimus](#), corticosteroids, [thalidomide](#) 100 mg daily, [sertraline](#) 50 mg daily, [morphine](#), and [alprazolam](#). On day 5 of [linezolid](#) therapy, the patient experienced confusion, restlessness, [delirium](#), and agitation. He developed [hypertension](#) and a high fever (40 degrees C). WBC and [platelet](#) counts began to diminish considerably. On day 6 of therapy, all medications



with neurological effects were discontinued, including [sertraline](#), [thalidomide](#), [alprazolam](#), and [morphine](#). The patient's symptoms subsided within a day. [Thalidomide](#), [alprazolam](#), and [morphine](#) were reinstated with no reoccurrence of symptoms [294].

### 3.5.1.DI] [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[393].
- 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[393].
- 7) Probable Mechanism: inhibition of CYP2D6-mediated metabolism of [amphetamine](#); additive serotonergic effects

### 3.5.1.DJ] [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[335]. 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](#) [336][337]. Two studies have failed to identify a pharmacokinetic interaction between [lithium](#) and [citalopram](#) [338][339]. 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 [340]. Concurrent use of [fluvoxamine](#) and [lithium](#) has led to case reports of increased [lithium](#) levels and [neurotoxicity](#), [serotonin syndrome](#), somnolence, and mania [335][341][342][343]. No pharmacokinetic interference was apparent during a multiple-dose study of coadministered [lithium](#) and [paroxetine](#) [344]. 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) [341][335].
- 3) Severity: moderate
- 4) Onset: delayed
- 5) Substantiation: established

6j) 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).

7j) Probable Mechanism: unknown

8j) 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](#) [327]. [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](#) [328].

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](#) [329].

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](#) [330].

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 [331].

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 [332].

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 [333].

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 [334].

### 3.5.1.DK] Lofepamine

1) Interaction Effect: modest elevations in lofepramine serum levels or possible **serotonin syndrome** (hypertension, hyperthermia, myoclonus, mental status changes)

2) Summary: There is limited evidence suggesting that **sertraline** may inhibit tricyclic antidepressant (TCA) metabolism resulting in higher TCA serum concentrations. Sertraline inhibits cytochrome P450 2D6 enzyme activity and may increase the plasma concentrations of coadministered drugs that are metabolized by this pathway, including the tricyclic antidepressants [222][223][224]. Effects of the interaction may have little or no clinical impact, however. Increases in TCA serum levels associated with **sertraline** coadministration were modest compared with those found when **fluoxetine** (another selective serotonin reuptake inhibitor) was combined with **desipramine** [225]. Monitor patients on lofepramine-sertraline therapy for TCA toxicity (dry mouth, urinary retention, CNS depression). Lofepamine doses may need to be reduced.

3) Severity: major

4) Onset: delayed

5) Substantiation: probable

6) Clinical Management: Concurrent use of lofepramine and **sertraline** 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). Lofepamine should not be used in combination with **sertraline** or other serotonin specific reuptake inhibitors.

7) Probable Mechanism: inhibition of lofepramine metabolism

8) Literature Reports

a) **Desipramine** pharmacokinetics were studied in 18 healthy male volunteers. Study subjects received only **desipramine** (50 mg daily) for 7 days followed by **desipramine** with **sertraline** (50 mg daily) for 21 days. When **sertraline** was added to **desipramine** therapy, the mean maximum concentration of **desipramine** increased by 34% and the area under the concentration-time curve

increased by 26%. Trough concentrations of [desipramine](#) were close to baseline one week after [sertraline](#) was discontinued. The changes in [desipramine](#) concentrations were modest and the interaction may not be clinically significant [221].

### 3.5.1.DL] 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[156].

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[156].

7) Probable Mechanism: additive serotonergic effects

### 3.5.1.DM] 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](#)[394] and [gastrointestinal bleeding](#) [398][399][395][396]. Bleeding events have included [epistaxis](#), ecchymosis, [hematoma](#), [petechiae](#), and life-threatening hemorrhages [401][400][402][403]. 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](#)[394] and [gastrointestinal bleeding](#) [395][396]. 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 [394].

**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 [397].

**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 [398] to 2.36 times [399], NSAIDs by 2.55 times [398], and the combination of SSRIs and NSAIDs by 4.02 [398] to 6.33 times [399].

**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 [400].

### 3.5.1.DN] 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](#)[394] and [gastrointestinal bleeding](#) [398][399][395][396]. Bleeding events have included [epistaxis](#), ecchymosis, [hematoma](#), [petechiae](#), and life-threatening hemorrhages [401][400][402][403]. 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](#)[394] and [gastrointestinal bleeding](#) [395][396]. 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 [394].

**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 [397].

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 [398] to 2.36 times [399], NSAIDs by 2.55 times [398], and the combination of SSRIs and NSAIDs by 4.02 [398] to 6.33 times [399].

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 [400].

### 3.5.1.DOJ 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](#)[394] and [gastrointestinal bleeding](#) [398][399][395][396]. Bleeding events have included [epistaxis](#), ecchymosis, [hematoma](#), [petechiae](#), and life-threatening hemorrhages [401][400][402][403]. 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](#)[394] and [gastrointestinal bleeding](#) [395][396]. 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 [394].

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 [397].

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 [398] to 2.36 times [399], NSAIDs by 2.55 times [398], and the combination of SSRIs and NSAIDs by 4.02 [398] to 6.33 times [399].



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 [400].

### 3.5.1.DP] [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](#)[394] and [gastrointestinal bleeding](#) [398][399][395][396]. Bleeding events have included [epistaxis](#), ecchymosis, [hematoma](#), [petechiae](#), and life-threatening hemorrhages [401][400][402][403]. 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](#)[394] and [gastrointestinal bleeding](#) [395][396]. 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 [394].

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 [397].

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 [398] to 2.36 times [399], NSAIDs by 2.55 times [398], and the combination of SSRIs and NSAIDs by 4.02 [398] to 6.33 times [399].

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 [400].

### 3.5.1.DQ] [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](#)[394] and [gastrointestinal bleeding](#)

[398][399][395][396]. Bleeding events have included [epistaxis](#), ecchymosis, [hematoma](#), [petechiae](#), and life-threatening hemorrhages [401][400][402][403]. 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](#)[394] and [gastrointestinal bleeding](#) [395][396]. 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 [394].

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 [397].

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 [398] to 2.36 times [399], NSAIDs by 2.55 times [398], and the combination of SSRIs and NSAIDs by 4.02 [398] to 6.33 times [399].

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 [400].

### 3.5.1.DR] [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](#)[394] and [gastrointestinal bleeding](#) [398][399][395][396]. Bleeding events have included [epistaxis](#), ecchymosis, [hematoma](#), [petechiae](#), and life-threatening hemorrhages [401][400][402][403]. 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](#)[394] and [gastrointestinal](#)

bleeding [395][396]. 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 [394].

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 [397].

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 [398] to 2.36 times [399], NSAIDs by 2.55 times [398], and the combination of SSRIs and NSAIDs by 4.02 [398] to 6.33 times [399].

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 [400].

### 3.5.1.DS] Meperidine

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

2) Summary: Meperidine is considered a proserotonergic opioid and has been associated with serotonin syndrome when used concomitantly with other serotonergic agents[159]. Increased serotonin levels which may produce additive serotonergic effects can occur if serotonergic agents are taken concurrently with meperidine. Symptoms of serotonin syndrome include neuromuscular abnormalities (including hyperreflexia, tremor, muscle rigidity, clonus, peripheral hypertonicity, and shivering), autonomic hyperactivity (including tachycardia, mydriasis, diaphoresis, the presence of bowel sounds, and diarrhea), and mental status changes (including agitation and delirium). Serotonin syndrome can be life-threatening. If serotonin syndrome develops, discontinue the offending agents and provide supportive care and other therapy as necessary [148]. Use caution if meperidine and a serotonergic agent are coadministered and monitor patients for signs and symptoms of serotonin syndrome.

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

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

7) Probable Mechanism: additive serotonergic effects

**3.5.1.DT] 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[393].
- 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[393].
- 7J) Probable Mechanism: inhibition of CYP2D6-mediated metabolism of [amphetamine](#); additive serotonergic effects

**3.5.1.DU] Methylene Blue**

- 1J) Interaction Effect: an increased risk of [serotonin syndrome](#) ([hypertension](#), [tachycardia](#), [hyperthermia](#), [myoclonus](#), [mental status changes](#))
- 2J) Summary: Concurrent use of IV methylene blue, an MAOI, and [sertraline](#) is contraindicated due to reports of [serotonin syndrome](#) with coadministration of an SSRI and methylene blue 1 to 8 mg/kg administered IV[106]. No cases have been identified in patients receiving methylene blue up to 5 mg for lymphatic mapping in [breast cancer](#) [162], nor with other routes of administration (eg, oral, local tissue injection), or with lower doses. If urgent treatment with IV methylene blue is necessary in a patient receiving [sertraline](#), alternatives are not available, and if risk/benefit has been evaluated, promptly discontinue [sertraline](#) and then administer IV methylene blue [106]. Use the lowest possible dose of methylene blue [160]. Monitor for 2 weeks or until 24 hours after the last dose of IV methylene blue, whichever comes first. [Sertraline](#) can be resumed 24 hours after the last methylene blue dose [106]. While the risk of concurrent [sertraline](#) with other forms of methylene blue is unclear, interactions are possible with methylene blue administered orally, by local injection, or in IV doses lower than 1 mg/kg.
- 3J) Severity: contraindicated
- 4J) Onset: unspecified
- 5J) Substantiation: theoretical
- 6J) Clinical Management: Concurrent use of [sertraline](#) and an MAOI, such as IV methylene blue, is contraindicated. If urgent treatment with IV methylene blue is necessary in a patient receiving [sertraline](#), alternatives are not available, and if risk/benefit has been evaluated, promptly discontinue [sertraline](#) and then administer IV methylene blue[106]. Use the lowest possible dose of methylene blue [160]. Monitor for [serotonin syndrome](#) for 2 weeks or until 24 hours after the last dose of IV methylene blue, whichever comes first. [Sertraline](#) can be resumed 24 hours after the last dose of methylene blue [106]. While the risk of concurrent [sertraline](#) with other forms of methylene blue is unclear, interactions are possible with methylene blue administered orally, by local injection, or in IV doses lower than 1 mg/kg.
- 7J) Probable Mechanism: additive serotonergic effect

**8) Literature Reports**

**a)** Serious CNS reactions have occurred following administration of methylene blue in a patient currently receiving an SSRI, such as [sertraline](#). In most reported cases, the patient was undergoing [parathyroid surgery](#), with use of methylene blue as a visualizing agent in doses ranging from 1 to 8 mg/kg. The risk of [serotonin syndrome](#) in patients taking SSRIs who receive methylene blue by alternative routes (eg, orally or by local tissue injection) or at doses lower than 1 mg/kg is unknown [161].

**b)** Patients treated with SSRIs who are undergoing lymphatic mapping for [breast cancer](#) are not expected to experience an interaction with concomitant use of methylene blue. Doses of methylene blue used in lymphatic mapping are many times lower (5 mg total) compared with doses used when [serotonin syndrome](#) occurred with concomitant use of an SSRI and methylene blue (eg, 1 to 8 mg/kg). No case reports of [serotonin syndrome](#) have been reported in patients taking SSRIs who received methylene blue in lymphatic mapping; however, healthcare providers should still be aware of the potential for an interaction between methylene blue and SSRIs in this setting [162].

**3.5.1.DV] [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[272].

**3)** Severity: moderate

**4)** Onset: unspecified

**5)** Substantiation: theoretical

**6)** Clinical Management: Use caution when prescribing [methylphenidate](#) to patients who take a selective serotonin reuptake inhibitor (SSRI). Concomitant use of [methylphenidate](#) and an SSRI may cause elevated SSRI plasma concentrations. Consider a decrease in the dose of SSRI when these agents are coadministered. Additionally, consider adjusting the SSRI dose if necessary when initiating or discontinuing [methylphenidate](#) therapy[272].

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

**3.5.1.DW] [Metoclopramide](#)**

**1)** Interaction Effect: an increased risk of developing extrapyramidal symptoms

**2)** Summary: In a case report, a 23-year old woman developed extrapyramidal symptoms after [sertraline](#) was added to a regimen of [metoclopramide](#)[126]. Another case report describes a 14-year old female who experienced mandibular [dystonia](#) five days after starting [metoclopramide](#) therapy in conjunction with [sertraline](#) [127]. Further case reports or controlled studies are necessary to confirm the clinical implications of this interaction.

**3)** Severity: moderate

**4)** Onset: delayed

**5)** Substantiation: probable

**6)** Clinical Management: Clinicians should be alerted to the possibility that patients may have an increased risk of experiencing extrapyramidal symptoms during coadministration of [sertraline](#) and [metoclopramide](#). Close patient monitoring is warranted.

**7)** Probable Mechanism: synergistic dopaminergic inhibition

**8)** Literature Reports

a) A 23-year-old woman developed mandibular **dystonia** after **sertraline** was added to a chronic regimen of **metoclopramide**. The patient had been taking **metoclopramide** 15 mg four times daily for six months when she was admitted to the hospital with depression. After two 50 mg doses of **sertraline**, the patient developed symptoms consistent with mandibular **dystonia**, including periauricular pain, jaw tightness, and the sensation of teeth clenching and grinding. After **diphenhydramine** 50 mg was given, the patient improved. The following day, the patient experienced a recurrence of symptoms after her third dose of **sertraline**. After **sertraline** was discontinued the patient experienced no further side effects and was successfully started on **trazodone** therapy [123].

b) A 14-year-old patient stabilized on **sertraline** 100 mg for the previous two months presented to her physician with severe nausea and vomiting. **Metoclopramide** 10 mg was prescribed three times daily. Five days later, the patient was taken to the emergency room because of mandibular **dystonia** and was successfully treated with **benztropine** 2 mg intramuscularly [124].

c) A risk of **serotonin syndrome** with serious extrapyramidal reactions may occur with the concomitant use of **sertraline** and **metoclopramide**. A 72-year-old female was treated with **sertraline** for 18 months for depression and **agoraphobia**. Other medications were **celecoxib** and **hydrocortisone**. After surgery for a fractured tibia she was given **acetaminophen** and morphine sulfate. **Metoclopramide** was initiated on postoperative day 2 because of nausea. Two hours after the first **metoclopramide** dose the patient developed tremor and involuntary twitching in her arms, shoulders, twitching of the lips, stiffness of the tongue and jaw and difficulties in controlling tongue movements. She had increased muscle tone in the limbs and neck with brisk reflexes on exam. Symptoms resolved in 4 hours after administration of **diazepam**. Upon reinstitution of **metoclopramide**, the patient experienced similar symptoms but more severe. **Creatine kinase** (CK) concentrations rose to 535 U/L, but CK MB fraction, troponin concentrations and ECG remained normal. **Diazepam** helped in resolution of symptoms within 6 hours, and the CK returned to normal the following day. Two days later a similar pattern of clinical features occurred 1.5 hours after she was mistakenly readministered **metoclopramide**. **Metoclopramide** was discontinued and there was no recurrence of the previous symptoms. According to the Naranjo probability scale, the combination of **sertraline** and **metoclopramide** was highly probable as the cause of **serotonin syndrome** [125].

### 3.5.1.DX] 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[273].

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[273].



7J) Probable Mechanism: additive serotonergic effect

### 3.5.1.DY] Mirtazapine

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

2J) Summary: Concomitant use of [mirtazapine](#) with other serotonergic agents may increase the risk of [serotonin syndrome](#) 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[264]. 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 [148].

3J) Severity: major

4J) Onset: unspecified

5J) Substantiation: theoretical

6J) Clinical Management: If concomitant use with other serotonergic drugs is clinically warranted, monitor for the emergence of [serotonin syndrome](#), particularly during treatment initiation and dose increases. Discontinue use of both agents if a patient shows symptoms of [serotonin syndrome](#)[264].

7J) Probable Mechanism: additive serotonin effects

8J) Literature Reports

aJ) Within a few hours of starting [mirtazapine](#) and shortly after stopping [fluoxetine](#), a 75-year-old woman experienced symptoms consistent with [serotonin syndrome](#). 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 [265].

bJ) 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 [266].

### 3.5.1.DZ] Moclobemide

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

2J) Summary: Concurrent administration or overlapping therapy with [sertraline](#) 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[359][360][361][362]

[363]. Although not reported specifically with moclobemide in therapeutic doses, a similar reaction may occur. Concomitant use is contraindicated.

3) Severity: contraindicated

4) Onset: rapid

5) Substantiation: probable

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

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

8) Literature Reports

a) Concomitant use of selective serotonin reuptake inhibitors and monoamine oxidase inhibitors can produce a toxic reaction known as [serotonin syndrome](#) [355]. [Serotonin syndrome](#) is a condition of serotonergic hyperstimulation and manifests as restlessness, myoclonus, changes in mental status, hyperreflexia, diaphoresis, shivering, and tremor. If the syndrome is not recognized and correctly treated, death can result.

b) A 26-year old woman who had been taking [isocarboxazid](#) for 8 weeks stopped taking the drug for 11 days before beginning therapy with [sertraline](#). After a single 100 mg [sertraline](#) dose, the patient became restless and developed leg twitches. The patient was later admitted to the emergency room with diaphoresis, [tachycardia](#), hyperreflexia, and various neuromuscular disturbances. The patient did not improve after treatment with [diazepam](#) and [propranolol](#). The patient was then given two 4 mg doses of [cypheptadine](#) an hour apart, with notable improvement in symptoms after the second dose [356].

c) A drug interaction was reported in a 61-year old woman in which [sertraline](#) 100 mg twice daily was added to a regimen of [lithium](#), [phenelzine](#), [thioridazine](#), and [doxepin](#). Three hours after taking the first [sertraline](#) dose, the patient was found in a semicomatose state, with elevated body temperature, increased pulse, increased respiration rate, and a blood pressure of 140/110 mmHg. After transportation to the hospital, the patient was misdiagnosed as having [neuroleptic malignant syndrome](#) (NMS) which was later changed to [serotonin syndrome](#) due to a reaction between [sertraline](#) and [phenelzine](#). The authors suggest that MAO inhibitor therapy should be discontinued for at least two weeks before initiation of therapy with a selective serotonin reuptake inhibitor (SSRI) and that before starting a MAOI, SSRI therapy should be discontinued for at least five half-lives of the parent drug and any active metabolites [357].

d) Five fatal cases of [serotonin syndrome](#) following overdoses have been reported. In three of the five cases, the drug combination that induced the fatal syndrome included moclobemide, a selective monoamine oxidase inhibitor, and [citalopram](#). Of these three patients, moclobemide blood concentrations ranged from five to 50 times the therapeutic level, and [citalopram](#) concentrations ranged from normal to five times the therapeutic level [358].

### 3.5.1.EA] 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](#)[394] and [gastrointestinal bleeding](#) [398][399][395][396]. Bleeding events have included [epistaxis](#), ecchymosis, [hematoma](#), [petechiae](#), and life-threatening hemorrhages [401][400][402][403]. 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](#)[394] and [gastrointestinal bleeding](#) [395][396]. 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 [394].

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 [397].

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 [398] to 2.36 times [399], NSAIDs by 2.55 times [398], and the combination of SSRIs and NSAIDs by 4.02 [398] to 6.33 times [399].

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 [400].

### 3.5.1.EB] [Nabumetone](#)

- 1) Interaction Effect: an increased risk of bleeding
- 2) Summary: Caution is recommended with the concomitant use of NSAIDs and antidepressants, including SSRIs due to an increased risk of [intracranial hemorrhage](#)[394] and [gastrointestinal bleeding](#) [398][399][395][396]. Bleeding events have included [epistaxis](#), ecchymosis, [hematoma](#), [petechiae](#), and life-threatening hemorrhages [401][400][402][403]. 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](#)[394] and [gastrointestinal bleeding](#) [395][396]. 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 [394].

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 [397].

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 [398] to 2.36 times [399], NSAIDs by 2.55 times [398], and the combination of SSRIs and NSAIDs by 4.02 [398] to 6.33 times [399].

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 [400].

### 3.5.1.EC] 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 (such as [sertraline](#)) and anticoagulants has been associated with an increased risk of bleeding[129][130][128]. Bleeding events reported have included [epistaxis](#), ecchymosis, [hematoma](#), [petechiae](#), and life-threatening hemorrhages. Altered anticoagulant effects (including increased bleeding) have been reported with the coadministration of SSRIs with [warfarin](#) [128]. Prothrombin time should be monitored in patients receiving both [warfarin](#) and [sertraline](#) [132].

3) Severity: major

4) Onset: delayed

5) Substantiation: probable

6) Clinical Management: When [sertraline](#) 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 [sertraline](#) therapy is initiated or discontinued[128].

7) Probable Mechanism: unknown

8) Literature Reports

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

group, and 10 patients experienced 14 bleedings during 586.4 treatment years in the warfarin-only group. The corresponding total incidences of bleedings were 51.4 and 23.9 per 1000 treatment years, respectively. The hazard ratio for first bleedings during treatment with [warfarin](#) plus SSRI was 3.49 (95% CI; 1.37 to 8.91,  $p=0.009$ ) compared with [warfarin](#) only. The SSRI implicated in patients experiencing bleeding at the time of concomitant administration were [sertraline](#) or [citalopram](#). The addition of an SSRI was not associated with a change in [warfarin](#) dose or INR ( $p=0.48$  and  $p=0.31$  respectively). The results of the study may be limited by earlier bleeding events, unknown patient adherence, and exclusion of [clopidogrel](#), dipyridamol, corticosteroids and anticoagulants other than [warfarin](#) in the model [129].

**b))** A population-based, case-controlled study of new coumarin users (acenocoumarol and phenprocoumon) with concomitant selective serotonin reuptake inhibitors (SSRIs) resulted in an increased risk of hospitalization due to non-gastrointestinal bleeding. Using national pharmacy and hospitalization records in the Netherlands, researchers identified 1848 cases that were admitted for abnormal bleeding and compared them with 5818 control subjects who were also taking a coumarin. Median duration of treatment in patients was 220 days (range, 1 to 4690 days). Patients on SSRIs showed greater risk for hospitalization for nongastrointestinal bleeding (adjusted odds ratio (OR) 1.7, 95% confidence interval (CI), 1.1 to 2.5); however, the rate of [gastrointestinal bleeding](#) (adjusted OR 0.8, 95% CI, 0.4 to 1.5) was not significantly different [130].

**c))** [Sertraline](#) 50 mg to 200 mg daily for 21 days produced an 8% increase in prothrombin time in subjects who received a single dose of [warfarin](#) 0.75 mg/kg relative to the same [warfarin](#) dose given prior to [sertraline](#); this compared with a 1% decrease with placebo. Normalization of the prothrombin time was also delayed as compared with placebo. The clinical significance of these findings is unknown [128].

**d))** In a non-blinded, randomized, placebo-controlled trial involving 12 healthy volunteers, the effect of [sertraline](#) on the plasma protein binding of [warfarin](#) was assessed. On days 1 and 32 of the study, all participants received [warfarin](#) 0.75 mg/kg. Beginning on day 11, each volunteer was randomized to either the [sertraline](#) or placebo group; the [sertraline](#) was gradually increased from 50 mg/day to 200 mg/day. Prothrombin time was measured prior to each dose of [warfarin](#) and periodically thereafter. The researchers concluded that the anticoagulant effects of [warfarin](#) were not enhanced by [sertraline](#) to a clinically significant degree, despite the fact that [sertraline](#) was given in a higher-than-usual dose [131].

### 3.5.1.ED] [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](#)[394] and [gastrointestinal bleeding](#) [398][399][395][396]. Bleeding events have included [epistaxis](#), ecchymosis, [hematoma](#), [petechiae](#), and life-threatening hemorrhages [401][400][402][403]. 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](#)[394] and [gastrointestinal bleeding](#) [395][396]. 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 [394].

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 [397].

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 [398] to 2.36 times [399], NSAIDs by 2.55 times [398], and the combination of SSRIs and NSAIDs by 4.02 [398] to 6.33 times [399].

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 [400].

### 3.5.1.EE] [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 [219]. 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](#) [220].

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.EF] [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[204] as it may increase plasma concentrations of nebivolol [204][205]. If coadministration is required, patients should be closely monitored, and dose adjustment may be required [205].

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Concomitant use of nebivolol and a CYP2D6 inhibitor should be avoided[204] as it may increase plasma concentrations of nebivolol[204][205]. If coadministration is required, patients should be closely monitored, and dose adjustment may be required [205].

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 Cmax (1.78 to 4.24 ng/mL), Tmax (1.37 to 3.11 hours), and AUC (17.26 to 106.2 ng x hr/mL) [206].

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 Cmax of d-nebivolol (pharmacologically active isomer) [204].

### 3.5.1.EG] [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](#)[394] and [gastrointestinal bleeding](#) [398][399][395][396]. Bleeding events have included [epistaxis](#), ecchymosis, [hematoma](#), [petechiae](#), and life-threatening hemorrhages [401][400][402][403]. 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](#)[394] and [gastrointestinal bleeding](#) [395][396]. 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 [394].

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 [397].

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 [398] to 2.36 times [399], NSAIDs by 2.55 times [398], and the combination of SSRIs and NSAIDs by 4.02 [398] to 6.33 times [399].

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 [400].

### 3.5.1.EH] Nialamide

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

2) Summary: Concurrent administration or overlapping therapy with [sertraline](#) and a monoamine oxidase (MAO) inhibitor may result in CNS toxicity or [serotonin syndrome](#), a hyperserotonergic state characterized by symptoms such as restlessness, myoclonus, changes in mental status, hyperreflexia, diaphoresis, shivering, and tremor. Serious, even fatal, reactions have been reported with concomitant use of serotonin specific reuptake inhibitors and MAO inhibitors[178][179][180][181][182]. Concomitant use is contraindicated.

3) Severity: contraindicated

4) Onset: rapid

5) Substantiation: probable

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

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

8) Literature Reports

a) Concomitant use of SSRIs and monoamine oxidase inhibitors can produce a toxic reaction known as [serotonin syndrome](#) [174]. [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, fatality can result.

b) A 26-year old woman who had been taking [isocarboxazid](#) for eight weeks stopped taking the drug for 11 days before beginning therapy with [sertraline](#). After a single 100 mg [sertraline](#) dose, the patient became restless and developed leg twitches. The patient was later admitted to the emergency room with diaphoresis, [tachycardia](#), hyperreflexia, and various neuromuscular disturbances. After treatment with [diazepam](#) and [propranolol](#) the patient did not improve. The patient was then given two 4 mg doses of [cyproheptadine](#) an hour apart, with notable improvement in symptoms after the second dose [175].

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

After transportation to the hospital, the patient was misdiagnosed as having [neuroleptic malignant syndrome](#) (NMS) which was later changed to [serotonin syndrome](#) due to a reaction between [sertraline](#) and [phenelzine](#). The authors suggest that monoamine oxidase inhibitor (MAOI) therapy should be discontinued for at least two weeks before initiation of therapy with a selective serotonin reuptake inhibitor (SSRI) and that before starting a MAOI, SSRI therapy should be discontinued for at least five half-lives of the parent drug and any active metabolites [176].

d) Two cases reports suggested a possible interaction between [fluoxetine](#) and [selegiline](#) [177]. One case involved a first episode of mania being observed approximately one month after adding [selegiline](#) to [fluoxetine](#). 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](#) to [selegiline](#). Both drugs were discontinued, with relatively quick resolution of symptoms. Rechallenge with [fluoxetine](#) alone occurred without incident.

### 3.5.1.EI] 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](#)[394] and [gastrointestinal bleeding](#) [398][399][395][396]. Bleeding events have included [epistaxis](#), ecchymosis, [hematoma](#), [petechiae](#), and life-threatening hemorrhages [401][400][402][403]. 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](#)[394] and [gastrointestinal bleeding](#) [395][396]. 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 [394].

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 [397].

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 [398] to 2.36 times [399], NSAIDs by 2.55 times [398], and the combination of SSRIs and NSAIDs by 4.02 [398] to 6.33 times [399].

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 [400].

### 3.5.1.EJ] Nimesulide

1) Interaction Effect: an increased risk of bleeding

2) Summary: Caution is recommended with the concomitant use of NSAIDs and antidepressants, including SSRIs due to an increased risk of [intracranial hemorrhage](#)[394] and [gastrointestinal bleeding](#) [398][399][395][396]. Bleeding events have included [epistaxis](#), ecchymosis, [hematoma](#), [petechiae](#), and life-threatening hemorrhages [401][400][402][403]. 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](#)[394] and [gastrointestinal bleeding](#) [395][396]. 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 [394].

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 [397].

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 [398] to 2.36 times [399], NSAIDs by 2.55 times [398], and the combination of SSRIs and NSAIDs by 4.02 [398] to 6.33 times [399].

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 [400].

**3.5.1.EK] 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](#)[394] and [gastrointestinal bleeding](#) [398][399][395][396]. Bleeding events have included [epistaxis](#), ecchymosis, [hematoma](#), [petechiae](#), and life-threatening hemorrhages [401][400][402][403]. 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](#)[394] and [gastrointestinal bleeding](#) [395][396]. 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 [394].

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 [397].

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 [398] to 2.36 times [399], NSAIDs by 2.55 times [398], and the combination of SSRIs and NSAIDs by 4.02 [398] to 6.33 times [399].

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 [400].

**3.5.1.EL] Nortriptyline**

- 1) Interaction Effect: elevated [nortriptyline](#) serum levels or possible [serotonin syndrome](#) (hypertension, [hyperthermia](#), myoclonus, mental status changes)
- 2) Summary: There is limited evidence suggesting that [sertraline](#) may inhibit tricyclic antidepressant (TCA) metabolism resulting in higher TCA serum concentrations. Sertraline weakly inhibits cytochrome P450 2D6 enzyme activity and may increase the plasma concentrations of coadministered drugs that are metabolized by this pathway, including the tricyclic antidepressants[248][249]. Effects of the interaction

may have little or no clinical impact, however. Increases in TCA serum levels associated with [sertraline](#) coadministration were modest compared with those found when [fluoxetine](#) (another selective serotonin reuptake inhibitor) was combined with [desipramine](#) [250]. Monitor patients on nortriptyline-sertraline therapy for TCA toxicity (dry mouth, urinary retention, CNS depression). [Nortriptyline](#) doses may need to be reduced [251].

3) Severity: major

4) Onset: delayed

5) Substantiation: probable

6) Clinical Management: The combined use of tricyclic antidepressants (TCAs) and selective serotonin reuptake inhibitors (SSRIs) may result in the inhibition of the TCA metabolism. A few cases of [serotonin syndrome](#) have also been reported with concurrent TCA and SSRI therapy. Caution should be observed when drugs in these two classes are used together. Monitor plasma [nortriptyline](#) concentrations as the dose of TCA may need to be reduced.

7) Probable Mechanism: inhibition of [nortriptyline](#) metabolism

8) Literature Reports

a) [Desipramine](#) pharmacokinetics were studied in 18 healthy male volunteers. Study subjects received only [desipramine](#) (50 mg daily) for 7 days followed by [desipramine](#) with [sertraline](#) (50 mg daily) for 21 days. When [sertraline](#) was added to [desipramine](#) therapy, the mean maximum concentration of [desipramine](#) increased by 34% and the area under the concentration-time curve increased by 26%. Trough concentrations of [desipramine](#) were close to baseline one week after [sertraline](#) was discontinued. The changes in [desipramine](#) concentrations were modest and the interaction may not be clinically significant [246].

b) Fourteen elderly depressed patients were retrospectively studied to determine the effect that [sertraline](#) therapy had on their [nortriptyline](#) levels. [Sertraline](#) was initiated at 25 mg or 50 mg daily, and increased up to 150 mg daily. Overall, [sertraline](#) caused a median increase of only 2% in [nortriptyline](#) levels. However, two patients experienced changes of 51% and 117%, which could have clinical implications. In patients taking [sertraline](#) in doses of 100 mg or 150 mg daily, the [nortriptyline](#) level increase was 40%, with a range of -12% to 239%. Because of the wide variations seen in the change of [nortriptyline](#) levels, careful monitoring of [nortriptyline](#) concentrations should be practiced in patients treated with [sertraline](#) and [nortriptyline](#) [247].

### 3.5.1.EM] 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](#)[394] and [gastrointestinal bleeding](#) [398][399][395][396]. Bleeding events have included [epistaxis](#), ecchymosis, [hematoma](#), [petechiae](#), and life-threatening hemorrhages [401][400][402][403]. 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](#)[394] and [gastrointestinal bleeding](#) [395][396]. 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 [394].

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 [397].

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 [398] to 2.36 times [399], NSAIDs by 2.55 times [398], and the combination of SSRIs and NSAIDs by 4.02 [398] to 6.33 times [399].

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 [400].

### 3.5.1.EN] [Oxcarbazepine](#)

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

2) Summary: Coadministration of [oxcarbazepine](#), a CYP2C19 inhibitor[388], and [sertraline](#), a CYP2C19 substrate [389], may result in the development of symptoms suggestive of [serotonin syndrome](#). In a case report, an 87-year-old man developed [serotonin syndrome](#) symptoms 24 hours following coadministration [387]. When [oxcarbazepine](#) and [sertraline](#) are coadministered, use cautiously and monitor the patient for signs of [serotonin syndrome](#) (tachycardia, [hyperthermia](#), myoclonus, mental status changes).

3) Severity: major

4) Onset: rapid

5) Substantiation: probable

6) Clinical Management: Coadministration of [oxcarbazepine](#) and [sertraline](#) may result in [serotonin syndrome](#)[387]. If these agents are used together, closely monitor the patient for signs of [serotonin syndrome](#) (restlessness, [hyperthermia](#), hyperreflexia, incoordination).

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

8) Literature Reports

a) Symptoms of [serotonin syndrome](#) developed in an 87-year-old man following concurrent administration of [oxcarbazepine](#) and [sertraline](#). The man was hospitalized for suspected [cellulitis](#) after an 8-day history of bilateral lower extremity swelling and redness. Prior to admission, medications included [sertraline](#) 50 mg daily. The patient was started on [levofloxacin](#) 500 mg daily for the [cellulitis](#). After 5 days of treatment, pain and burning continued in his legs, and he was started on [oxcarbazepine](#) 150 mg a day for [neuropathy](#). Vomiting, fever, [hypertension](#), lethargy, mild stiffness, and upper body tremor developed the following day. The patient was intubated, and started on IV [fentanyl](#) and [midazolam](#). Body temperature measured 109 degrees F and mean arterial pressure was 30 mmHg. [Leukocytosis](#) (WBC 22.4 x 10(4), increased from 9.3 on admission)

and elevated [creatinine](#) kinase (592 units/L) developed. Sedation was discontinued and cooling blankets were applied. The patient developed [septic shock](#) and continued to deteriorate despite treatment with aggressive hydration, vasopressors, [hydrocortisone](#), [amikacin](#), [metronidazole](#), [ciprofloxacin](#), and [linezolid](#). Absent brain stem reflexes were noted within 30 hours of intubation. The patient was extubated and died [387].

### 3.5.1.EO] [Oxycodone](#)

- 1) Interaction Effect: an increased risk of [serotonin syndrome](#) ([tachycardia](#), [hyperthermia](#), myoclonus, mental status changes)
- 2) Summary: Coadministration of [oxycodone](#) and [sertraline](#) has resulted in the development of symptoms suggestive of [serotonin syndrome](#)[367][368]. Caution is advised if [oxycodone](#) and [sertraline](#) are coadministered. Monitor patients for signs and symptoms of [serotonin syndrome](#) ([tachycardia](#), [hyperthermia](#), myoclonus, mental status changes).
- 3) Severity: major
- 4) Onset: delayed
- 5) Substantiation: probable
- 6) Clinical Management: Concomitant administration of [oxycodone](#) and [sertraline](#) may increase the risk of developing [serotonin syndrome](#). If these agents are coadministered, monitor patients for symptoms of [serotonin syndrome](#) ([tachycardia](#), [hyperthermia](#), myoclonus, mental status changes).
- 7) Probable Mechanism: additive pharmacologic effects resulting in excessive serotonergic stimulation
- 8) Literature Reports

a) Symptoms of [serotonin syndrome](#) developed in an 86-year-old woman following concurrent administration of [oxycodone](#) and [sertraline](#). The woman was hospitalized subsequent to a fall which resulted in a sacral fracture. Prior to hospitalization, medications included extended-release [oxycodone](#) 10 mg twice daily and [sertraline](#) 150 mg once daily. The [oxycodone](#) dose was increased to 20 mg twice daily for pain control and following a brief hospital stay, she was transferred to a long-term care facility for rehabilitation. Within days, she appeared agitated and had markedly increased muscle tone in lower extremities, truncal ataxia, and coarse tremors, with myoclonic jerks, in both her feet. Subsequently, [sertraline](#) was rapidly tapered off and the [oxycodone](#) dose was decreased which resolved the myoclonus, rigidity, and tremors within 2 days. It was postulated that the increase in opiate dose may have precipitated the [serotonin syndrome](#) in this patient [367].

b) A 34-year-old [bone marrow transplant](#) male patient experienced visual hallucinations and tremors following concurrent use of [sertraline](#) and high-dose [oxycodone](#). Three days prior to presentation, the patient had been discharged from the hospital, following extensive evaluation (including a [bone marrow biopsy](#)) and treatment of [pneumonia](#). Discharge medications comprised of [sertraline](#) 50 mg once daily, [oxycodone](#) 10 mg as needed (average daily dose 10 to 20 mg/day), and [cyclosporine](#) 75 mg (total daily dose). Additional medications included [methylprednisolone](#), [omeprazole](#), folic acid, [acyclovir](#), [fluconazole](#), and [trimethoprim/sulfamethoxazole](#). Within 48 hours after discharge, the patient consumed a total of 200 mg [oxycodone](#) over 48 hours for severe biopsy-site related pain and during this interval, he experienced severe tremors and visual hallucinations. Since the patient had experienced similar tremors with initiation of [cyclosporine](#) therapy 1 year ago and his current [cyclosporine](#) level was 467 ng/mL (388.31 nanomol/L), [cyclosporine](#) was believed to be the offending agent, with contribution from the narcotic usage. Both [cyclosporine](#) and [oxycodone](#) were discontinued and [hydromorphone](#) (maximum 6 mg/day) was initiated for pain control. However, 72 hours later, severe tremor and visual hallucinations, to a lesser degree, persisted and the [cyclosporine](#) level had decreased to 128 ng/mL (106.4 nanomol/L). It was postulated that increased [oxycodone](#) doses in combination with [sertraline](#) use may have

precipitated an increase in central serotonin. Subsequently, [sertraline](#) was discontinued and oral [ciproheptadine](#) 8 mg was administered, which resolved the hallucinations and lessened the tremor after 12 hours [368].

### 3.5.1.EP] Oxyphenbutazone

- 1) Interaction Effect: an increased risk of bleeding
- 2) Summary: Caution is recommended with the concomitant use of NSAIDs and antidepressants, including SSRIs due to an increased risk of [intracranial hemorrhage](#)[394] and [gastrointestinal bleeding](#) [398][399][395][396]. Bleeding events have included [epistaxis](#), ecchymosis, [hematoma](#), [petechiae](#), and life-threatening hemorrhages [401][400][402][403]. 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](#)[394] and [gastrointestinal bleeding](#) [395][396]. 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 [394].

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 [397].

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 [398] to 2.36 times [399], NSAIDs by 2.55 times [398], and the combination of SSRIs and NSAIDs by 4.02 [398] to 6.33 times [399].

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 [400].

### 3.5.1.EQ] 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](#)[326].

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](#)[326].

7) Probable Mechanism: unknown

### 3.5.1.ER] Parecoxib

1) Interaction Effect: an increased risk of bleeding

2) Summary: Caution is recommended with the concomitant use of NSAIDs and antidepressants, including SSRIs due to an increased risk of [intracranial hemorrhage](#)[394] and [gastrointestinal bleeding](#) [398][399][395][396]. Bleeding events have included [epistaxis](#), ecchymosis, [hematoma](#), [petechiae](#), and life-threatening hemorrhages [401][400][402][403]. 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](#)[394] and [gastrointestinal bleeding](#) [395][396]. 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 [394].

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 [397].

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 [398] to 2.36 times [399], NSAIDs by 2.55 times [398], and the combination of SSRIs and NSAIDs by 4.02 [398] to 6.33 times [399].

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 [400].

### 3.5.1.ES] Pargyline

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

2)) Summary: Concurrent administration or overlapping therapy with [sertraline](#) and a monoamine oxidase (MAO) inhibitor may result in CNS toxicity or [serotonin syndrome](#), a hyperserotonergic state characterized by symptoms such as restlessness, myoclonus, changes in mental status, hyperreflexia, diaphoresis, shivering, and tremor. Serious, even fatal, reactions have been reported with concomitant use of serotonin specific reuptake inhibitors and MAO inhibitors[187][188][189][190][191]. Concomitant use is contraindicated.

3)) Severity: contraindicated

4)) Onset: rapid

5)) Substantiation: probable

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

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

8)) Literature Reports

a)) Concomitant use of SSRIs and monoamine oxidase inhibitors can produce a toxic reaction known as [serotonin syndrome](#) [183]. [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, fatality can result.

b)) A 26-year old woman who had been taking [isocarboxazid](#) for eight weeks stopped taking the drug for 11 days before beginning therapy with [sertraline](#). After a single 100 mg [sertraline](#) dose, the patient became restless and developed leg twitches. The patient was later admitted to the emergency room with diaphoresis, [tachycardia](#), hyperreflexia, and various neuromuscular disturbances. After treatment with [diazepam](#) and [propranolol](#) the patient did not improve. The patient was then given two 4 mg doses of [cyproheptadine](#) an hour apart, with notable improvement in symptoms after the second dose [184].

c)) A drug interaction was reported in a 61-year old woman in which [sertraline](#) 100 mg twice daily was added to a regimen of [lithium](#), [phenelzine](#), [thioridazine](#), and [doxepin](#). Three hours after taking the first [sertraline](#) dose, the patient was found in a semicomatose state, with elevated body temperature, increased pulse, increased respiration rate, and a blood pressure of 140/110 mm Hg. After transportation to the hospital, the patient was misdiagnosed as having [neuroleptic malignant syndrome](#) (NMS) which was later changed to [serotonin syndrome](#) due to a reaction between [sertraline](#) and [phenelzine](#). The authors suggest that monoamine oxidase inhibitor (MAOI) therapy should be discontinued for at least two weeks before initiation of therapy with a selective serotonin reuptake inhibitor (SSRI) and that before starting a MAOI, SSRI therapy should be discontinued for at least five half-lives of the parent drug and any active metabolites [185].

d)) Two cases reports suggested a possible interaction between [fluoxetine](#) and [selegiline](#) [186]. One case involved a first episode of mania being observed approximately one month after adding



[selegiline](#) to [fluoxetine](#). 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](#) to [selegiline](#). Both drugs were discontinued, with relatively quick resolution of symptoms. Rechallenge with [fluoxetine](#) alone occurred without incident.

### 3.5.1.ET] Parnaparin

1) Interaction Effect: an increased risk of bleeding

2) Summary: The release of serotonin by [platelets](#) is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs (such as [sertraline](#)) and anticoagulants has been associated with an increased risk of bleeding[129][130][128]. Bleeding events reported have included [epistaxis](#), ecchymosis, [hematoma](#), [petechiae](#), and life-threatening hemorrhages. Altered anticoagulant effects (including increased bleeding) have been reported with the coadministration of SSRIs with [warfarin](#) [128]. Prothrombin time should be monitored in patients receiving both [warfarin](#) and [sertraline](#) [132].

3) Severity: major

4) Onset: delayed

5) Substantiation: probable

6) Clinical Management: When [sertraline](#) 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 [sertraline](#) therapy is initiated or discontinued[128].

7) Probable Mechanism: unknown

8) Literature Reports

a) According to a retrospective cohort study (n=234), there was an increased risk of clinically relevant bleeding (hospital admission due to bleeding) in patients receiving [warfarin](#) for [atrial fibrillation](#) during concomitant SSRI therapy or within 2 weeks following SSRI therapy termination. Patients with a mean age of 72 +/- 7 years receiving [warfarin](#) plus SSRI (n=117) were matched with randomly selected patients who received [warfarin](#) only (n=117). SSRI included [fluoxetine](#), [citalopram](#), [paroxetine](#), [sertraline](#), [fluvoxamine](#), or escitalopram. Nine patients experienced 11 bleeding episodes during 213.9 treatment years in the [warfarin](#) plus SSRI group, and 10 patients experienced 14 bleedings during 586.4 treatment years in the warfarin-only group. The corresponding total incidences of bleedings were 51.4 and 23.9 per 1000 treatment years, respectively. The hazard ratio for first bleedings during treatment with [warfarin](#) plus SSRI was 3.49 (95% CI; 1.37 to 8.91, p=0.009) compared with [warfarin](#) only. The SSRI implicated in patients experiencing bleeding at the time of concomitant administration were [sertraline](#) or [citalopram](#). The addition of an SSRI was not associated with a change in [warfarin](#) dose or INR (p=0.48 and p=0.31 respectively). The results of the study may be limited by earlier bleeding events, unknown patient adherence, and exclusion of [clopidogrel](#), dipyridamol, corticosteroids and anticoagulants other than [warfarin](#) in the model [129].

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



(adjusted odds ratio (OR) 1.7, 95% confidence interval (CI), 1.1 to 2.5); however, the rate of [gastrointestinal bleeding](#) (adjusted OR 0.8, 95% CI, 0.4 to 1.5) was not significantly different [130].

c) [Sertraline](#) 50 mg to 200 mg daily for 21 days produced an 8% increase in prothrombin time in subjects who received a single dose of [warfarin](#) 0.75 mg/kg relative to the same [warfarin](#) dose given prior to [sertraline](#); this compared with a 1% decrease with placebo. Normalization of the prothrombin time was also delayed as compared with placebo. The clinical significance of these findings is unknown [128].

d) In a non-blinded, randomized, placebo-controlled trial involving 12 healthy volunteers, the effect of [sertraline](#) on the plasma protein binding of [warfarin](#) was assessed. On days 1 and 32 of the study, all participants received [warfarin](#) 0.75 mg/kg. Beginning on day 11, each volunteer was randomized to either the [sertraline](#) or placebo group; the [sertraline](#) was gradually increased from 50 mg/day to 200 mg/day. Prothrombin time was measured prior to each dose of [warfarin](#) and periodically thereafter. The researchers concluded that the anticoagulant effects of [warfarin](#) were not enhanced by [sertraline](#) to a clinically significant degree, despite the fact that [sertraline](#) was given in a higher-than-usual dose [131].

### 3.5.1.EU] [Paroxetine](#)

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[21].

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[21].

7) Probable Mechanism: inhibition of CYP2D6-mediated metabolism; additive serotonergic effects

### 3.5.1.EV] [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 (such as [sertraline](#)) and anticoagulants has been associated with an increased risk of bleeding[129][130][128]. Bleeding events reported have included [epistaxis](#), ecchymosis, [hematoma](#), [petechiae](#), and life-threatening hemorrhages. Altered anticoagulant effects (including increased bleeding) have been reported with the coadministration of SSRIs with [warfarin](#) [128]. Prothrombin time should be monitored in patients receiving both [warfarin](#) and [sertraline](#) [132].

3) Severity: major

4) Onset: delayed

**5) Substantiation: probable**

**6) Clinical Management:** When [sertraline](#) 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 [sertraline](#) therapy is initiated or discontinued[128].

**7) Probable Mechanism: unknown****8) Literature Reports**

**a)** According to a retrospective cohort study (n=234), there was an increased risk of clinically relevant bleeding (hospital admission due to bleeding) in patients receiving [warfarin](#) for [atrial fibrillation](#) during concomitant SSRI therapy or within 2 weeks following SSRI therapy termination. Patients with a mean age of 72 +/- 7 years receiving [warfarin](#) plus SSRI (n=117) were matched with randomly selected patients who received [warfarin](#) only (n=117). SSRI included [fluoxetine](#), [citalopram](#), [paroxetine](#), [sertraline](#), [fluvoxamine](#), or escitalopram. Nine patients experienced 11 bleeding episodes during 213.9 treatment years in the [warfarin](#) plus SSRI group, and 10 patients experienced 14 bleedings during 586.4 treatment years in the warfarin-only group. The corresponding total incidences of bleedings were 51.4 and 23.9 per 1000 treatment years, respectively. The hazard ratio for first bleedings during treatment with [warfarin](#) plus SSRI was 3.49 (95% CI; 1.37 to 8.91, p=0.009) compared with [warfarin](#) only. The SSRI implicated in patients experiencing bleeding at the time of concomitant administration were [sertraline](#) or [citalopram](#). The addition of an SSRI was not associated with a change in [warfarin](#) dose or INR (p=0.48 and p=0.31 respectively). The results of the study may be limited by earlier bleeding events, unknown patient adherence, and exclusion of [clopidogrel](#), dipyridamol, corticosteroids and anticoagulants other than [warfarin](#) in the model [129].

**b)** A population-based, case-controlled study of new coumarin users (acenocoumarol and phenprocoumon) with concomitant selective serotonin reuptake inhibitors (SSRIs) resulted in an increased risk of hospitalization due to non-gastrointestinal bleeding. Using national pharmacy and hospitalization records in the Netherlands, researchers identified 1848 cases that were admitted for abnormal bleeding and compared them with 5818 control subjects who were also taking a coumarin. Median duration of treatment in patients was 220 days (range, 1 to 4690 days). Patients on SSRIs showed greater risk for hospitalization for nongastrointestinal bleeding (adjusted odds ratio (OR) 1.7, 95% confidence interval (CI), 1.1 to 2.5); however, the rate of [gastrointestinal bleeding](#) (adjusted OR 0.8, 95% CI, 0.4 to 1.5) was not significantly different [130].

**c)** [Sertraline](#) 50 mg to 200 mg daily for 21 days produced an 8% increase in prothrombin time in subjects who received a single dose of [warfarin](#) 0.75 mg/kg relative to the same [warfarin](#) dose given prior to [sertraline](#); this compared with a 1% decrease with placebo. Normalization of the prothrombin time was also delayed as compared with placebo. The clinical significance of these findings is unknown [128].

**d)** In a non-blinded, randomized, placebo-controlled trial involving 12 healthy volunteers, the effect of [sertraline](#) on the plasma protein binding of [warfarin](#) was assessed. On days 1 and 32 of the study, all participants received [warfarin](#) 0.75 mg/kg. Beginning on day 11, each volunteer was randomized to either the [sertraline](#) or placebo group; the [sertraline](#) was gradually increased from 50 mg/day to 200 mg/day. Prothrombin time was measured prior to each dose of [warfarin](#) and periodically thereafter. The researchers concluded that the anticoagulant effects of [warfarin](#) were not enhanced by [sertraline](#) to a clinically significant degree, despite the fact that [sertraline](#) was given in a higher-than-usual dose [131].

**3.5.1.EW] Phenelzine**

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

**2)** Summary: Concurrent administration or overlapping therapy with [sertraline](#) 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[373][374][375][376][377]. Concomitant use is contraindicated.

**3)** Severity: contraindicated

**4)** Onset: rapid

**5)** Substantiation: probable

**6)** Clinical Management: Concurrent use of [sertraline](#) and a MAO inhibitor is contraindicated. Wait at least 14 days after discontinuing a MAO inhibitor before initiating therapy with [sertraline](#). Wait at least 14 days after discontinuing [sertraline](#) 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](#) [369]. [Serotonin syndrome](#) is a condition of serotonergic hyperstimulation and manifests as restlessness, myoclonus, changes in mental status, hyperreflexia, diaphoresis, shivering, and tremor. If the syndrome is not recognized and correctly treated, death can result.

**b)** A 26-year old woman who had been taking [isocarboxazid](#) for eight weeks stopped taking the drug for 11 days before beginning therapy with [sertraline](#). After a single 100 mg [sertraline](#) dose, the patient became restless and developed leg twitches. The patient was later admitted to the emergency room with diaphoresis, [tachycardia](#), hyperreflexia, and various neuromuscular disturbances. The patient did not improve after treatment with [diazepam](#) and [propranolol](#). The patient was then given two 4 mg doses of [cyproheptadine](#) an hour apart, with notable improvement in symptoms after the second dose [370].

**c)** A drug interaction was reported in a 61-year old woman in which [sertraline](#) 100 mg twice daily was added to a regimen of [lithium](#), [phenelzine](#), [thioridazine](#), and [doxepin](#). Three hours after taking the first [sertraline](#) dose, the patient was found in a semicomatose state, with elevated body temperature, increased pulse, increased respiration rate, and a blood pressure of 140/110 mmHg. After transportation to the hospital, the patient was misdiagnosed as having [neuroleptic malignant syndrome](#) (NMS) which was later changed to [serotonin syndrome](#) due to a reaction between [sertraline](#) and [phenelzine](#). The authors suggest that MAO inhibitor therapy should be discontinued for at least two weeks before initiation of therapy with a selective serotonin reuptake inhibitor (SSRI) and that before starting a MAOI, SSRI therapy should be discontinued for at least 5 half-lives of the parent drug and any active metabolites [371].

**d)** Two cases reports suggested a possible interaction between [fluoxetine](#) and [selegiline](#) [372]. One case involved a first episode of mania being observed approximately 1 month after adding [selegiline](#) to [fluoxetine](#) therapy. The patient improved 2 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.EX] 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 (such as [sertraline](#)) and anticoagulants has been associated with an increased risk of bleeding[129][130][128]. Bleeding events reported have included [epistaxis](#), ecchymosis, [hematoma](#), [petechiae](#), and life-threatening hemorrhages. Altered anticoagulant effects (including increased bleeding) have been reported with the coadministration of SSRIs with [warfarin](#) [128]. Prothrombin time should be monitored in patients receiving both [warfarin](#) and [sertraline](#) [132].

**3)** Severity: major

**4)** Onset: delayed

**5)** Substantiation: probable

**6)** Clinical Management: When [sertraline](#) 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 [sertraline](#) therapy is initiated or discontinued[128].

**7)** Probable Mechanism: unknown

**8)** Literature Reports

**a)** According to a retrospective cohort study (n=234), there was an increased risk of clinically relevant bleeding (hospital admission due to bleeding) in patients receiving [warfarin](#) for [atrial fibrillation](#) during concomitant SSRI therapy or within 2 weeks following SSRI therapy termination. Patients with a mean age of 72 +/- 7 years receiving [warfarin](#) plus SSRI (n=117) were matched with randomly selected patients who received [warfarin](#) only (n=117). SSRI included [fluoxetine](#), [citalopram](#), [paroxetine](#), [sertraline](#), [fluvoxamine](#), or escitalopram. Nine patients experienced 11 bleeding episodes during 213.9 treatment years in the [warfarin](#) plus SSRI group, and 10 patients experienced 14 bleedings during 586.4 treatment years in the warfarin-only group. The corresponding total incidences of bleedings were 51.4 and 23.9 per 1000 treatment years, respectively. The hazard ratio for first bleedings during treatment with [warfarin](#) plus SSRI was 3.49 (95% CI; 1.37 to 8.91, p=0.009) compared with [warfarin](#) only. The SSRI implicated in patients experiencing bleeding at the time of concomitant administration were [sertraline](#) or [citalopram](#). The addition of an SSRI was not associated with a change in [warfarin](#) dose or INR (p=0.48 and p=0.31 respectively). The results of the study may be limited by earlier bleeding events, unknown patient adherence, and exclusion of [clopidogrel](#), dipyridamol, corticosteroids and anticoagulants other than [warfarin](#) in the model [129].

**b)** A population-based, case-controlled study of new coumarin users (acenocoumarol and phenprocoumon) with concomitant selective serotonin reuptake inhibitors (SSRIs) resulted in an increased risk of hospitalization due to non-gastrointestinal bleeding. Using national pharmacy and hospitalization records in the Netherlands, researchers identified 1848 cases that were admitted for abnormal bleeding and compared them with 5818 control subjects who were also taking a coumarin. Median duration of treatment in patients was 220 days (range, 1 to 4690 days). Patients on SSRIs showed greater risk for hospitalization for nongastrointestinal bleeding (adjusted odds ratio (OR) 1.7, 95% confidence interval (CI), 1.1 to 2.5); however, the rate of [gastrointestinal bleeding](#) (adjusted OR 0.8, 95% CI, 0.4 to 1.5) was not significantly different [130].

**c)** [Sertraline](#) 50 mg to 200 mg daily for 21 days produced an 8% increase in prothrombin time in subjects who received a single dose of [warfarin](#) 0.75 mg/kg relative to the same [warfarin](#) dose given prior to [sertraline](#); this compared with a 1% decrease with placebo. Normalization of the

prothrombin time was also delayed as compared with placebo. The clinical significance of these findings is unknown [128].

**d))** In a non-blinded, randomized, placebo-controlled trial involving 12 healthy volunteers, the effect of [sertraline](#) on the plasma protein binding of [warfarin](#) was assessed. On days 1 and 32 of the study, all participants received [warfarin](#) 0.75 mg/kg. Beginning on day 11, each volunteer was randomized to either the [sertraline](#) or placebo group; the [sertraline](#) was gradually increased from 50 mg/day to 200 mg/day. Prothrombin time was measured prior to each dose of [warfarin](#) and periodically thereafter. The researchers concluded that the anticoagulant effects of [warfarin](#) were not enhanced by [sertraline](#) to a clinically significant degree, despite the fact that [sertraline](#) was given in a higher-than-usual dose [131].

### 3.5.1.EY] 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 (such as [sertraline](#)) and anticoagulants has been associated with an increased risk of bleeding[129][130][128]. Bleeding events reported have included [epistaxis](#), ecchymosis, [hematoma](#), [petechiae](#), and life-threatening hemorrhages. Altered anticoagulant effects (including increased bleeding) have been reported with the coadministration of SSRIs with [warfarin](#) [128]. Prothrombin time should be monitored in patients receiving both [warfarin](#) and [sertraline](#) [132].

**3))** Severity: major

**4))** Onset: delayed

**5))** Substantiation: probable

**6))** Clinical Management: When [sertraline](#) 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 [sertraline](#) therapy is initiated or discontinued[128].

**7))** Probable Mechanism: unknown

**8))** Literature Reports

**a))** According to a retrospective cohort study (n=234), there was an increased risk of clinically relevant bleeding (hospital admission due to bleeding) in patients receiving [warfarin](#) for [atrial fibrillation](#) during concomitant SSRI therapy or within 2 weeks following SSRI therapy termination. Patients with a mean age of 72 +/- 7 years receiving [warfarin](#) plus SSRI (n=117) were matched with randomly selected patients who received [warfarin](#) only (n=117). SSRI included [fluoxetine](#), [citalopram](#), [paroxetine](#), [sertraline](#), [fluvoxamine](#), or escitalopram. Nine patients experienced 11 bleeding episodes during 213.9 treatment years in the [warfarin](#) plus SSRI group, and 10 patients experienced 14 bleedings during 586.4 treatment years in the warfarin-only group. The corresponding total incidences of bleedings were 51.4 and 23.9 per 1000 treatment years, respectively. The hazard ratio for first bleedings during treatment with [warfarin](#) plus SSRI was 3.49 (95% CI; 1.37 to 8.91, p=0.009) compared with [warfarin](#) only. The SSRI implicated in patients experiencing bleeding at the time of concomitant administration were [sertraline](#) or [citalopram](#). The addition of an SSRI was not associated with a change in [warfarin](#) dose or INR (p=0.48 and p=0.31 respectively). The results of the study may be limited by earlier bleeding events, unknown patient adherence, and exclusion of [clopidogrel](#), dipyridamol, corticosteroids and anticoagulants other than [warfarin](#) in the model [129].

**b))** A population-based, case-controlled study of new coumarin users (acenocoumarol and phenprocoumon) with concomitant selective serotonin reuptake inhibitors (SSRIs) resulted in an increased risk of hospitalization due to non-gastrointestinal bleeding. Using national pharmacy



and hospitalization records in the Netherlands, researchers identified 1848 cases that were admitted for abnormal bleeding and compared them with 5818 control subjects who were also taking a coumarin. Median duration of treatment in patients was 220 days (range, 1 to 4690 days). Patients on SSRIs showed greater risk for hospitalization for nongastrointestinal bleeding (adjusted odds ratio (OR) 1.7, 95% confidence interval (CI), 1.1 to 2.5); however, the rate of [gastrointestinal bleeding](#) (adjusted OR 0.8, 95% CI, 0.4 to 1.5) was not significantly different [130].

c) [Sertraline](#) 50 mg to 200 mg daily for 21 days produced an 8% increase in prothrombin time in subjects who received a single dose of [warfarin](#) 0.75 mg/kg relative to the same [warfarin](#) dose given prior to [sertraline](#); this compared with a 1% decrease with placebo. Normalization of the prothrombin time was also delayed as compared with placebo. The clinical significance of these findings is unknown [128].

d) In a non-blinded, randomized, placebo-controlled trial involving 12 healthy volunteers, the effect of [sertraline](#) on the plasma protein binding of [warfarin](#) was assessed. On days 1 and 32 of the study, all participants received [warfarin](#) 0.75 mg/kg. Beginning on day 11, each volunteer was randomized to either the [sertraline](#) or placebo group; the [sertraline](#) was gradually increased from 50 mg/day to 200 mg/day. Prothrombin time was measured prior to each dose of [warfarin](#) and periodically thereafter. The researchers concluded that the anticoagulant effects of [warfarin](#) were not enhanced by [sertraline](#) to a clinically significant degree, despite the fact that [sertraline](#) was given in a higher-than-usual dose [131].

### 3.5.1.EZ] [Phenylbutazone](#)

1) Interaction Effect: an increased risk of bleeding

2) Summary: Caution is recommended with the concomitant use of NSAIDs and antidepressants, including SSRIs due to an increased risk of [intracranial hemorrhage](#)[394] and [gastrointestinal bleeding](#) [398][399][395][396]. Bleeding events have included [epistaxis](#), ecchymosis, [hematoma](#), [petechiae](#), and life-threatening hemorrhages [401][400][402][403]. 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](#)[394] and [gastrointestinal bleeding](#) [395][396]. 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 [394].

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 [397].

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 [398] to 2.36 times [399], NSAIDs by 2.55 times [398], and the combination of SSRIs and NSAIDs by 4.02 [398] to 6.33 times [399].

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 [400].

### 3.5.1.FA] [Phenytoin](#)

1) Interaction Effect: increased risk of [phenytoin](#) toxicity and decreased efficacy of [sertraline](#)

2) Summary: The concomitant use of [phenytoin](#), a CYP2C9 and CYP2C19 substrate and potent CYP-enzyme inducer, and [sertraline](#) may increase the risk of [phenytoin](#) toxicity and reduce [sertraline](#) efficacy[285][286]. Coadministration of [phenytoin](#) with [sertraline](#) has resulted in elevated serum [phenytoin](#) levels in 2 elderly patients [291]. To achieve optimal clinical outcomes, consider [phenytoin](#) and [sertraline](#) dose adjustments when [phenytoin](#) is added to or withdrawn from a patient's regimen. [Phenytoin](#) serum drug level monitoring is suggested during concurrent use of [phenytoin](#) and [sertraline](#) [285][286].

3) Severity: major

4) Onset: unspecified

5) Substantiation: probable

6) Clinical Management: Use caution with coadministration of [phenytoin](#) and [sertraline](#), as concurrent use may increase the risk of [phenytoin](#) toxicity and reduce [sertraline](#) efficacy. Consider [phenytoin](#) and [sertraline](#) dose adjustments when [phenytoin](#) is added to or withdrawn from a patient's regimen. [Phenytoin](#) serum drug level monitoring is suggested during concurrent use of [phenytoin](#) and [sertraline](#)[285][286].

7) Probable Mechanism: inhibition of CYP-mediated [phenytoin](#) metabolism by [sertraline](#); induction of CYP-mediated [sertraline](#) metabolism by [phenytoin](#)

8) Literature Reports

a) Two elderly patients developed elevated serum [phenytoin](#) concentrations during coadministration with [sertraline](#). Patient 1, a 78-year old man, was taking [phenytoin](#) 300 mg per day in addition to several other medications. After [sertraline](#) 25 mg every night was added to his regimen for depression, serum [phenytoin](#) levels increased from 5.2 mcg/mL to 12.3 mcg/mL. After serial increases in the [sertraline](#) dose to 75 mg per day, the patient's serum [phenytoin](#) level rose to 30.9 mcg/mL. [Phenytoin](#) was discontinued but was later successfully restarted at a dose of 200 mg per day. [Sertraline](#) 100 mg per day was also administered without further adverse effects. Patient 2, an 85-year old man, developed increased serum [phenytoin](#) levels (from 15.6 mcg/mL to 20 mcg/mL) after the addition of [sertraline](#) 25 mg every other day to [phenytoin](#) 260 mg per day. The authors recommend checking serum [phenytoin](#) concentrations within one week after starting [sertraline](#) therapy or initiating a change in [sertraline](#) dose [287].

b) [Sertraline](#) is known to be a moderate to weak inhibitor of the CYP2D6 isoenzyme and is suspected of inhibiting the CYP2C9 and CYP3A4 hepatic isoenzymes. The metabolism of [phenytoin](#) may involve the CYP2D6 [288] and CYP2C9 hepatic isoenzymes [289][290]. Given this overlap of hepatic enzyme activity and pathways, it seems theoretically possible that concurrent [sertraline](#) may act to inhibit metabolic clearance of [phenytoin](#), thereby producing higher [phenytoin](#) serum concentrations.

**3.5.1.FB] 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](#)[394] and [gastrointestinal bleeding](#) [398][399][395][396]. Bleeding events have included [epistaxis](#), ecchymosis, [hematoma](#), [petechiae](#), and life-threatening hemorrhages [401][400][402][403]. 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](#)[394] and [gastrointestinal bleeding](#) [395][396]. 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 [394].

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 [397].

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 [398] to 2.36 times [399], NSAIDs by 2.55 times [398], and the combination of SSRIs and NSAIDs by 4.02 [398] to 6.33 times [399].

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 [400].

**3.5.1.FC] Pimozide**

- 1) Interaction Effect: an increase in plasma [pimozide](#) levels
- 2) Summary: Due to the narrow therapeutic index of [pimozide](#) and due to the interaction noted at low dose of [pimozide](#), concomitant administration of [sertraline](#) and [pimozide](#) is contraindicated[433].
- 3) Severity: contraindicated
- 4) Onset: unspecified
- 5) Substantiation: probable

- 6) Clinical Management: Concomitant use of [sertraline](#) in patients taking [pimozide](#) is contraindicated.
- 7) Probable Mechanism: unknown
- 8) Literature Reports

a) In a controlled trial of a single 2 mg dose of [pimozide](#), [sertraline](#) 200 mg daily coadministration to steady state was associated with a mean increase in [pimozide](#) area under the concentration-time curve (AUC) and maximum plasma concentrations (C<sub>max</sub>) of about 40%, but was not associated with any changes in EKG. Since the highest recommended [pimozide](#) dose (10 mg) has not been evaluated in combination with [sertraline](#), the effect on QT interval and pharmacokinetic parameters at higher than 2 mg are not known. Considering the narrow therapeutic index of [pimozide](#) and observed interaction data with low doses, the combination should be avoided [432].

### 3.5.1.FD] [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](#)[394] and [gastrointestinal bleeding](#) [398][399][395][396]. Bleeding events have included [epistaxis](#), ecchymosis, [hematoma](#), [petechiae](#), and life-threatening hemorrhages [401][400][402][403]. 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](#)[394] and [gastrointestinal bleeding](#) [395][396]. 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 [394].

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 [397].

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 [398] to 2.36 times [399], NSAIDs by 2.55 times [398], and the combination of SSRIs and NSAIDs by 4.02 [398] to 6.33 times [399].

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 [400].

### 3.5.1.FE] 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](#)[394] and [gastrointestinal bleeding](#) [398][399][395][396]. Bleeding events have included [epistaxis](#), ecchymosis, [hematoma](#), [petechiae](#), and life-threatening hemorrhages [401][400][402][403]. 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](#)[394] and [gastrointestinal bleeding](#) [395][396]. 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 [394].

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 [397].

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 [398] to 2.36 times [399], NSAIDs by 2.55 times [398], and the combination of SSRIs and NSAIDs by 4.02 [398] to 6.33 times [399].

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 [400].

### 3.5.1.FF] Prasugrel

1)) Interaction Effect: increased risk of bleeding

2)) Summary: Exercise caution when coadministering a SSRI and an antiplatelet agent as this may increase the risk of bleeding events[141][21][140].

- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Concomitant use of [sertraline](#) and an antiplatelet agent should be undertaken with caution as this may increase the risk of bleeding events[21].
- 7) Probable Mechanism: unknown
- 8) Literature Reports

a) In a retrospective study of patients over 50 years of age with the diagnosis of acute [myocardial infarction](#) (N=27,058), SSRI use with any antiplatelet therapy significantly increased the risk of bleeding by 1.42-fold compared with [aspirin](#) use alone. Therapy with [aspirin](#), [clopidogrel](#), and an SSRI significantly increased risk by 2.35-fold compared with [aspirin](#) use alone and by 1.57-fold compared with [clopidogrel](#) and [aspirin](#) combination therapy [140].

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) [141].

### 3.5.1.FG] [Procarbazine](#)

- 1) Interaction Effect: CNS toxicity or [serotonin syndrome](#) ([hypertension](#), [hyperthermia](#), myoclonus, mental status changes)
- 2) Summary: Concurrent administration or overlapping therapy with [sertraline](#) and a monoamine oxidase (MAO) inhibitor may result in CNS toxicity or [serotonin syndrome](#), a hyperserotonergic state characterized by symptoms such as restlessness, myoclonus, changes in mental status, hyperreflexia, diaphoresis, shivering, and tremor. Serious, even fatal, reactions have been reported with concomitant use of serotonin specific reuptake inhibitors and MAO inhibitors[169][170][171][172][173]. Concomitant use is contraindicated.
- 3) Severity: contraindicated
- 4) Onset: rapid
- 5) Substantiation: probable
- 6) Clinical Management: Concurrent use of [sertraline](#) and a MAO inhibitor is contraindicated. Wait at least 14 days after discontinuing a MAO inhibitor before initiating therapy with [sertraline](#). Wait at least 14 days after discontinuing [sertraline](#) before initiating therapy with a MAO inhibitor.
- 7) Probable Mechanism: inhibition of serotonin metabolism by monoamine oxidase
- 8) Literature Reports

a) Concomitant use of SSRIs and monoamine oxidase inhibitors can produce a toxic reaction known as [serotonin syndrome](#) [165]. [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, fatality can result.

b) A 26-year old woman who had been taking [isocarboxazid](#) for eight weeks stopped taking the drug for 11 days before beginning therapy with [sertraline](#). After a single 100 mg [sertraline](#) dose, the patient became restless and developed leg twitches. The patient was later admitted to the emergency room with diaphoresis, [tachycardia](#), hyperreflexia, and various neuromuscular disturbances. After treatment with [diazepam](#) and [propranolol](#) the patient did not improve. The patient was then given two 4 mg doses of [cyproheptadine](#) an hour apart, with notable improvement in symptoms after the second dose [166].

c) A drug interaction was reported in a 61-year old woman in which [sertraline](#) 100 mg twice daily was added to a regimen of [lithium](#), [phenelzine](#), [thioridazine](#), and [doxepin](#). Three hours after taking the first [sertraline](#) dose, the patient was found in a semicomatose state, with elevated body temperature, increased pulse, increased respiration rate, and a blood pressure of 140/110 mm Hg. After transportation to the hospital, the patient was misdiagnosed as having [neuroleptic malignant syndrome](#) (NMS) which was later changed to [serotonin syndrome](#) due to a reaction between [sertraline](#) and [phenelzine](#). The authors suggest that monoamine oxidase inhibitor (MAOI) therapy should be discontinued for at least two weeks before initiation of therapy with a selective serotonin reuptake inhibitor (SSRI) and that before starting a MAOI, SSRI therapy should be discontinued for at least five half-lives of the parent drug and any active metabolites [167].

d) Two cases reports suggested a possible interaction between [fluoxetine](#) and [selegiline](#) [168]. One case involved a first episode of mania being observed approximately one month after adding [selegiline](#) to [fluoxetine](#). 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](#) to [selegiline](#). Both drugs were discontinued, with relatively quick resolution of symptoms. Rechallenge with [fluoxetine](#) alone occurred without incident.

### 3.5.1.FH] 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](#)[394] and [gastrointestinal bleeding](#) [398][399][395][396]. Bleeding events have included [epistaxis](#), ecchymosis, [hematoma](#), [petechiae](#), and life-threatening hemorrhages [401][400][402][403]. 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](#)[394] and [gastrointestinal bleeding](#) [395][396]. 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 [394].

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 [397].

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 [398] to 2.36 times [399], NSAIDs by 2.55 times [398], and the combination of SSRIs and NSAIDs by 4.02 [398] to 6.33 times [399].

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 [400].

### 3.5.1.FI] Propafenone

1) Interaction Effect: increased [propafenone](#) exposure and risk toxicity ([cardiac arrhythmias](#))

2) Summary: Coadministration of [propafenone](#) with a CYP2D6 inhibitor, such as [sertraline](#), may increase exposure to [propafenone](#) and increase the risk for toxicity, including proarrhythmia[208] and QT prolongation. If concomitant use is required additional caution is advised [60]. Consider dose adjustments and monitoring the EKG.

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Coadministration of [propafenone](#) with a CYP2D6 inhibitor, such as [sertraline](#), may increase exposure to [propafenone](#) and increase the risk for toxicity, including proarrhythmia[208] and QT prolongation. If concomitant use is required additional caution is advised [60]. Consider dose adjustments and monitoring the EKG.

7) Probable Mechanism: inhibition of CYP2D6-mediated [propafenone](#) metabolism; additive prolongation effects on QT interval

### 3.5.1.FJ] 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](#)[394] and [gastrointestinal bleeding](#) [398][399][395][396]. Bleeding events have included [epistaxis](#), ecchymosis, [hematoma](#), [petechiae](#), and life-threatening hemorrhages [401][400][402][403]. 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](#)[394] and [gastrointestinal bleeding](#) [395][396]. 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 [394].

**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 [397].

**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 [398] to 2.36 times [399], NSAIDs by 2.55 times [398], and the combination of SSRIs and NSAIDs by 4.02 [398] to 6.33 times [399].

**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 [400].

### 3.5.1.FK] [Propranolol](#)

**1)** Interaction Effect: an increased risk of chest pain

**2)** Summary: [Sertraline](#) is a moderate to weak inhibitor of the hepatic cytochrome P450IID6 isoenzyme (CYP2D6) which may be involved in the metabolism of [propranolol](#)[365]. One case report describes sudden chest pain when [sertraline](#) was added to existing [propranolol](#) therapy [366].

**3)** Severity: moderate

**4)** Onset: delayed

**5)** Substantiation: probable

**6)** Clinical Management: Monitor patients receiving [propranolol](#) and [sertraline cotherapy](#) for an increased incidence of chest pain. This effect may be more pronounced in patients with preexisting [coronary artery disease](#).

**7)** Probable Mechanism: endothelium vasoconstriction caused by serotonin

**8)** Literature Reports

**a)** A 53-year-old male physician was maintained on [propranolol](#) 160 mg daily and [aspirin](#) 200 mg daily for [coronary artery disease](#). Two days after beginning [sertraline](#) 50 mg daily therapy for depression, he experienced sudden precordial chest pain that was responsive to 2 mg of sublingual glyceryl trinitrate. [Sinus tachycardia](#) was also present, but no other significant changes occurred on the [electrocardiogram](#). The next day, a similar reaction happened soon after the administration of [sertraline](#). The patient refused further treatment with [sertraline](#), and was started on [nortriptyline](#) 50 mg daily with no further episodes of chest pain. Possible mechanisms for this interaction include vasoconstriction in the endothelium which is already damaged from [coronary artery disease](#) [364].

### 3.5.1.FL] [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](#)[394] and [gastrointestinal bleeding](#) [398][399][395][396]. Bleeding events have included [epistaxis](#), ecchymosis, [hematoma](#), [petechiae](#), and life-

threatening hemorrhages [401][400][402][403]. 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](#)[394] and [gastrointestinal bleeding](#) [395][396]. 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 [394].

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 [397].

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 [398] to 2.36 times [399], NSAIDs by 2.55 times [398], and the combination of SSRIs and NSAIDs by 4.02 [398] to 6.33 times [399].

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 [400].

### 3.5.1.FM] 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](#)[394] and [gastrointestinal bleeding](#) [398][399][395][396]. Bleeding events have included [epistaxis](#), ecchymosis, [hematoma](#), [petechiae](#), and life-threatening hemorrhages [401][400][402][403]. 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](#)[394] and [gastrointestinal bleeding](#) [395][396]. 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 [394].

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 [397].

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 [398] to 2.36 times [399], NSAIDs by 2.55 times [398], and the combination of SSRIs and NSAIDs by 4.02 [398] to 6.33 times [399].

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 [400].

### 3.5.1.FN] [Protriptyline](#)

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

2j) Summary: Use caution with concomitant administration of [sertraline](#) and [protriptyline](#) as both are 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[21].

3j) Severity: major

4j) Onset: unspecified

5j) Substantiation: theoretical

6j) Clinical Management: Concomitant use of [sertraline](#) and [protriptyline](#) increases the risk of [serotonin syndrome](#). If coadministration of [protriptyline](#) and [sertraline](#) 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[21].

7j) Probable Mechanism: additive serotonergic effects

### 3.5.1.FO] [Rasagiline](#)

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

2j) Summary: Concurrent use of [sertraline](#) and an MAOI, such as [rasagiline](#), is contraindicated. Wait at least 14 days after discontinuing [rasagiline](#) before initiating [sertraline](#). Wait at least 14 days after discontinuing [sertraline](#) before initiating therapy with [rasagiline](#)[106].

- 3) Severity: contraindicated
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Concurrent use of [sertraline](#) and an MAOI, such as [rasagiline](#), is contraindicated. Wait at least 14 days after discontinuing [rasagiline](#) before initiating [sertraline](#). Wait at least 14 days after discontinuing [sertraline](#) before initiating therapy with [rasagiline](#)[106].
- 7) Probable Mechanism: additive serotonergic effect

### 3.5.1.FP] Reviparin

- 1) Interaction Effect: an increased risk of bleeding
- 2) Summary: The release of serotonin by [platelets](#) is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs (such as [sertraline](#)) and anticoagulants has been associated with an increased risk of bleeding[129][130][128]. Bleeding events reported have included [epistaxis](#), ecchymosis, [hematoma](#), [petechiae](#), and life-threatening hemorrhages. Altered anticoagulant effects (including increased bleeding) have been reported with the coadministration of SSRIs with [warfarin](#) [128]. Prothrombin time should be monitored in patients receiving both [warfarin](#) and [sertraline](#) [132].
- 3) Severity: major
- 4) Onset: delayed
- 5) Substantiation: probable
- 6) Clinical Management: When [sertraline](#) 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 [sertraline](#) therapy is initiated or discontinued[128].
- 7) Probable Mechanism: unknown
- 8) Literature Reports

a) According to a retrospective cohort study (n=234), there was an increased risk of clinically relevant bleeding (hospital admission due to bleeding) in patients receiving [warfarin](#) for [atrial fibrillation](#) during concomitant SSRI therapy or within 2 weeks following SSRI therapy termination. Patients with a mean age of 72 +/- 7 years receiving [warfarin](#) plus SSRI (n=117) were matched with randomly selected patients who received [warfarin](#) only (n=117). SSRI included [fluoxetine](#), [citalopram](#), [paroxetine](#), [sertraline](#), [fluvoxamine](#), or [escitalopram](#). Nine patients experienced 11 bleeding episodes during 213.9 treatment years in the [warfarin](#) plus SSRI group, and 10 patients experienced 14 bleedings during 586.4 treatment years in the warfarin-only group. The corresponding total incidences of bleedings were 51.4 and 23.9 per 1000 treatment years, respectively. The hazard ratio for first bleedings during treatment with [warfarin](#) plus SSRI was 3.49 (95% CI; 1.37 to 8.91, p=0.009) compared with [warfarin](#) only. The SSRI implicated in patients experiencing bleeding at the time of concomitant administration were [sertraline](#) or [citalopram](#). The addition of an SSRI was not associated with a change in [warfarin](#) dose or INR (p=0.48 and p=0.31 respectively). The results of the study may be limited by earlier bleeding events, unknown patient adherence, and exclusion of [clopidogrel](#), dipyridamol, corticosteroids and anticoagulants other than [warfarin](#) in the model [129].

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

days). Patients on SSRIs showed greater risk for hospitalization for nongastrointestinal bleeding (adjusted odds ratio (OR) 1.7, 95% confidence interval (CI), 1.1 to 2.5); however, the rate of [gastrointestinal bleeding](#) (adjusted OR 0.8, 95% CI, 0.4 to 1.5) was not significantly different [130].

c) [Sertraline](#) 50 mg to 200 mg daily for 21 days produced an 8% increase in prothrombin time in subjects who received a single dose of [warfarin](#) 0.75 mg/kg relative to the same [warfarin](#) dose given prior to [sertraline](#); this compared with a 1% decrease with placebo. Normalization of the prothrombin time was also delayed as compared with placebo. The clinical significance of these findings is unknown [128].

d) In a non-blinded, randomized, placebo-controlled trial involving 12 healthy volunteers, the effect of [sertraline](#) on the plasma protein binding of [warfarin](#) was assessed. On days 1 and 32 of the study, all participants received [warfarin](#) 0.75 mg/kg. Beginning on day 11, each volunteer was randomized to either the [sertraline](#) or placebo group; the [sertraline](#) was gradually increased from 50 mg/day to 200 mg/day. Prothrombin time was measured prior to each dose of [warfarin](#) and periodically thereafter. The researchers concluded that the anticoagulant effects of [warfarin](#) were not enhanced by [sertraline](#) to a clinically significant degree, despite the fact that [sertraline](#) was given in a higher-than-usual dose [131].

### 3.5.1.FQ] [Rifampin](#)

1) Interaction Effect: loss of [sertraline](#) efficacy

2) Summary: Sertraline is metabolized by cytochrome P450 3A4 enzymes, which are induced by [rifampin](#) therapy. In one case report, a patient experienced loss of [sertraline](#) efficacy and precipitation of selective serotonin reuptake inhibitor (SSRI) withdrawal syndrome following seven days of concurrent [rifampin](#) and [sertraline](#) administration[392].

3) Severity: moderate

4) Onset: delayed

5) Substantiation: probable

6) Clinical Management: Monitor patients for [sertraline](#) efficacy and signs of selective serotonin reuptake inhibitor (SSRI) withdrawal syndrome. Doses of [sertraline](#) may need to be increased when [rifampin](#) is given concomitantly.

7) Probable Mechanism: induction of cytochrome P450 3A4-mediated [sertraline](#) metabolism

8) Literature Reports

a) [Rifampin](#) administration was thought to precipitate selective serotonin reuptake inhibitor withdrawal syndrome and loss of [sertraline](#) efficacy in a 34-year-old male patient after seven days of concurrent therapy. The patient had been stabilized on [sertraline](#) 200 mg nightly for [generalized anxiety disorder](#) when [rifampin](#) 300 mg twice daily and [sulfamethoxazole/trimethoprim](#) 800 mg/160 mg was started for a methicillin-resistant *Staphylococcus aureus* skin infection. Seven days later, the patient complained of significant anxiety, excessive worrying, and loss of energy. At that time, a blood sample was drawn to determine the plasma [sertraline](#) concentration. Laboratory analysis revealed a [sertraline](#) concentration of 18 ng/mL and an N-desmethylertraline concentration of 62 ng/mL. The patient finished the remainder of the 10-day course of [rifampin](#). Seven days after [rifampin](#) was completed, another blood sample revealed a [sertraline](#) concentration of 55 ng/mL and an N-desmethylertraline concentration of 136 ng/mL. Anxiety was still persistent in this patient, so [sertraline](#) was tapered off and he was successfully treated with [paroxetine](#) and [clonazepam](#) [391].

### 3.5.1.FR] [Risperidone](#)



- 1) Interaction Effect: increased [risperidone](#) exposure
- 2) Summary: Caution is advised with administration of CYP2D6 substrates, such as [risperidone](#), with [sertraline](#) (a CYP2D6 inhibitor) because concomitant use may increase exposure to the CYP2D6 substrate and increase the risk for toxicity[21]. If concomitant use of these agents is required, reduce the initial dose of [risperidone](#) and do not exceed a final dose of [risperidone](#) 8 mg/day [146].
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Use caution with administration of CYP2D6 substrates, such as [risperidone](#), with [sertraline](#) (a CYP2D6 inhibitor) because concomitant use may increase exposure to the CYP2D6 substrate and increase the risk for toxicity[21]. If concomitant use of these agents is required, reduce the initial dose of [risperidone](#) and do not exceed a final dose of [risperidone](#) 8 mg/day [146].
- 7) Probable Mechanism: inhibition of CYP2D6-mediated [risperidone](#) metabolism

### 3.5.1.FS] [Ritonavir](#)

- 1) Interaction Effect: increased [ritonavir](#) exposure, potential increase in SSRI exposure
- 2) Summary: Caution is advised with concomitant administration of CYP2D6 substrates, such as [ritonavir](#), with [sertraline](#) (a CYP2D6 inhibitor) because concurrent use may increase CYP2D6 substrate exposure and risk for toxicity[21]. Coadministration may also result in increased SSRI exposure. Although CYP2D6 is not the primary metabolic pathway for [ritonavir](#) degradation, and the maximum mean time-matched difference between [ritonavir](#) and placebo in QTc Fridericia (after baseline correction) was 5.5 msec in healthy subjects (n=45). A dose reduction of [sertraline](#) may be needed [315].
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Use caution with concomitant administration of CYP2D6 substrates, such as [ritonavir](#), with [sertraline](#) (a CYP2D6 inhibitor) because concurrent use may increase CYP2D6 substrate exposure and risk of toxicity[21]. Coadministration may also result in increased SSRI exposure. If concomitant use of [ritonavir](#) and an SSRI is required, dose reduction of [sertraline](#) may be needed [315].
- 7) Probable Mechanism: inhibition of CYP2D6-mediated [ritonavir](#) metabolism by [sertraline](#), altered SSRI metabolism by [ritonavir](#)

### 3.5.1.FT] [Rivaroxaban](#)

- 1) Interaction Effect: increased risk of bleeding
- 2) Summary: Use caution with concomitant use of rivaroxaban and a serotonin [norepinephrine](#) reuptake inhibitor or SSRI, as additive effects on bleeding may occur. If signs or symptoms of blood loss occur following coadministration, promptly evaluate the patient and consider whether blood replacement is needed, as bleeding may be serious or fatal[203].
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Use caution with concomitant use of rivaroxaban and a serotonin [norepinephrine](#) reuptake inhibitor or SSRI, as additive effects on bleeding may occur. If signs or symptoms of blood loss occur following coadministration, promptly evaluate the patient and consider whether blood replacement is needed, as bleeding may be serious or fatal[203].
- 7) Probable Mechanism: additive effects on bleeding

### 3.5.1.FU] [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)[233]. Because [rizatriptan](#) is a 5HT 1B/1D receptor agonist, a similar interaction between SSRIs and [rizatriptan](#) may occur [234]. 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](#) [220].
- 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](#) [232].

### 3.5.1.FV] [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](#)[394] and [gastrointestinal bleeding](#) [398][399][395][396]. Bleeding events have included [epistaxis](#), ecchymosis, [hematoma](#), [petechiae](#), and life-threatening hemorrhages [401][400][402][403]. 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](#)[394] and [gastrointestinal bleeding](#) [395][396]. 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 [394].

**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 [397].

**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 [398] to 2.36 times [399], NSAIDs by 2.55 times [398], and the combination of SSRIs and NSAIDs by 4.02 [398] to 6.33 times [399].

**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 [400].

### 3.5.1.FW] 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[164].

**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[164].

**7))** Probable Mechanism: Additive serotonergic effects

### 3.5.1.FX] 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](#)[394] and [gastrointestinal bleeding](#) [398][399][395][396]. Bleeding events have included [epistaxis](#), ecchymosis, [hematoma](#), [petechiae](#), and life-threatening hemorrhages [401][400][402][403]. 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](#)[394] and [gastrointestinal bleeding](#) [395][396]. 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 [394].

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 [397].

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 [398] to 2.36 times [399], NSAIDs by 2.55 times [398], and the combination of SSRIs and NSAIDs by 4.02 [398] to 6.33 times [399].

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 [400].

### 3.5.1.FY] [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](#)[394] and [gastrointestinal bleeding](#) [398][399][395][396]. Bleeding events have included [epistaxis](#), ecchymosis, [hematoma](#), [petechiae](#), and life-threatening hemorrhages [401][400][402][403]. 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](#)[394] and [gastrointestinal bleeding](#) [395][396]. 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 [394].

**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 [397].

**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 [398] to 2.36 times [399], NSAIDs by 2.55 times [398], and the combination of SSRIs and NSAIDs by 4.02 [398] to 6.33 times [399].

**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 [400].

### 3.5.1.FZ| [Selegiline](#)

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

**2)** Summary: Concurrent administration or overlapping therapy with [sertraline](#) 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[416][417][418][419][420]. Concomitant administration of [selegiline](#) and [sertraline](#) is contraindicated, and a minimum of 14 days should elapse after discontinuing [selegiline](#) before initiating therapy with [sertraline](#) or a minimum of 7 days should elapse after discontinuing [sertraline](#) before initiating therapy with [selegiline](#) [421].

**3)** Severity: contraindicated

**4)** Onset: rapid

**5)** Substantiation: probable

**6)** Clinical Management: Concurrent use of [sertraline](#) and [selegiline](#) is contraindicated. Wait at least 14 days after discontinuing [selegiline](#) before initiating therapy with [sertraline](#). Wait at least 7 days after discontinuing [sertraline](#) before initiating therapy with [selegiline](#).

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

**8)** Literature Reports

**a)** Concomitant use of serotonin specific reuptake inhibitors and monoamine oxidase inhibitors can produce a toxic reaction known as [serotonin syndrome](#) [412]. [Serotonin syndrome](#) is a condition of serotonergic hyperstimulation and manifests as restlessness, myoclonus, changes in mental status, hyperreflexia, diaphoresis, shivering, and tremor. If the syndrome is not recognized and correctly treated, death can result.

**b)** A 26-year old woman who had been taking [isocarboxazid](#) for eight weeks stopped taking the drug for 11 days before beginning therapy with [sertraline](#). After a single 100 mg [sertraline](#) dose, the patient became restless and developed leg twitches. The patient was later admitted to the emergency room with diaphoresis, [tachycardia](#), hyperreflexia, and various neuromuscular disturbances. The patient did not improve after treatment with [diazepam](#) and [propranolol](#). The patient was then given two 4 mg doses of [cyproheptadine](#) an hour apart, with notable improvement in symptoms after the second dose [413].

c) A drug interaction was reported in a 61-year old woman in which [sertraline](#) 100 mg twice daily was added to a regimen of [lithium](#), [phenelzine](#), [thioridazine](#), and [doxepin](#). Three hours after taking the first [sertraline](#) dose, the patient was found in a semicomatose state, with elevated body temperature, increased pulse, increased respiration rate, and a blood pressure of 140/110 mmHg. After transportation to the hospital, the patient was misdiagnosed as having [neuroleptic malignant syndrome](#) (NMS) which was later changed to [serotonin syndrome](#) due to a reaction between [sertraline](#) and [phenelzine](#). The authors suggest that MAO inhibitor therapy should be discontinued for at least two weeks before initiation of therapy with a selective serotonin reuptake inhibitor (SSRI) and that before starting a MAOI, SSRI therapy should be discontinued for at least 5 half-lives of the parent drug and any active metabolites [414].

d) Two case reports suggested a possible interaction between [fluoxetine](#) and [selegiline](#) [415]. One case involved a first episode of mania being observed approximately 1 month after adding [selegiline](#) to [fluoxetine](#) therapy. The patient improved 2 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.GA] Selexipag

- 1) Interaction Effect: increased risk of bleeding
- 2) Summary: Exercise caution when coadministering a SSRI and an antiplatelet agent as this may increase the risk of bleeding events[141][21][140].
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Concomitant use of [sertraline](#) and an antiplatelet agent should be undertaken with caution as this may increase the risk of bleeding events[21].
- 7) Probable Mechanism: unknown
- 8) Literature Reports

a) In a retrospective study of patients over 50 years of age with the diagnosis of acute [myocardial infarction](#) (N=27,058), SSRI use with any antiplatelet therapy significantly increased the risk of bleeding by 1.42-fold compared with [aspirin](#) use alone. Therapy with [aspirin](#), [clopidogrel](#), and an SSRI significantly increased risk by 2.35-fold compared with [aspirin](#) use alone and by 1.57-fold compared with [clopidogrel](#) and [aspirin](#) combination therapy [140].

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) [141].

### 3.5.1.GB] 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[319].

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 [318].

### 3.5.1.GC] [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](#)[394] and [gastrointestinal bleeding](#) [398][399][395][396]. Bleeding events have included [epistaxis](#), ecchymosis, [hematoma](#), [petechiae](#), and life-threatening hemorrhages [401][400][402][403]. 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](#)[394] and [gastrointestinal bleeding](#) [395][396]. 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 [394].

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 [397].

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 [398] to 2.36 times [399], NSAIDs by 2.55 times [398], and the combination of SSRIs and NSAIDs by 4.02 [398] to 6.33 times [399].

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 [400].

### 3.5.1.GD) St John's Wort

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

2)) Summary: Case reports describe the onset of serotonin syndrome-like symptoms, mania, and [hypomania](#) following the addition of St. John's Wort to [sertraline](#), [fluoxetine](#), and [paroxetine](#) therapy[303][304][305][306]. A patient exhibited a syndrome resembling sedative/[hypnotic intoxication](#) after adding St. John's Wort to [paroxetine](#) therapy [307]. St. John's Wort is thought to inhibit serotonin reuptake and may have mild monoamine oxidase inhibitory activity [308][309], which when added to selective serotonin reuptake inhibitors may result in [serotonin syndrome](#).

3)) Severity: major

4)) Onset: rapid

5)) Substantiation: probable

6)) Clinical Management: Patients should be advised to wait two weeks after stopping St. John's Wort before restarting selective serotonin reuptake inhibitor therapy. If a patient plans to replace selective serotonin reuptake inhibitor (SSRI) therapy with St. John's Wort, the half-life of the specific SSRI should be taken into consideration, waiting at least 5 half-lives for the SSRI to be metabolized out of the body.

7)) Probable Mechanism: additive serotonergic effect

8)) Literature Reports

a)) Five cases have been reported of [serotonin syndrome](#) in the elderly after combining prescription antidepressants and St. John's Wort. Case 1 developed dizziness, nausea, vomiting and a headache 4 days after starting St. John's Wort 300 milligrams (mg) three times daily combined with [sertraline](#) 50 mg daily. Her symptoms resolved 2 to 3 days after stopping all medications. Case 2 developed nausea, epigastric pain and anxiety 3 days after starting St. John's Wort 300 mg twice daily combined with [sertraline](#) 75 mg daily. His symptoms resolved in one week after discontinuing both medications, and he resumed [sertraline](#) use without complications. The third case developed nausea, vomiting, anxiety, and confusion 2 days after starting St. John's Wort 300 mg twice daily combined with [sertraline](#) 50 mg daily. His symptoms improved in 4 to 5 days after stopping both medications and taking [cyproheptadine](#) 4 mg three times daily. Case 4 developed nausea, anxiety, restless, and irritability 2 days after starting St. John's Wort 300 mg three times daily combined with [sertraline](#) 50 mg daily. [Cyproheptadine](#) 4 mg twice daily was administered for seven days, and his symptoms improved in 1 week after stopping the medication. Cases 1 through 4 resumed their prescriptive [sertraline](#) after symptoms subsided and had no further problems. Case 5 developed nausea, vomiting and restlessness 3 days after starting St. John's Wort 300 mg three times daily combined with [nefazodone](#) 100 mg twice daily. She continued to take St. John's Wort but discontinued the [nefazodone](#) and over 1 week her symptoms improved. She refused to resume therapy with [nefazodone](#), but continued therapy with St. John's Wort and mild to moderate symptoms of depression and anxiety returned [298].

b)) A 50-year-old female taking St. John's Wort 600 mg daily experienced symptoms of sedative intoxication when she ingested a single dose of [paroxetine](#) 20 mg. She was incoherent, groggy, slow-moving, and complained of nausea and weakness. Prior to starting St. John's Wort, she had been receiving [paroxetine](#) 40 mg daily for eight months without adverse effects. After a night of sleep, she returned to her baseline mental status [299].

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 [300].

d) A 28-year-old male developed a manic syndrome following comedication with St. John's Wort and [sertraline](#). The patient was also on [testosterone](#) replacement therapy following [bilateral orchiectomy](#) 2 years earlier, but [testosterone](#) levels were subtherapeutic. The patient was prescribed [sertraline](#) 50 milligrams daily for depression following a 2 week trial of St. John's Wort per patient preference (dose not specified). Before [sertraline](#) was started, the patient was instructed to discontinue St. John's Wort, but continued it despite this advice. The patient experienced improved mood so did not see his physician, believing that he did not need further treatment. Over 2 months, the patient had elated mood, was irritable, and overspent, buying a car he could not afford, and was ultimately arrested for stealing fuel for the car. On arrest, he was referred to psychiatric services due to irritability and disinhibition. He was observed to be over-aroused, distractible, have flight of ideas, and [grandiose delusions](#), leading to a diagnosis of a [manic episode](#). The authors state the possibility of the manic state resulting from [sertraline](#) therapy alone, and that St. John's Wort may have increased the risk as a result of monoamine oxidase inhibition. Since the patient's [testosterone](#) level was subnormal, the possibility of its contribution to the manic state was considered low. However, the patient had elevated gonadotropin levels ([luteinizing hormone](#) and [follicle-stimulating hormone](#)) which may have predisposed the patient to mania [301].

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 [302].

### 3.5.1.GE] [Sulfinpyrazone](#)

- 1) Interaction Effect: increased risk of bleeding
- 2) Summary: Exercise caution when coadministering a SSRI and an antiplatelet agent as this may increase the risk of bleeding events[141][21][140].
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Concomitant use of [sertraline](#) and an antiplatelet agent should be undertaken with caution as this may increase the risk of bleeding events[21].
- 7) Probable Mechanism: unknown
- 8) Literature Reports

a) In a retrospective study of patients over 50 years of age with the diagnosis of acute [myocardial infarction](#) (N=27,058), SSRI use with any antiplatelet therapy significantly increased the risk of bleeding by 1.42-fold compared with [aspirin](#) use alone. Therapy with [aspirin](#), [clopidogrel](#), and an SSRI significantly increased risk by 2.35-fold compared with [aspirin](#) use alone and by 1.57-fold compared with [clopidogrel](#) and [aspirin](#) combination therapy [140].

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) [141].

### 3.5.1.GF] [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](#)[394] and [gastrointestinal bleeding](#) [398][399][395][396]. Bleeding events have included [epistaxis](#), ecchymosis, [hematoma](#), [petechiae](#), and life-threatening hemorrhages [401][400][402][403]. 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](#)[394] and [gastrointestinal bleeding](#) [395][396]. 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 [394].

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 [397].

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 [398] to 2.36 times [399], NSAIDs by 2.55 times [398], and the combination of SSRIs and NSAIDs by 4.02 [398] to 6.33 times [399].

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 [400].

### 3.5.1.GG] [Sumatriptan](#)

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

2)) Summary: There have been case reports of weakness, hyperreflexia, and incoordination following concomitant use of [sumatriptan](#) and a serotonin specific reuptake inhibitor (SSRI)[409][410]. 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](#) [220].

3)) Severity: major

4)) Onset: delayed

5)) Substantiation: theoretical

6)) Clinical Management: Coadministration of a triptan, such as [sumatriptan](#), and an SSRI, such as [sertraline](#), 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.GH] [Tamoxifen](#)

1)) Interaction Effect: decreased exposure of active [tamoxifen](#) metabolites

2)) Summary: Coadministration of [sertraline](#) and [tamoxifen](#) may decrease the plasma concentration of the major active metabolite of [tamoxifen](#)[322] but large retrospective studies have found no significant impact of antidepressants, including [sertraline](#), on the risk of subsequent [breast cancer](#) [324] nor an increased risk of death from [breast cancer](#) with concomitant use of [tamoxifen](#) and [sertraline](#), despite an increased risk found with [paroxetine](#) [323]. Clinical relevance of this interaction depends on the extent of CYP2D6 inhibition on the concomitant drug (eg, [tamoxifen](#)) and may vary directly with [sertraline](#) dose [21]. When concomitant antidepressant therapy is necessary, alternatives with little or no CYP2D6 inhibition should be considered [323].

3)) Severity: major

4)) Onset: delayed

5)) Substantiation: theoretical

6)) Clinical Management: Coadministration of [tamoxifen](#) and CYP2D6 inhibitors, such as [sertraline](#), may decrease exposure to the active [tamoxifen](#) metabolite[322] but data have not supported a significant effect of [sertraline](#) on [breast cancer](#) events with [tamoxifen](#) despite conflicting clinical results with [paroxetine](#) [323] [324]. Clinical relevance of this interaction depends on the extent of CYP2D6 inhibition on the concomitant drug (eg, [tamoxifen](#)) and may vary directly with [sertraline](#) dose [21]. When concomitant antidepressant therapy is necessary, consider alternatives with little or no CYP2D6 inhibition [323].

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

8)) Literature Reports



a) 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 [324].

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 **sertraline**. 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 [323].

c) Concomitant use of **paroxetine**, a potent inhibitor of CYP2D6, and **tamoxifen**, which requires activation by CYP2D6 enzymes to the antiestrogenic metabolite (endoxifen), results in substantially reduced plasma concentrations of endoxifen. Eighty newly diagnosed **breast cancer** patients taking **tamoxifen** 20 mg/day were genotyped for the common alleles of the CYP2D6, CYP2C9, CYP3A5, and sulfotransferase (SULT) 1A1 genes. After 1 and 4 months of **tamoxifen** treatment, plasma concentrations of **tamoxifen** and endoxifen were measured. After 4 months of **tamoxifen**, plasma endoxifen concentrations were significantly lower in those with a CYP2D6 homozygous variant genotype (20 nM) or a heterozygous genotype (43.1 nM) than those with a homozygous wild-type genotype (78 nM). The mean plasma endoxifen concentration for subjects with a homozygous wild-type genotype who were taking CYP2D6 inhibitors was 58% lower than those not taking such inhibitors (38.6 nM vs 91.4 nM). Concomitant use of **venlafaxine**, a weak inhibitor of CYP2D6, resulted in slightly reduced plasma concentrations of endoxifen, while the use of **paroxetine**, a potent inhibitor of CYP2D6, resulted in substantial reductions in endoxifen concentrations, and **sertraline** resulted in intermediate reductions in endoxifen levels between those of **venlafaxine** and **paroxetine** [322].

### 3.5.1.GI| 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[404].

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[404].

7) Probable Mechanism: additive serotonergic effect

### 3.5.1.GJ] 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](#)[394] and [gastrointestinal bleeding](#) [398][399][395][396]. Bleeding events have included [epistaxis](#), ecchymosis, [hematoma](#), [petechiae](#), and life-threatening hemorrhages [401][400][402][403]. 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](#)[394] and [gastrointestinal bleeding](#) [395][396]. 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 [394].

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 [397].

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 [398] to 2.36 times [399], NSAIDs by 2.55 times [398], and the combination of SSRIs and NSAIDs by 4.02 [398] to 6.33 times [399].

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 [400].

### 3.5.1.GK] [Thiotepa](#)

- 1)) Interaction Effect: increased plasma concentrations of CYP2B6 substrates
- 2)) Summary: Coadministration of [thiotepa](#) (a potent CYP2B6 inhibitor) may result in increased plasma concentrations of CYP2B6 substrates. In a [pharmacokinetic study](#), CYP2B6 activity was inhibited by 78.1% +/- 0.2% when [thiotepa](#) was used with S-mephenytoin (CYP2B6 substrate probe) in human liver microsomes. Due to the potential for higher levels of the CYP2B6 substrate, coadministration should be done cautiously[245]. Monitor during coadministration for increased adverse events or signs of toxicity.
- 3)) Severity: moderate
- 4)) Onset: unspecified
- 5)) Substantiation: probable
- 6)) Clinical Management: Coadministration of [thiotepa](#) and CYP2B6 substrates should be done cautiously[245]. Monitor during coadministration for increased adverse events or signs of toxicity.
- 7)) Probable Mechanism: inhibition of CYP2B6-mediated metabolism by [thiotepa](#)
- 8)) Literature Reports

a)) In a [pharmacokinetic study](#) using S-mephenytoin as a CYP2B6 substrate probe with [thiotepa](#) in human liver microsomes, CYP2B6 activity was inhibited by 78.1% +/- 0.2%. [Thiotepa](#) in the range of 50 to 100 mcml inhibited the activity of CYP2B6 by 78% and 83%, respectively, with a plateau effect seen around 50 mcml [245].

### 3.5.1.GL] [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](#)[394] and [gastrointestinal bleeding](#) [398][399][395][396]. Bleeding events have included [epistaxis](#), ecchymosis, [hematoma](#), [petechiae](#), and life-threatening hemorrhages [401][400][402][403]. 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](#)[394] and [gastrointestinal bleeding](#) [395][396]. 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 [394].

**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 [397].

**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 [398] to 2.36 times [399], NSAIDs by 2.55 times [398], and the combination of SSRIs and NSAIDs by 4.02 [398] to 6.33 times [399].

**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 [400].

### 3.5.1.GM] Ticagrelor

- 1)) Interaction Effect: increased risk of bleeding
- 2)) Summary: Exercise caution when coadministering a SSRI and an antiplatelet agent as this may increase the risk of bleeding events[141][21][140].
- 3)) Severity: major
- 4)) Onset: unspecified
- 5)) Substantiation: theoretical
- 6)) Clinical Management: Concomitant use of [sertraline](#) and an antiplatelet agent should be undertaken with caution as this may increase the risk of bleeding events[21].
- 7)) Probable Mechanism: unknown
- 8)) Literature Reports

**a))** In a retrospective study of patients over 50 years of age with the diagnosis of acute [myocardial infarction](#) (N=27,058), SSRI use with any antiplatelet therapy significantly increased the risk of bleeding by 1.42-fold compared with [aspirin](#) use alone. Therapy with [aspirin](#), [clopidogrel](#), and an SSRI significantly increased risk by 2.35-fold compared with [aspirin](#) use alone and by 1.57-fold compared with [clopidogrel](#) and [aspirin](#) combination therapy [140].

**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) [141].

### 3.5.1.GN] Ticlopidine

- 1)) Interaction Effect: increased risk of bleeding
- 2)) Summary: Exercise caution when coadministering a SSRI and an antiplatelet agent as this may increase the risk of bleeding events[141][21][140].
- 3)) Severity: major
- 4)) Onset: unspecified
- 5)) Substantiation: theoretical
- 6)) Clinical Management: Concomitant use of [sertraline](#) and an antiplatelet agent should be undertaken with caution as this may increase the risk of bleeding events[21].

7) Probable Mechanism: unknown

8) Literature Reports

a) In a retrospective study of patients over 50 years of age with the diagnosis of acute [myocardial infarction](#) (N=27,058), SSRI use with any antiplatelet therapy significantly increased the risk of bleeding by 1.42-fold compared with [aspirin](#) use alone. Therapy with [aspirin](#), [clopidogrel](#), and an SSRI significantly increased risk by 2.35-fold compared with [aspirin](#) use alone and by 1.57-fold compared with [clopidogrel](#) and [aspirin](#) combination therapy [140].

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) [141].

### 3.5.1.GO| [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 (such as [sertraline](#)) and anticoagulants has been associated with an increased risk of bleeding[129][130][128]. Bleeding events reported have included [epistaxis](#), ecchymosis, [hematoma](#), [petechiae](#), and life-threatening hemorrhages. Altered anticoagulant effects (including increased bleeding) have been reported with the coadministration of SSRIs with [warfarin](#) [128]. Prothrombin time should be monitored in patients receiving both [warfarin](#) and [sertraline](#) [132].

3) Severity: major

4) Onset: delayed

5) Substantiation: probable

6) Clinical Management: When [sertraline](#) 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 [sertraline](#) therapy is initiated or discontinued[128].

7) Probable Mechanism: unknown

8) Literature Reports

a) According to a retrospective cohort study (n=234), there was an increased risk of clinically relevant bleeding (hospital admission due to bleeding) in patients receiving [warfarin](#) for [atrial fibrillation](#) during concomitant SSRI therapy or within 2 weeks following SSRI therapy termination. Patients with a mean age of 72 +/- 7 years receiving [warfarin](#) plus SSRI (n=117) were matched with randomly selected patients who received [warfarin](#) only (n=117). SSRI included [fluoxetine](#), [citalopram](#), [paroxetine](#), [sertraline](#), [fluvoxamine](#), or escitalopram. Nine patients experienced 11 bleeding episodes during 213.9 treatment years in the [warfarin](#) plus SSRI group, and 10 patients experienced 14 bleedings during 586.4 treatment years in the warfarin-only group. The corresponding total incidences of bleedings were 51.4 and 23.9 per 1000 treatment years, respectively. The hazard ratio for first bleedings during treatment with [warfarin](#) plus SSRI was 3.49 (95% CI; 1.37 to 8.91, p=0.009) compared with [warfarin](#) only. The SSRI implicated in patients experiencing bleeding at the time of concomitant administration were [sertraline](#) or [citalopram](#). The addition of an SSRI was not associated with a change in [warfarin](#) dose or INR (p=0.48 and p=0.31 respectively). The results of the study may be limited by earlier bleeding events, unknown patient adherence, and exclusion of [clopidogrel](#), dipyridamol, corticosteroids and anticoagulants other than [warfarin](#) in the model [129].

**b)** A population-based, case-controlled study of new coumarin users (acenocoumarol and phenprocoumon) with concomitant selective serotonin reuptake inhibitors (SSRIs) resulted in an increased risk of hospitalization due to non-gastrointestinal bleeding. Using national pharmacy and hospitalization records in the Netherlands, researchers identified 1848 cases that were admitted for abnormal bleeding and compared them with 5818 control subjects who were also taking a coumarin. Median duration of treatment in patients was 220 days (range, 1 to 4690 days). Patients on SSRIs showed greater risk for hospitalization for nongastrointestinal bleeding (adjusted odds ratio (OR) 1.7, 95% confidence interval (CI), 1.1 to 2.5); however, the rate of [gastrointestinal bleeding](#) (adjusted OR 0.8, 95% CI, 0.4 to 1.5) was not significantly different [130].

**c)** [Sertraline](#) 50 mg to 200 mg daily for 21 days produced an 8% increase in prothrombin time in subjects who received a single dose of [warfarin](#) 0.75 mg/kg relative to the same [warfarin](#) dose given prior to [sertraline](#); this compared with a 1% decrease with placebo. Normalization of the prothrombin time was also delayed as compared with placebo. The clinical significance of these findings is unknown [128].

**d)** In a non-blinded, randomized, placebo-controlled trial involving 12 healthy volunteers, the effect of [sertraline](#) on the plasma protein binding of [warfarin](#) was assessed. On days 0 and 32 of the study, all participants received [warfarin](#) 0.75 mg/kg. Beginning on day 11, each volunteer was randomized to either the [sertraline](#) or placebo group; the [sertraline](#) was gradually increased from 50 mg/day to 200 mg/day. Prothrombin time was measured prior to each dose of [warfarin](#) and periodically thereafter. The researchers concluded that the anticoagulant effects of [warfarin](#) were not enhanced by [sertraline](#) to a clinically significant degree, despite the fact that [sertraline](#) was given in a higher-than-usual dose [131].

### 3.5.1.GP] [Tipranavir](#)

- 1) Interaction Effect: increased [sertraline](#) plasma concentrations
- 2) Summary: Although the drug interaction between [sertraline](#) and [tipranavir/ritonavir](#) has not been studied, coadministration of [sertraline](#) with [tipranavir/ritonavir](#) may result in increased [sertraline](#) plasma concentrations. [Sertraline](#) doses may need to be adjusted when [tipranavir/ritonavir](#) therapy is initiated[263].
- 3) Severity: moderate
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Concurrent administration of [sertraline](#) and [tipranavir/ritonavir](#) may increase [sertraline](#) plasma concentrations. Use caution when these agents are coadministered and consider adjusting the [sertraline](#) dose as needed upon initiation of [tipranavir/ritonavir](#)[263].
- 7) Probable Mechanism: unknown

### 3.5.1.GQ] [Tirofiban](#)

- 1) Interaction Effect: increased risk of bleeding
- 2) Summary: Exercise caution when coadministering a SSRI and an antiplatelet agent as this may increase the risk of bleeding events[141][21][140].
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Concomitant use of [sertraline](#) and an antiplatelet agent should be undertaken with caution as this may increase the risk of bleeding events[21].

7) Probable Mechanism: unknown

8) Literature Reports

a) In a retrospective study of patients over 50 years of age with the diagnosis of acute [myocardial infarction](#) (N=27,058), SSRI use with any antiplatelet therapy significantly increased the risk of bleeding by 1.42-fold compared with [aspirin](#) use alone. Therapy with [aspirin](#), [clopidogrel](#), and an SSRI significantly increased risk by 2.35-fold compared with [aspirin](#) use alone and by 1.57-fold compared with [clopidogrel](#) and [aspirin](#) combination therapy [140].

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) [141].

### 3.5.1.GR] 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](#)[394] and [gastrointestinal bleeding](#) [398][399][395][396]. Bleeding events have included [epistaxis](#), ecchymosis, [hematoma](#), [petechiae](#), and life-threatening hemorrhages [401][400][402][403]. 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](#)[394] and [gastrointestinal bleeding](#) [395][396]. 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 [394].

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 [397].

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 [398] to 2.36 times [399], NSAIDs by 2.55 times [398], and the combination of SSRIs and NSAIDs by 4.02 [398] to 6.33 times [399].



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 [400].

### 3.5.1.GS] Tolmetin

1)) Interaction Effect: an increased risk of bleeding

2)) Summary: Caution is recommended with the concomitant use of NSAIDs and antidepressants, including SSRIs due to an increased risk of [intracranial hemorrhage](#)[394] and [gastrointestinal bleeding](#) [398][399][395][396]. Bleeding events have included [epistaxis](#), ecchymosis, [hematoma](#), [petechiae](#), and life-threatening hemorrhages [401][400][402][403]. 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](#)[394] and [gastrointestinal bleeding](#) [395][396]. 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 [394].

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 [397].

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 [398] to 2.36 times [399], NSAIDs by 2.55 times [398], and the combination of SSRIs and NSAIDs by 4.02 [398] to 6.33 times [399].

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 [400].

### 3.5.1.GT] Toloxatone

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

2j) Summary: Concurrent administration or overlapping therapy with [sertraline](#) and a monoamine oxidase (MAO) inhibitor may result in CNS toxicity or [serotonin syndrome](#), a hyperserotonergic state characterized by symptoms such as restlessness, myoclonus, changes in mental status, hyperreflexia, diaphoresis, shivering, and tremor. Serious, even fatal, reactions have been reported with concomitant use of serotonin specific reuptake inhibitors and MAO inhibitors[196][197][198][199][200]. 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.

3j) Severity: contraindicated

4j) Onset: rapid

5j) Substantiation: probable

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

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

8j) Literature Reports

a) Concomitant use of SSRIs and monoamine oxidase inhibitors can produce a toxic reaction known as [serotonin syndrome](#) [192]. [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, fatality can result.

b) A 26-year old woman who had been taking [isocarboxazid](#) for eight weeks stopped taking the drug for 11 days before beginning therapy with [sertraline](#). After a single 100 mg [sertraline](#) dose, the patient became restless and developed leg twitches. The patient was later admitted to the emergency room with diaphoresis, [tachycardia](#), hyperreflexia, and various neuromuscular disturbances. After treatment with [diazepam](#) and [propranolol](#) the patient did not improve. The patient was then given two 4 mg doses of [cyproheptadine](#) an hour apart, with notable improvement in symptoms after the second dose [193].

c) A drug interaction was reported in a 61-year old woman in which [sertraline](#) 100 mg twice daily was added to a regimen of [lithium](#), [phenelzine](#), [thioridazine](#), and [doxepin](#). Three hours after taking the first [sertraline](#) dose, the patient was found in a semicomatose state, with elevated body temperature, increased pulse, increased respiration rate, and a blood pressure of 140/110 mm Hg. After transportation to the hospital, the patient was misdiagnosed as having [neuroleptic malignant syndrome](#) (NMS) which was later changed to [serotonin syndrome](#) due to a reaction between [sertraline](#) and [phenelzine](#). The authors suggest that monoamine oxidase inhibitor (MAOI) therapy should be discontinued for at least two weeks before initiation of therapy with a selective serotonin reuptake inhibitor (SSRI) and that before starting a MAOI, SSRI therapy should be discontinued for at least five half-lives of the parent drug and any active metabolites [194].

d) Two cases reports suggested a possible interaction between [fluoxetine](#) and [selegiline](#) [195]. One case involved a first episode of mania being observed approximately one month after adding [selegiline](#) to [fluoxetine](#). 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](#) to [selegiline](#). Both drugs were discontinued, with relatively quick resolution of symptoms. Rechallenge with [fluoxetine](#) alone occurred without incident.

**3.5.1.GU] Tramadol**

1) Interaction Effect: an increased risk of seizures, [serotonin syndrome](#) (hypertension, hyperthermia, myoclonus, mental status changes), opioid toxicity, and increased concentrations of [tramadol](#) and decreased concentrations of [tramadol](#) active metabolite, M1

2) Summary: Caution is advised with concomitant use of [sertraline](#) and [tramadol](#). [Sertraline](#) is an SSRI and a CYP2D6 inhibitor. Concomitant use of [tramadol](#) with SSRIs, such as [sertraline](#), may increase the risk for seizures and [serotonin syndrome](#) even if [tramadol](#) is used within the recommended dosage range. Additionally, concomitant use of [tramadol](#) and CYP2D6 inhibitors, such as [sertraline](#), can decrease metabolism of [tramadol](#) to the active metabolite, M1, potentially causing reduced analgesia. Furthermore, elevated [tramadol](#) concentrations because of inhibition of CYP2D6-mediated metabolism may cause opioid toxicity. If concomitant use of [tramadol](#) with an SSRI is clinically warranted, careful observation of the patient is recommended, particularly during treatment initiation and dose increases[262]. Consider monitoring patients for signs and symptoms of opioid toxicity or decreased analgesic effect of [tramadol](#).

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Caution is advised with concomitant use of [sertraline](#) and [tramadol](#). Concomitant use of [tramadol](#) with SSRIs may increase the risk for seizures and [serotonin syndrome](#), even if [tramadol](#) is used within the recommended dosage range. Additionally, opioid toxicity and reduced analgesia may occur. If concomitant use of [tramadol](#) with an SSRI is clinically warranted, careful observation is recommended, particularly during treatment initiation and dose increases[262]. Consider monitoring patients for signs and symptoms of opioid toxicity and decreased analgesic effect of [tramadol](#).

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

**3.5.1.GV] Tranlycypromine**

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

2) Summary: Concurrent administration or overlapping therapy with [sertraline](#) 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[427][428][429][430][431]. Concomitant use is contraindicated.

3) Severity: contraindicated

4) Onset: rapid

5) Substantiation: probable

6) Clinical Management: Concurrent use of [sertraline](#) and a MAO inhibitor is contraindicated. Wait at least 14 days after discontinuing a MAO inhibitor before initiating therapy with [sertraline](#). Wait at least 14 days after discontinuing [sertraline](#) 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](#) [423]. [Serotonin syndrome](#) is a condition of serotonergic hyperstimulation and manifests as restlessness, myoclonus, changes in mental status, hyperreflexia, diaphoresis, shivering, and tremor. If the syndrome is not recognized and correctly treated, death can result.

b)) A 26-year old woman who had been taking [isocarboxazid](#) for eight weeks stopped taking the drug for 11 days before beginning therapy with [sertraline](#). After a single 100 mg [sertraline](#) dose, the patient became restless and developed leg twitches. The patient was later admitted to the emergency room with diaphoresis, [tachycardia](#), hyperreflexia, and various neuromuscular disturbances. The patient did not improve after treatment with [diazepam](#) and [propranolol](#). The patient was then given two 4 mg doses of [cypheptadine](#) an hour apart, with notable improvement in symptoms after the second dose [424].

c)) A drug interaction was reported in a 61-year old woman in which [sertraline](#) 100 mg twice daily was added to a regimen of [lithium](#), [phenelzine](#), [thioridazine](#), and [doxepin](#). Three hours after taking the first [sertraline](#) dose, the patient was found in a semicomatose state, with elevated body temperature, increased pulse, increased respiration rate, and a blood pressure of 140/110 mmHg. After transportation to the hospital, the patient was misdiagnosed as having [neuroleptic malignant syndrome](#) (NMS) which was later changed to [serotonin syndrome](#) due to a reaction between [sertraline](#) and [phenelzine](#). The authors suggest that MAO inhibitor therapy should be discontinued for at least two weeks before initiation of therapy with a selective serotonin reuptake inhibitor (SSRI) and that before starting a MAOI, SSRI therapy should be discontinued for at least 5 half-lives of the parent drug and any active metabolites [425].

d)) Two cases reports suggested a possible interaction between [fluoxetine](#) and [selegiline](#) [426]. One case involved a first episode of mania being observed approximately 1 month after adding [selegiline](#) to [fluoxetine](#) therapy. The patient improved 2 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.GW] [Trazodone](#)

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

2)) Summary: Caution is advised with concomitant use of [sertraline](#) and [trazodone](#) should be avoided due to an increased risk of [serotonin syndrome](#), especially during treatment initiation and dose increases. Discontinue any concomitant serotonergic agents immediately and initiate supportive treatment if [serotonin syndrome](#) is suspected. Monitor patients closely for [serotonin syndrome](#), especially during treatment initiation and dose increases. Symptoms of [serotonin syndrome](#) include neuromuscular abnormalities (eg, hyperreflexia, tremor, and ataxia), autonomic instability (eg, [tachycardia](#), diaphoresis, and [hyperthermia](#)), gastrointestinal symptoms (eg, nausea, vomiting, diarrhea), or mental status changes (eg, agitation and confusion)[21][261].

3)) Severity: major

4)) Onset: unspecified

5)) Substantiation: theoretical

6)) Clinical Management: Exercise caution with concomitant use of [sertraline](#) and [trazodone](#) due to an increased risk of [serotonin syndrome](#), especially during treatment initiation and dose increases. Discontinue any concomitant serotonergic agents immediately and initiate supportive treatment if [serotonin syndrome](#) is suspected. Monitor patients closely for [serotonin syndrome](#), especially during treatment initiation and dose increases. Symptoms of [serotonin syndrome](#) include neuromuscular abnormalities (eg, hyperreflexia, tremor, and ataxia), autonomic instability (eg, [tachycardia](#), diaphoresis, and [hyperthermia](#)), gastrointestinal symptoms (eg, nausea, vomiting, diarrhea), or mental status changes (eg, agitation and confusion)[21][261].

7)) Probable Mechanism: additive serotonergic effects

**3.5.1.GX] Treprostinil**

- 1) Interaction Effect: increased risk of bleeding
- 2) Summary: Exercise caution when coadministering a SSRI and an antiplatelet agent as this may increase the risk of bleeding events[141][21][140].
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Concomitant use of [sertraline](#) and an antiplatelet agent should be undertaken with caution as this may increase the risk of bleeding events[21].
- 7) Probable Mechanism: unknown
- 8) Literature Reports

a) In a retrospective study of patients over 50 years of age with the diagnosis of acute [myocardial infarction](#) (N=27,058), SSRI use with any antiplatelet therapy significantly increased the risk of bleeding by 1.42-fold compared with [aspirin](#) use alone. Therapy with [aspirin](#), [clopidogrel](#), and an SSRI significantly increased risk by 2.35-fold compared with [aspirin](#) use alone and by 1.57-fold compared with [clopidogrel](#) and [aspirin](#) combination therapy [140].

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) [141].

**3.5.1.GY] Triazolam**

- 1) Interaction Effect: increased serum concentrations of [triazolam](#) and risk of adverse effects (excessive sedation, confusion)
- 2) Summary: To date, no information is available related to the effects of coadministered [triazolam](#) and [sertraline](#). A study of [alprazolam](#) (a pharmacologically related benzodiazepine) found that [sertraline](#) was a moderate inhibitor in vitro of [alprazolam](#) metabolism[137]. It is theoretically possible that an interaction might occur because [triazolam](#) is metabolized by the cytochrome P450 system and [sertraline](#) is thought to inhibit one or more P450 isoenzymes [138]. Current evidence indicates that [triazolam](#) is metabolized at least in part by the CYP3A family of isoenzymes and [sertraline](#) is suspected of inhibiting the CYP3A4 isozyme. Until further information is available, caution should be used when [triazolam](#) and [sertraline](#) are combined.
- 3) Severity: minor
- 4) Onset: rapid
- 5) Substantiation: probable
- 6) Clinical Management: Caution is warranted if [triazolam](#) and [sertraline](#) are to be coadministered. Monitor patients for signs of [triazolam](#) toxicity ([psychomotor impairment](#) or excessive sedation). [Triazolam](#) doses may need to be reduced.
- 7) Probable Mechanism: decreased [triazolam](#) metabolism

**3.5.1.GZ] Trimipramine**

- 1) Interaction Effect: increased risk of [serotonin syndrome](#)
- 2) Summary: Caution should be used with concomitant administration of [sertraline](#) and other serotonergic agents, such as [trimipramine](#). 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[21][163].

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Use caution with concomitant administration of [sertraline](#) and other serotonergic agents, such as [trimipramine](#). 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[21][163].

7) Probable Mechanism: additive serotonergic effects

### 3.5.1.HA] 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[149].

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[149].

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 [150].

### 3.5.1.HB] Valdecoxib

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](#)[394] and [gastrointestinal bleeding](#) [398][399][395][396]. Bleeding events have included [epistaxis](#), ecchymosis, [hematoma](#), [petechiae](#), and life-threatening hemorrhages [401][400][402][403]. 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](#)[394] and [gastrointestinal bleeding](#) [395][396]. 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 [394].

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 [397].

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 [398] to 2.36 times [399], NSAIDs by 2.55 times [398], and the combination of SSRIs and NSAIDs by 4.02 [398] to 6.33 times [399].

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 [400].

### 3.5.1.HC] [Venlafaxine](#)

1j) Interaction Effect: increased exposure of CYP2D6 substrate and risk of [serotonin syndrome](#)

2j) 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[21].

3j) Severity: major

4j) Onset: unspecified

5j) Substantiation: theoretical

6j) 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[21].

7j) Probable Mechanism: inhibition of CYP2D6-mediated metabolism; additive serotonergic effects

### 3.5.1.HD] [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](#)[147]. 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 [148]. 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 [147].
- 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[147].
- 7) Probable Mechanism: additive serotonergic effects

### 3.5.1.HE] Vorapaxar

- 1) Interaction Effect: increased risk of bleeding
- 2) Summary: Exercise caution when coadministering a SSRI and an antiplatelet agent as this may increase the risk of bleeding events[141][21][140].
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Concomitant use of [sertraline](#) and an antiplatelet agent should be undertaken with caution as this may increase the risk of bleeding events[21].
- 7) Probable Mechanism: unknown
- 8) Literature Reports

a) In a retrospective study of patients over 50 years of age with the diagnosis of acute [myocardial infarction](#) (N=27,058), SSRI use with any antiplatelet therapy significantly increased the risk of bleeding by 1.42-fold compared with [aspirin](#) use alone. Therapy with [aspirin](#), [clopidogrel](#), and an SSRI significantly increased risk by 2.35-fold compared with [aspirin](#) use alone and by 1.57-fold compared with [clopidogrel](#) and [aspirin](#) combination therapy [140].

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) [141].

### 3.5.1.HF] Vortioxetine

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

2) Summary: Vortioxetine is a serotonergic drug; concomitant use with another agent that affects the serotonergic neurotransmitter system may result in an increased risk of [serotonin syndrome](#) and should be approached with caution. [Serotonin syndrome](#) may be life-threatening. Symptoms may include mental status changes (eg, agitation, hallucinations, coma), autonomic instability (eg, [tachycardia](#), labile blood pressure, [hyperthermia](#)), neuromuscular aberrations (eg, hyperreflexia, incoordination), and/or gastrointestinal symptoms (eg, nausea, vomiting, diarrhea). If coadministration is required, monitor closely for signs and symptoms of [serotonin syndrome](#), especially during initiation of the coadministered drug and during dosage increases of either drug. If [serotonin syndrome](#) develops, discontinue both agents and initiate supportive symptomatic therapy[411].

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Concomitant use of vortioxetine with serotonergic agents may increase the risk for [serotonin syndrome](#) and should be undertaken with caution. If concomitant use of vortioxetine with a serotonergic agent is clinically warranted, close monitoring of the patient is recommended, particularly during treatment initiation and dosage increases. If [serotonin syndrome](#) develops, discontinue vortioxetine and concomitant serotonergic agents and initiate supportive care[411].

7) Probable Mechanism: additive serotonergic effects

### 3.5.1.HG] [Warfarin](#)

1) Interaction Effect: an increased risk of bleeding

2) Summary: The release of serotonin by [platelets](#) is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs (such as [sertraline](#)) and anticoagulants has been associated with an increased risk of bleeding[129][130][128]. Bleeding events reported have included [epistaxis](#), ecchymosis, [hematoma](#), [petechiae](#), and life-threatening hemorrhages. Altered anticoagulant effects (including increased bleeding) have been reported with the coadministration of SSRIs with [warfarin](#) [128]. Prothrombin time should be monitored in patients receiving both [warfarin](#) and [sertraline](#) [132].

3) Severity: major

4) Onset: delayed

5) Substantiation: probable

6) Clinical Management: When [sertraline](#) 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 [sertraline](#) therapy is initiated or discontinued[128].

7) Probable Mechanism: unknown

8) Literature Reports

a) According to a retrospective cohort study (n=234), there was an increased risk of clinically relevant bleeding (hospital admission due to bleeding) in patients receiving [warfarin](#) for [atrial fibrillation](#) during concomitant SSRI therapy or within 2 weeks following SSRI therapy termination. Patients with a mean age of 72 +/- 7 years receiving [warfarin](#) plus SSRI (n=117) were matched with randomly selected patients who received [warfarin](#) only (n=117). SSRI included [fluoxetine](#), [citalopram](#), [paroxetine](#), [sertraline](#), [fluvoxamine](#), or escitalopram. Nine patients experienced 11 bleeding episodes during 213.9 treatment years in the [warfarin](#) plus SSRI group, and 10 patients experienced 14 bleedings during 586.4 treatment years in the warfarin-only group. The corresponding total incidences of bleedings were 51.4 and 23.9 per 1000 treatment years, respectively. The hazard ratio for first bleedings during treatment with [warfarin](#) plus SSRI was 3.49 (95% CI; 1.37 to 8.91, p=0.009) compared with [warfarin](#) only. The SSRI implicated in patients experiencing bleeding at the time of concomitant administration were [sertraline](#) or

[citalopram](#). The addition of an SSRI was not associated with a change in [warfarin](#) dose or INR ( $p=0.48$  and  $p=0.31$  respectively). The results of the study may be limited by earlier bleeding events, unknown patient adherence, and exclusion of [clopidogrel](#), dipyridamol, corticosteroids and anticoagulants other than [warfarin](#) in the model [129].

**b)** A population-based, case-controlled study of new coumarin users (acenocoumarol and phenprocoumon) with concomitant selective serotonin reuptake inhibitors (SSRIs) resulted in an increased risk of hospitalization due to non-gastrointestinal bleeding. Using national pharmacy and hospitalization records in the Netherlands, researchers identified 1848 cases that were admitted for abnormal bleeding and compared them with 5818 control subjects who were also taking a coumarin. Median duration of treatment in patients was 220 days (range, 1 to 4690 days). Patients on SSRIs showed greater risk for hospitalization for nongastrointestinal bleeding (adjusted odds ratio (OR) 1.7, 95% confidence interval (CI), 1.1 to 2.5); however, the rate of [gastrointestinal bleeding](#) (adjusted OR 0.8, 95% CI, 0.4 to 1.5) was not significantly different [130].

**c)** [Sertraline](#) 50 mg to 200 mg daily for 21 days produced an 8% increase in prothrombin time in subjects who received a single dose of [warfarin](#) 0.75 mg/kg relative to the same [warfarin](#) dose given prior to [sertraline](#); this compared with a 1% decrease with placebo. Normalization of the prothrombin time was also delayed as compared with placebo. The clinical significance of these findings is unknown [128].

**d)** In a non-blinded, randomized, placebo-controlled trial involving 12 healthy volunteers, the effect of [sertraline](#) on the plasma protein binding of [warfarin](#) was assessed. On days 1 and 32 of the study, all participants received [warfarin](#) 0.75 mg/kg. Beginning on day 11, each volunteer was randomized to either the [sertraline](#) or placebo group; the [sertraline](#) was gradually increased from 50 mg/day to 200 mg/day. Prothrombin time was measured prior to each dose of [warfarin](#) and periodically thereafter. The researchers concluded that the anticoagulant effects of [warfarin](#) were not enhanced by [sertraline](#) to a clinically significant degree, despite the fact that [sertraline](#) was given in a higher-than-usual dose [131].

### 3.5.1.HH] [Ziprasidone](#)

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

**2)** Summary: [Serotonin syndrome](#) has been reported with [ziprasidone](#) monotherapy and in combination with other serotonergic drugs[274][275]; coadministration with another serotonergic drug may increase risk for [serotonin syndrome](#). Therefore, exercise caution with concomitant use.

**3)** Severity: major

**4)** Onset: unspecified

**5)** Substantiation: theoretical

**6)** Clinical Management: [Serotonin syndrome](#) has been reported with [ziprasidone](#) monotherapy and in combination with other serotonergic drugs[274][275]; coadministration with another serotonergic drug may increase risk for [serotonin syndrome](#). Therefore, exercise caution with concomitant use.

**7)** Probable Mechanism: Additive serotonergic effect

### 3.5.1.HI] [Zolmitriptan](#)

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

**2)** Summary: Concurrent use of a triptan and an SSRI has resulted in life-threatening [serotonin syndrome](#). Onset of symptoms is usually rapid, occurring within minutes to hours of initiation or dose escalation of a serotonergic agent[316]. 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](#) [220]. Discontinue use of [zolmitriptan](#) if [serotonin syndrome](#) is suspected [316].

3) Severity: major

4) Onset: rapid

5) Substantiation: probable

6) Clinical Management: Life-threatening [serotonin syndrome](#) has been reported with coadministration of triptans and SSRIs[316]. Consider potential intermittent use of triptans in patients who receive SSRIs and closely monitor patients receiving both medications for symptoms of [serotonin syndrome](#) [220]. Discontinue [zolmitriptan](#) if [serotonin syndrome](#) is suspected [316].

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

8) Literature Reports

a) The pharmacokinetics of a single 10 mg dose of [zolmitriptan](#) were not altered by four weeks of [fluoxetine](#) 20 mg daily pretreatment in healthy volunteers. The effects of [zolmitriptan](#) on blood pressure were also not changed by [fluoxetine](#) therapy [317].

### 3.5.1.HJ] [Zolpidem](#)

1) Interaction Effect: an increased risk of hallucinations

2) Summary: 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](#)[321].

3) Severity: moderate

4) Onset: delayed

5) Substantiation: probable

6) Clinical Management: Observe patients for hallucinatory activity. Alternative anti-insomnia medication may be warranted.

7) Probable Mechanism: unknown

8) Literature Reports

a) 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 [320].

## 3.5.2] Drug-Food Combinations

### 3.5.2.A] [Ethanol](#)

1) Interaction Effect: an increased risk of impairment of mental and motor skills

2) Summary: In experiments with healthy subjects, [sertraline](#) did not potentiate cognitive or psychomotor effects associated with ethanol consumption[439]. However, the manufacturer of [sertraline](#) recommends that depressed patients be advised to avoid alcohol while using [sertraline](#).

- 3) Severity: moderate
- 4) Onset: rapid
- 5) Substantiation: theoretical
- 6) Clinical Management: Patients receiving [sertraline](#) should be advised to avoid the use of alcohol.
- 7) Probable Mechanism: unknown

### 3.5.2.B) Grapefruit Juice

- 1) Interaction Effect: elevated [sertraline](#) serum concentrations and an increased risk of adverse side effects
- 2) Summary: In a small study, grapefruit juice was shown to inhibit the metabolism of [sertraline](#), resulting in increased [sertraline](#) trough levels. Grapefruit juice is a known inhibitor of intestinal cytochrome P450 3A4 (CYP3A4) enzymes, and [sertraline](#) relies on CYP3A4 for metabolism to its metabolite, N-desmethylsertraline. A larger study is warranted to confirm the clinical significance of this interaction[441].
- 3) Severity: moderate
- 4) Onset: delayed
- 5) Substantiation: probable
- 6) Clinical Management: Counsel patients to avoid grapefruit juice while taking [sertraline](#). Orange juice may be substituted as it provides the same basic nutrients but is not known to inhibit drug metabolism.
- 7) Probable Mechanism: inhibition of cytochrome P450 3A4-mediated [sertraline](#) metabolism
- 8) Literature Reports

a) Five depressed patients stabilized on [sertraline](#) for more than six weeks participated in a prospective, open-label study to determine the effect of grapefruit juice ingestion on the pharmacokinetics of [sertraline](#). During the first seven days of the study, each patient received their usual [sertraline](#) dose with water. From days 8 through 14, [sertraline](#) was administered with 240 mL of grapefruit juice. The mean [sertraline](#) trough levels increased from 13.6 mcg/L to 20.2 mcg/L during the grapefruit juice phase, although there were no differences in the frequency of side effects reported between the two periods. Grapefruit juice had minimal effects on [sertraline](#) metabolism in one patient, possibly because of high interindividual variability in cytochrome P450 3A4 activity. A larger study is needed to substantiate the clinical significance of the interaction between grapefruit juice and [sertraline](#) [440].

### 3.5.3] Drug-Lab Modifications

#### 3.5.3.A] [Benzodiazepine measurement, urine](#)

- 1) Interaction Effect: false-positive urine [immunoassay](#) tests for benzodiazepines
- 2) Summary: Interpret urine [immunoassay](#) screening tests for benzodiazepines with caution in patients taking [sertraline](#) because false-positive results have been reported, and such results may occur several days after stopping [sertraline](#) therapy. [Sertraline](#) can be distinguished from benzodiazepines with the use of confirmatory tests such as [gas chromatography/mass spectrometry](#)[78].
- 3) Severity: moderate
- 4) Onset: unspecified
- 5) Substantiation: probable
- 6) Clinical Management: Use caution when interpreting urine [immunoassay](#) screening tests for benzodiazepines in patients receiving [sertraline](#) as false-positive results have been reported. These false-positive results may be expected to occur several days after discontinuation of [sertraline](#) therapy. Confirmatory tests, such as [gas chromatography/mass spectrometry](#), can be used to distinguish [sertraline](#) from benzodiazepines[78].
- 7) Probable Mechanism: lack of specificity of the screening test



## 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) [Sertraline](#) Hydrochloride

##### 1) Therapeutic

##### a) Depression

1) Improvement in target symptoms (depressed mood, suicidal thoughts or intent, change in appetite, lack of energy, change in sleep patterns, lack of pleasure/interest in usual activities, feeling of excessive guilt/worthlessness, psychomotor retardation or agitation, difficulties in thinking/concentration/memory).

2) Reevaluate the usefulness of therapy periodically during long-term therapy [78].

##### b) [Obsessive-Compulsive Disorder](#)

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

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

##### c) [Panic Disorder](#), [Posttraumatic Stress Disorder](#), [Premenstrual Dysphoric Disorder](#)

1) Reduction or resolution of signs/symptoms is indicative of efficacy.

##### 2) Toxic

##### a) Laboratory Parameters

1) Monitor for signs and symptoms of glucose fluctuations, especially in patients with diabetes [78].

2) Patients with thyroid disease who are also receiving treatment for depression should have thyroid function tested periodically. There are reports of small decreases in serum thyroxine levels and small increases in serum thyrotropin levels after starting treatment with sertraline and other antidepressants [509].

##### b) Physical Findings

1J) Since extrapyramidal reactions including dystonic reactions, parkinsonian-like movement disorders, and neuroleptic malignant syndrome usually occur early in therapy, monitoring weekly during the first 4 weeks of therapy is recommended [68].

2J) Monitor patients receiving antidepressants for worsening of depression, suicidality, or unusual changes in behavior, especially at the initiation of therapy or when the dose increases or decreases. Such monitoring should include at least weekly face-to-face contact with patients or their family members or caregivers during the initial 4 weeks of treatment, then visits every other week for the next 4 weeks, then at 12 weeks, and then as clinically indicated beyond 12 weeks. Families and caregivers should be advised of the need for close observation (i.e., daily observation) of patients and communication with the prescriber [111][510].

3J) Patients who experience symptoms of anxiety, agitation, panic attacks, insomnia, irritability, hostility, impulsivity, akathisia, hypomania, or mania may be at an increased risk for worsening depression or suicidality. If these symptoms are observed, therapy should be re-evaluated and it may be necessary to discontinue medications when symptoms are severe, sudden in onset, or were not part of the patient's initial symptoms [111][510].

#### 4.2J Patient Instructions

##### AJ) Sertraline (By mouth)

##### Sertraline

Treats depression, [obsessive-compulsive disorder \(OCD\)](#), [posttraumatic stress disorder \(PTSD\)](#), [premenstrual dysphoric disorder \(PMDD\)](#), [social anxiety disorder](#), and [panic disorder](#). This medicine is an SSRI.

When This Medicine Should Not Be Used:

This medicine is not right for everyone. Do not use it if you had an [allergic reaction to sertraline](#).

How to Use This Medicine:

Liquid, Tablet

Take your medicine as directed. Your dose may need to be changed several times to find what works best for you. You may need to take it for a few weeks or months before you feel better.

Oral liquid: Use the dropper provided to remove the medicine and mix it with 1/2 cup (4 ounces) of water, ginger ale, lemon-lime soda, lemonade, or orange juice. Drink the mixture right away. It is normal for it to look a bit hazy.

This medicine should come with a Medication Guide. Ask your pharmacist for a copy if you do not have one.

Missed dose: Take a dose as soon as you remember. If it is almost time for your next dose, wait until then and take a regular dose. Do not take extra medicine to make up for a missed dose.

Store the medicine in a closed container at room temperature, away from heat, moisture, and direct light.

Drugs and Foods to Avoid:

Ask your doctor or pharmacist before using any other medicine, including over-the-counter medicines, vitamins, and herbal products.

Do not use this medicine together with [pimozide](#). Do not use this medicine and an MAO inhibitor (MAOI) within 14 days of each other. Do not use the oral liquid form of [sertraline](#) if you are also using [disulfiram](#).

Some medicines can affect how [sertraline](#) works. Tell your doctor if you are using the following:

Buspirone, cimetidine, cisapride, diazepam, digitoxin, fentanyl, flecainide, lithium, phenytoin, propafenone, St John's wort, tramadol, tryptophan supplements, or valproate

A blood thinner (such as warfarin), a diuretic (water pill), an NSAID pain or arthritis medicine (such as aspirin, diclofenac, ibuprofen), a tricyclic antidepressant, a triptan medicine for migraine headaches

Do not drink alcohol while you are using this medicine.

#### Warnings While Using This Medicine:

Tell your doctor if you are pregnant or breastfeeding, or if you have liver disease, bleeding problems, glaucoma, heart disease, or a seizure disorder.

For some children, teenagers, and young adults, this medicine may increase mental or emotional problems. This may lead to thoughts of suicide and violence. Talk with your doctor right away if you have any thoughts or behavior changes that concern you. Tell your doctor if you or anyone in your family has a history of bipolar disorder or suicide attempts.

This medicine may cause the following problems:

**Serotonin syndrome** (when taken with certain medicines)

Low sodium levels (more common in elderly patients and those who take diuretics or become dehydrated)

Tell your doctor if you are sensitive to latex, because the oral liquid comes with a latex rubber dropper.

This medicine may make you dizzy or drowsy. Do not drive or do anything that could be dangerous until you know how this medicine affects you.

Do not stop using this medicine suddenly. Your doctor will need to slowly decrease your dose before you stop it completely.

Your doctor will check your progress and the effects of this medicine at regular visits. Keep all appointments.

Keep all medicine out of the reach of children. Never share your medicine with anyone.

#### Possible Side Effects While Using This Medicine:

Call your doctor right away if you notice any of these side effects:

**Allergic reaction:** Itching or hives, swelling in your face or hands, swelling or tingling in your mouth or throat, chest tightness, trouble breathing

Anxiety, restlessness, fast heartbeat, fever, sweating, muscle spasms, twitching, nausea, vomiting, diarrhea, seeing or hearing things that are not there

Blistering, peeling, or red skin rash

Confusion, weakness, and muscle twitching

Eye pain, vision changes, seeing halos around lights

Feeling more excited or energetic than usual

Thoughts of hurting yourself or others, unusual behavior

Unusual bleeding or bruising

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

Dry mouth

Loss of appetite, weight loss

Mild diarrhea, constipation, nausea, vomiting

Sexual problems

Sleepiness, or trouble sleeping

If you notice other side effects that you think are caused by this medicine, tell your doctor.

#### 4.3] Place In Therapy

##### A) Sertraline

###### 1) SUMMARY

a) Sertraline has received approval by the United States Food and Drug Administration for treating depression, [obsessive compulsive disorder](#), and [panic disorder](#). Sertraline has also been evaluated in numerous other psychiatric disorders.

###### 2) DEPRESSION

a) All of the selective serotonin reuptake inhibitors (SSRIs) are effective for treating depression although selected characteristics of each agent may offer greater benefit in some patients. Sertraline does NOT have any major therapeutic benefits over other SSRIs; however, it has less potential for drug interactions and fewer interactions have been reported than for other SSRIs. Ultimately, the selection of an SSRI is dependent on clinical judgement and response of patients to previous therapy [511].

b) Preliminary data suggest that a trial of a second serotonin reuptake inhibitor (SSRI) is a viable clinical alternative in depressed patients who have failed to respond to an adequate trial of the first SSRI [512]. In a retrospective review of 55 patients who had failed to respond to at least five weeks of therapy with either [fluoxetine](#), [sertraline](#), [fluvoxamine](#), or [paroxetine](#) (all at therapeutic dosages), 51% did respond to a trial of an alternative agent. The choice of the second agent was based on clinician preference; no difference between response rates of the different drugs was noted.

##### B) Sertraline Hydrochloride

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) Sertraline is a potent and selective inhibitor of synaptosomal serotonin reuptake in the brain. It has a higher degree of potency and specificity for the serotonin receptor than any other agent studied, including [clomipramine](#), [fluoxetine](#), [fluvoxamine](#), and [zimeldine](#) [497]. It appears to have little effect on [dopamine](#) and [norepinephrine](#) metabolism [469].

2) Like most other antidepressants (except [fluoxetine](#)), [sertraline](#) also causes an indirect down-regulation of postsynaptic beta-adrenergic receptors, which may be at least partially responsible for its therapeutic effect and for its delay in clinical efficacy [471][497].

##### B) REVIEW ARTICLES

1) A comparison of selective serotonin reuptake inhibitors with a guide to selection is provided [498].

2) Two reviews provide a discussion of the efficacy of selective serotonin reuptake inhibitors and other antidepressants for treatment of severe depression [499][500].

3) The efficacy of antidepressants in reducing panic attack frequency, symptoms of depression, social avoidance, and overall impairments from [panic disorder](#) are addressed [501].

- 4) A review article discusses the rational treatment of depression and each class of antidepressants [502].
- 5) A review article describes the treatment of [panic disorder](#), including the role of selective serotonin reuptake inhibitors[503].
- 6) Treatment of elderly patients with selective serotonin reuptake inhibitors is discussed with emphasis on improved tolerability compared to other antidepressants [504].
- 7) Pharmacological and therapeutic information about [sertraline](#) has been summarized (Peruche & Schulz, 1997 (language: German))[505][506].
- 8) Drug-interactions of antidepressants are reviewed in German language [507].

## 4.5] Therapeutic Uses

### 4.5.1] FDA Uses

#### 4.5.1.A] [Sertraline](#) Hydrochloride

##### 4.5.1.A.1] [Major depressive disorder](#)

###### FDA Labeled Indication

###### a) Overview

FDA Approval: Adult, yes; Pediatric, no

Efficacy: Adult, Effective; Pediatric, Evidence favors efficacy

Recommendation: Adult, Class I; Pediatric, Class IIb

Strength of Evidence: Adult, Category B; Pediatric, Category B

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

###### b) Summary:

###### Evidence (Adults)

In an 18-month continuation study (N=161) of patients with chronic depression or [dysthymic disorder](#) with [major depression](#), [sertraline](#) significantly reduced recurrence of depression compared with placebo (6% vs 23%). [Sertraline](#) also extended the time until recurrence of depressive symptoms [14].

After 6 weeks, treatment with [sertraline](#) 50, 100, or 200 mg/day produced significant improvement in depression compared with placebo in a study (N=289) [15].

###### Evidence (Geriatrics)

In a systematic review and metaanalysis in 15 randomized trials of patients aged 60 years or older with [major depressive disorder](#), treatment with [duloxetine](#) (62%), [paroxetine](#) (48%), or [sertraline](#) (28%) was associated with a significantly greater likelihood of achieving a partial response (defined as 50% or greater reduction from baseline in depression score based on the Hamilton Depression Rating Scale, which is preferred, or the Montgomery-Asberg Depression Rating Scale) compared with placebo. [Venlafaxine](#) and escitalopram each had a nonsignificant 20% likelihood of a partial response, while [fluoxetine](#) (8%) and [citalopram](#) (7%) had the lowest benefit. As for dizziness, [duloxetine](#) had a significant 194% increased risk

compared with placebo, while a nonsignificant risk was seen with [sertraline](#) (10% increase in risk) and [paroxetine](#) (47% increase risk) [16].

Following remission of depressive symptoms, no significant difference was found between [sertraline](#) and placebo in the prevention of recurrence of depression in elderly patients (mean age, 77.6 years of age) with [major depressive disorder](#) in an open-label maintenance phase for 100 weeks (n=113) [17].

#### Evidence (Pediatrics)

In children and adolescents (aged, 6 to 17 years) with moderate to severe depression, 10 weeks of [sertraline](#) therapy compared with placebo effectively treated depressive symptoms in 2 randomized trials (N=376). [Sertraline](#) was associated with significantly greater mean change in the Children's Depression Rating Scale-Revised (CDRS-R) Best Description of Child total score (-22.84 vs -20.19) and significantly more responders on both the CDRS-R (69% vs 59%) and Clinical Global Impression-Improvement (CGI-I) score of 2 or less (very much or much improved; 63% vs 53%). Most adverse effects were mild to moderate and serious adverse events in sertraline-treated patients included [suicidal ideation](#) (3 patients) and aggressive reaction (1 patient) [18].

In a single-arm, open-label study of adolescents (N=21; aged 12 to 18 years ) with [major depressive disorder](#) (MDD) and/or [dysthymic disorder](#) (DD), [sertraline](#) reduced depressive symptoms, although response patterns differed for MDD and DD. A 50% or greater improvement in the Hamilton-Depression (HAM-D) score, occurred in 10 of 13 patients of the MDD group at week 12 and was sustained to the end of the study (24 weeks). In the DD group (n=8), the HAM-D response rate was 100% at week 6, but diminished to 50% by the end of the study. A score of 2 or less on the Clinical Global Impression-Improvement Scale (CGI-I), was achieved by 77% of patients in the MDD group at week 20; that rate was sustained through the end of the study. In the DD group, the CGI-I maximal response rate was 75% at week 6. That maximum was sustained to week 12 but declined to 37.5% by week 24 [19].

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

#### 4.5.1.A.2] Obsessive-compulsive disorder

##### FDA Labeled Indication

##### a) Overview

FDA Approval: Adult, yes; [Pediatric, yes \(6 years or older\)](#)

Efficacy: Adult, Effective; Pediatric, Effective

Recommendation: Adult, Class IIa; Pediatric, Class IIa

Strength of Evidence: Adult, Category B; Pediatric, Category B

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

##### b) Summary:

##### Indication

[Sertraline](#) is indicated in adults and children 6 years or older for the treatment of obsessions and compulsions associated with [obsessive-compulsive disorder](#) (eg, obsessions or compulsions causing marked distress, are time consuming, or significantly interfere with social or occupational functioning) [21].

##### Evidence (Adult)



**Sertraline** maintained response in significantly more patients compared with placebo in a randomized withdrawal trial. Among patients successfully treated for 52 weeks (mean dose, 189 mg/day) and then randomized to continue **sertraline** or switch to placebo for an additional 28 weeks (N=223), significantly fewer patients on **sertraline** discontinued treatment because of **relapse** or insufficient clinical response (9% vs 24%) at week 80. Additionally, patients in the **sertraline** group showed gains in their quality of life scores, whereas those in the placebo showed decreases [22].

**Sertraline** significantly improved symptoms compared with placebo in 2 short-term randomized trials (N=167, 12 weeks, mean dose, 165 mg/day [23] and N=87, 10 weeks [24]), as measured by the Yale-Brown Obsessive Compulsive Scale (Y-BOCS), the National Institute of Mental Health Global Obsessive Compulsive Scale in both studies [23][24], and the Clinical Global Impression Scale in the larger trial (very much or much improved, 41% vs 23%) [23].

#### Evidence (Pediatric)

**Cognitive behavior therapy** (CBT) either alone or in combination with **sertraline** was more effective in the initial treatment of **obsessive compulsive disorder** (OCD) in pediatric patients as compared with **sertraline** monotherapy or placebo. In the 12-week randomized POTS study (N=112), pediatric patients (7 to 17 years; mean, 11.7 years) with a mean baseline Children's Young-Brown Obsessive-Compulsive Scale (CY-BOCS) score of 24.6 received 1 of 4 treatments: CBT alone; **sertraline** therapy alone; CBT plus **sertraline**; or placebo. Combination therapy significantly reduced CY-BOCS scores compared with CBT, **sertraline**, or placebo; neither monotherapy was significantly different when compared with each other, but each demonstrated significant reductions compared with placebo. Significantly higher rates of clinical remission (CY-BOCS score 10 or less) occurred with combination therapy (53.6%) compared with **sertraline** (21.4%) and placebo (3.6%), but did not significantly differ from CBT alone (39.3%). Neither monotherapy was significantly different from each other with regard to clinical remission rates; however, CBT was superior to placebo and **sertraline** was not [25].

**Sertraline** significantly improved symptoms, as measured by reduction in CY-BOCS score compared with placebo (7 vs 3 points), in a 12-week randomized trial (N=187; age, 6 to 17 years) followed by a 52-week open-label extension study (N=137) in children with a mean baseline CY-BOCS score of 22. Mean dosage at the end of the extension study period was 157 mg/day [13].

#### Guidelines

Serotonin reuptake inhibitors, including **sertraline**, and **cognitive behavioral therapy** are safe and effective first-line treatment of **obsessive-compulsive disorder** [20].

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

#### 4.5.1.A.3] **Panic disorder**

##### FDA Labeled Indication

##### a) Overview

FDA Approval: Adult, yes; **Pediatric, no**

Efficacy: Adult, Effective

Recommendation: Adult, Class IIa

Strength of Evidence: Adult, Category B

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

**b) Summary:**

**Indication**

[Sertraline](#) is indicated in adults for the treatment of [panic disorder](#) with or without [agoraphobia](#). Disease characterized by unexpected panic attacks and concern about having additional attacks, worry about the implications or consequences of the attack, and/or a significant change in behavior related to the attacks [21].

**Evidence**

[Sertraline](#) reduced the frequency of panic attacks in a 10-week (N=166) [26] and a 12-week blinded trial [27].

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

**c) Adult:**

**1) [Sertraline](#)** was an effective therapy for [panic disorder](#) in a 10-week, double-blind, multicenter study of 166 patients who were randomly assigned to placebo or [sertraline](#) 25 mg/day. Dose was titrated to a maximum of 200 mg/day; at study endpoint, the mean [sertraline](#) dose was 126 mg/day. Based on the primary efficacy variable, Panic and Anticipatory Anxiety Scale, the number of panic attacks per week significantly decreased in the [sertraline](#) group compared with placebo (77% vs 51%). At study endpoint, significantly more patients treated with [sertraline](#) (62%) than placebo (46%) were free of panic attacks. Investigators also noted significant improvement on the Clinical Global Impression scale with [sertraline](#). Adverse effects resulted in study discontinuation in 9% and 1% of patients treated with [sertraline](#) and placebo, respectively; the majority of adverse effects had a mild-to-moderate severity rating [26].

**2) [Sertraline](#)** was significantly more effective than placebo in the treatment of [panic disorder](#) in a study of patients who were randomized to receive [sertraline](#) 50 mg/day (n=42), 100 mg/day (n=41), 200 mg/day (n=44), or placebo (n=44) for 12 weeks. The primary measure of efficacy was the number of panic attacks a week. Patients treated with [sertraline](#) experienced a 65% reduction in the number of weekly panic attacks compared with a 39% reduction with placebo. There were no significant differences in efficacy between the different doses of [sertraline](#). [Sertraline](#) significantly decreased the frequency of situational and unexpected panic attacks, anticipatory anxiety, and limited symptom attacks (characterized by only 1 to 3 of the necessary panic attack symptoms). After 12 weeks, more patients were panic-free with [sertraline](#) than placebo, 57% and 41%, respectively. Forty-four percent of the [sertraline](#) 50-mg group, 23% of the 100-mg group, 44% of the 200-mg group, and 31% of the placebo group discontinued the study. A significantly greater number of patients experienced dry mouth and/or ejaculatory delay while taking [sertraline](#) than placebo. Because efficacy was independent of plasma concentrations, 50 mg of [sertraline](#) daily is the recommended dose for [panic disorder](#) (titrating upward from an initial 25-mg daily dose) [27].

**4.5.1.A.4) [Posttraumatic stress disorder](#)**

**FDA Labeled Indication**

**a) Overview**

FDA Approval: Adult, yes; **Pediatric, no**

Efficacy: Adult, Effective

Recommendation: Adult, Class I

Strength of Evidence: Adult, Category B

See Drug Consult reference: **RECOMMENDATION AND EVIDENCE RATINGS**

**b) Summary:**

**Indication**

**Sertraline** is indicated in adults for the treatment **posttraumatic stress disorder** [21].

**Evidence**

**Sertraline** was effective in improving of quality of life in patients with **posttraumatic stress disorder** (PTSD) in a randomized study (N=359) [28] and effectiveness was maintained during extended treatment in another study [29].

**Sertraline** was also more effective for preventing PTSD **relapse** in a 28-week study (Davidson, 2001).

**Sertraline** was more effective than placebo for treating patients with chronic PTSD in a 12-week trial (N=187) [30].

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

**c) Adult:**

**1) Quality of life (QOL)** was significantly improved in patients with **posttraumatic stress disorder** (PTSD) during treatment with **sertraline**; discontinuation of **sertraline** resulted in a decline in QOL in a manufacturer-funded study of 359 patients meeting DSM-III-R criteria for PTSD for at least 6 months. Patients were randomly assigned in a double-blind manner to receive **sertraline** 50 to 200 mg/day or placebo for 12 weeks. Completers of the acute phase (n=275), whether or not they were responders, could then enter an open-label, 24-week continuation phase (n=234). Responders during the continuation phase (n=172) were eligible for a 28-week, randomized, double-blind, placebo-controlled maintenance phase. Eighty-six patients entered the maintenance phase. In comparison to placebo treatment, acute **sertraline** treatment resulted in significant improvements in scores on the Quality of Life Enjoyment and Satisfaction Questionnaire (Q-LES-Q) of patients without comorbid depression. Improvement in scores of those with comorbid depression (43% of population) was modest and not statistically significant. Improvements in measures of psychological functioning and well-being were significant (relative to placebo) for sertraline-treated patients without comorbid depression but not for those with depression. **Social and occupational impairment** scores were significantly better with **sertraline** than with placebo. During the continuation phase, QOL and functioning scores increased another 20%, on average. During the double-blind, maintenance phase, QOL and functioning scores deteriorated somewhat for both groups, significantly more so for the placebo-treated patients [28].

**2) Effectiveness of **sertraline** for treating **posttraumatic stress disorder** (PTSD)** was maintained in most patients who continued treatment for 6 months after 12 weeks of acute treatment. Furthermore, half of the nonresponders to acute treatment became responders during the 6 months of continuation therapy. One hundred twenty eight patients who had received **sertraline** during the acute phase of 2 double-blind, placebo-controlled trials of

[sertraline](#) for treatment of severe DSM-III-R PTSD continued to receive [sertraline](#) in an open-label study, regardless of their response during the acute phase. Blinding to acute-phase treatment was maintained throughout the open label study. At the beginning of the open-label trial, patients were given [sertraline](#) 25 mg daily for the first week. The dose was then increased to 50 mg/day, which was titrated on an individual basis to a maximum of 200 mg/day. Ninety-two percent of acute-phase responders sustained their initial response. Average scores on various investigator-completed and patient-completed tools continued to show improvement, most of which was attributable to the 54% of patients who were nonresponders during the acute phase who became responders during the continuation phase. The only variable that was found to be a significant predictor ( $p=0.008$ ) of longer response time was having a high baseline severity score (higher than 75) on the Clinician Administered PTSD Scale Part 2 (CAPS-2). About 40% of patients discontinued prematurely. The most frequent moderate-to-severe treatment-related adverse events were headache, insomnia, dry mouth, and nausea. There were no serious abnormalities in [electrocardiogram](#), laboratory tests, or vital signs attributed to [sertraline](#) during the 24 weeks. Body weight increased by a mean of 0.8 kg [29].

3) [Sertraline](#) was more effective than placebo in prevention of [posttraumatic stress disorder](#) (PTSD) [relapse](#). Ninety-six patients (67 female), who had previously responded to [sertraline](#) therapy for PTSD, were enrolled in this 28-week continuation study (Londborg et al, 2001). Subjects were evaluated biweekly and were classified as relapsed if their Clinical Global Impression (CGI) improvement score increased by at least 3, their Clinician Administered PTSD Scale Part 2 (CAPS-2) score increased by at least 30%, and there was significant worsening of the patient's clinical condition on two consecutive evaluations. Patients in the placebo group were 4.5 to 6.4 times as likely to [relapse](#) than the patients treated with [sertraline](#) (mean endpoint dose, 137 mg). Forty percent of the patients who received placebo and 61% of those taking [sertraline](#) completed the entire 28-week trial (Davidson et al, 2001).

4) [Sertraline](#) was more effective than placebo for treating patients with chronic [posttraumatic stress disorder](#) (PTSD) in a 12-week trial (N=187) in which patients were randomly assigned to [sertraline](#) 25 mg/day or placebo. After the first week, the [sertraline](#) dose was titrated from 25 mg to 200 mg/day based on tolerability and response. Of the 187 patients who received treatment, 65 and 68 patients assigned to [sertraline](#) and placebo completed the trial, respectively; the majority of patients who did not complete the study were lost to follow-up. In patients completing the study, the mean daily dosage of [sertraline](#) was 151.3 mg. For 3 of the 4 primary efficacy measures, Clinician Administered PTSD Scale Part 2 (CAPS-2), the Clinical Global Impression-Severity scale (CGI-S), and the Clinical Global Impression-Improvement Scale (CGI-I), [sertraline](#) resulted in significantly greater improvement compared with placebo (CAPS-2, -33 vs -23.2; CGI-S, -1.2 vs -0.8; CGI-I, 2.5 vs 3). In addition, a trend toward greater improvement on the Impact of Event Scale (IES) was also observed in patients treated with [sertraline](#) compared with placebo. About 70% of the reduction on the CAPS-2 and IES was achieved during the first 4 weeks of treatment [30].

#### 4.5.1.A.5] [Premenstrual dysphoric disorder](#)

FDA Labeled Indication

a) Overview

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

Efficacy: Adult, Effective

Recommendation: Adult, Class IIa

Strength of Evidence: Adult, Category B

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

**b) Summary:**

**Indication**

[Sertraline](#) is indicated for the treatment of [premenstrual dysphoric disorder](#) [13].

**Evidence**

A meta-analysis of 8 randomized, double-blind, placebo-controlled studies of women with [premenstrual syndrome](#) (PMS) or [premenstrual dysphoric disorder](#) (PMDD; n=973) showed a significant 49% reduction in the risk of symptoms with [paroxetine](#) 25 to 150 mg [31].

Women with PMDD demonstrated greater improvement in psychosocial function after treatment with [sertraline](#) than placebo in two clinical trials [32][33].

Administration during the luteal phase was as effective as continuous [sertraline](#) and more effective than placebo for treating symptoms of dysphoric PMS [34].

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

**c) Adult:**

1) Women with [premenstrual dysphoric disorder](#) (PMDD) demonstrated greater improvement in psychosocial function after treatment with [sertraline](#) than placebo. This study is the same as the Yonkers' study reported below, with the psychosocial functioning results reported here. All women (n=243) completed the Daily Record of Severity of Problems (DRSP), the Social Adjustment Scale-Self Report (SAS), and short form of the Quality of Life Enjoyment and Satisfaction Questionnaire (Q-LES-Q) before and after treatment during the follicular and luteal phase of the menstrual cycle. Baseline scores of patients enrolled in this study showed impairment of psychosocial functioning during the luteal phase compared with a community sample. Treatment with [sertraline](#) 50 to 150 mg during the luteal phase of 3 menstrual cycles versus placebo resulted in significant improvement on the SAS total score, Q-LES-Q scores, and the DRSP scores related to reduction of productivity, interference of hobbies and social activities, and interference with relationships. The beneficial effect of [sertraline](#) was detected from the second menstrual cycle on [32].

2) [Sertraline](#) produced greater improvement in symptoms associated with [premenstrual dysphoric disorder](#) (PMDD) than placebo in a trial in which patients (N=243) were randomly assigned to receive [sertraline](#) or placebo. If needed, the [sertraline](#) dose was titrated from the initial first-cycle dose of 50 mg/day to 100 mg/day in cycle 2 and 150 mg/day in cycle 3. Patient evaluation of symptoms using the Daily Record of Severity of Problems (DRSP) showed a significant 32% decrease compared with an 11% decrease in total scores after treatment with [sertraline](#) and placebo, respectively. Observer evaluation confirmed the beneficial effects of [sertraline](#). This study also demonstrated significant improvement in productivity and relationships during [sertraline](#) versus placebo treatment. Patients tolerated treatment well; 8% and 2% of patients treated with [sertraline](#) and placebo withdrew from treatment. [Sertraline](#) is an effective treatment for PMDD [33].

3) [Sertraline](#) administered during the luteal phase was as effective as continuous [sertraline](#) and more effective than placebo for treating symptoms of dysphoric [premenstrual syndrome](#)

(PMS) in a study in which patients were initially treated with [sertraline](#) 100 mg daily for 1 menstrual cycle. If they responded to this therapy (n=11), they were randomly assigned to receive placebo or [sertraline](#) 100 mg daily for 2 weeks during the luteal phase; each treatment was used for 2 menstrual cycles. Standard assessment scales (ie, Hamilton Rating Scale for Depression (HAM-D), Clinical Global Impressions scale (CGI), and Daily Rating Forms (DRF)) were used to evaluate the efficacy of therapy [34].

#### 4.5.1.A.6] [Social phobia](#)

##### FDA Labeled Indication

##### a) Overview

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

Efficacy: Adult, Effective

Recommendation: Adult, Class I

Strength of Evidence: Adult, Category B

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

##### b) Summary:

##### Indication

[Sertraline](#) is indicated in adults for the treatment [social anxiety disorder \(social phobia\)](#) [21].

##### Evidence

Treatment with [sertraline](#) was more effective than placebo in reducing symptoms of severe generalized [social anxiety disorder \(social phobia\)](#) in a randomized flexible-dose study (N=415) [35].

[Sertraline](#) also significantly improved the severity of symptoms in patients with [generalized social phobia](#) in a randomized study (N=204) [36].

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

##### c) Adult:

1) Treatment with [sertraline](#) was more effective than placebo in reducing symptoms of severe generalized [social anxiety disorder \(social phobia\)](#) in a randomized, double-blind, placebo-controlled, flexible-dose study (N=415). Patients with a least a 2-year history of [generalized social phobia](#) and a Liebowitz Social Anxiety Scale (LSAS) score of 68 or greater received [sertraline](#) 50 to 200 mg daily (mean dose, 158.8 mg/day) or placebo for 12 weeks. Response was defined as a score of 2 or greater ("much" or "very much improved") on the Clinical Global Impressions-Improvement Scale (CGI-I). At endpoint, the CGI-I responder rate was significantly higher for sertraline-treated patients as compared with placebo (47% vs 26%). Additionally, the mean change in the LSAS score showed significantly greater reductions with [sertraline](#) treatment as compared with placebo at week 6, week 8 and endpoint. The most commonly reported adverse events with [sertraline](#) treatment were insomnia (24.4%), dizziness (16.7%), loose stools (20.6%), nausea (16.7%), dry mouth (14.4%), sweating (11.5%), and ejaculatory dysfunction (men, 14.3%) [35].

2) Treatment with [sertraline](#) significantly improved the severity of symptoms in patients with [generalized social phobia](#) in a randomized study (N=204). Adult outpatients with primary



[generalized social phobia](#) (defined by DSM-IV criteria) with a duration of at least one year, with or without concomitant diagnosis of avoidant personality or [major depression](#) and a Clinical Global Impression (CGI) severity rating of 4 or less were randomized in a 2:1 fashion to either [sertraline](#) 50 mg/day (n=135; mean age, 35.7 years, range 19 to 56 years) or placebo (n=69; mean age, 35.6 years, range 20 to 54 years) for 20 weeks. In the absence of a satisfactory response (CGI score of "much" or "very much" improvement) after 4 weeks, the [sertraline](#) dose could be increased by 50 mg/day every 3 weeks to a maximum dosage of 200 mg/day by week 10 or the dosage could be reduced to a minimum of 50 mg/day for intolerable side effects. The median duration of therapy was 140 days in each treatment arm. According to the CGI improvement ratings, a significant 53% (71 of 134) of patients who received [sertraline](#) compared with 29% (20 of 69) with placebo were "much" or "very much" improved at the end of treatment. Of the responders, a significant 30% in the [sertraline](#) arm compared with 13% in placebo arm were rated "very much" improved at the end of treatment. At week 20, for the patients who received [sertraline](#), the mean total scores on the Marks Fear Questionnaire [social phobia](#) subscale (baseline, [sertraline](#) arm 23.07 +/-6.64; placebo arm 21.72 +/-7.29) were significantly reduced by 32.6% (-7.53 +/-0.9) compared with 18.8% (-2.34 +/- 0.84) in the placebo arm). The mean total scores of the Brief [Social Phobia](#) Scale (baseline, [sertraline](#) arm 47.48 +/- 9.41; placebo arm 45.72 +/-8.98) was significantly reduced by 34.3% (-16.3 +/-1.87) and 18.6% (-8.49 +/- 1.52) in the [sertraline](#) and placebo arms, respectively. The mean dose at endpoint for responders in the [sertraline](#) arm was 154.5 +/- 45.84 mg/day compared with 179.7 +/- 38.89 mg/day in the placebo arm. [Sertraline](#) was associated with higher incidence of nausea (32.6% vs 14.5%), insomnia (30.4% vs 14.5%), [dyspepsia](#) (25.2% vs 7.2%), flu syndrome (17.8% vs 5.8%) and delayed ejaculation (11.4% vs 0%) [36].

#### 4.5.2] Non FDA Uses

##### 4.5.2.A] [Sertraline](#) Hydrochloride

##### 4.5.2.A.1] Aggressive behavior

###### a)] Overview

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

Efficacy: Adult, Evidence is inconclusive

Recommendation: Adult, Class IIb

Strength of Evidence: Adult, Category C

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

###### b)] Summary:

Evidence

[Sertraline](#) has been effective in the treatment of severe aggressiveness and self-injurious behavior associated with [Huntington disease](#), [mental retardation](#), and [autism](#) in a series of case reports [37][38].

###### c)] Adult:

1)] [Sertraline](#) has been effective in the treatment of severe aggressiveness and self-injurious behavior associated with [Huntington disease](#), [mental retardation](#), and [autism](#) in a series of case reports . Because serotonergic mechanisms have been implicated in aggressive behavior

in various neuropsychiatric and psychiatric disorders, [sertraline](#) was attempted after multiple pharmacologic interventions had failed. Dosages in these cases ranged from 25 to 150 mg daily; patients were generally started at a daily dosage of 25 mg to avoid [akathisia](#) or irritability. Marked improvement to complete cessation of aggressive behaviors was noted in the majority of cases [37][38].

#### 4.5.2.A.2] [Alzheimer's disease](#) - Depression

##### a) Overview

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

Efficacy: Adult, Ineffective

Recommendation: Adult, Class III

Strength of Evidence: Adult, Category B

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

##### b) Summary:

###### Evidence

Treatment with [sertraline](#) did not yield additional clinical benefit over placebo in patients with depression associated with [Alzheimer disease](#) (AD) in 2 randomized trials. In the 12-week, placebo-controlled Depression in [Alzheimer Disease](#)-2 (DIADS-2) study (N=131), there was no difference between [sertraline](#) and placebo on the modified Alzheimer Disease Cooperative Study Clinical Global Impression of Change index (mADCS-CGIC) at 12 weeks [5] or during the 12-week, open-label, extension (N=124) [6]. In another 39-week, randomized trial (N=326), there was no significant difference between [sertraline](#) or [mirtazapine](#) compared with placebo when added to usual care (nonpharmacologic) for the treatment of AD depression [7]. Improvement in depression (assessed using the Cornell Scale for Depression in [Dementia](#) score) from baseline to week 13, which was sustained to week 39, occurred among all study arms; notably, initial improvement was greatest with placebo in this study. [Sertraline](#) therapy was also associated with a higher incidence [5] and greater severity [7] of adverse events compared with placebo.

#### 4.5.2.A.3] [Anorexia nervosa](#)

##### a) Overview

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

Efficacy: Pediatric, Evidence is inconclusive

Recommendation: [Pediatric, Class III](#)

Strength of Evidence: Pediatric, Category B

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

##### b) Summary:

###### Evidence

[Sertraline](#) was not better than non-drug treatment for [anorexia nervosa](#) in a study in patients aged 14 to 34 years [39].

**c) Pediatric:**

1) Addition of [sertraline](#) to a multidisciplinary treatment of [anorexia nervosa](#) was not more effective than the multidisciplinary treatment alone. Eleven patients, 14 to 34 years of age and meeting DSM-IV criteria for [restricting-type anorexia nervosa](#), were treated with open-label [sertraline](#) 50 mg daily for 14 weeks. The dose was raised to 100 mg daily at 1 month for 4 patients whose response had been unsatisfactory. Eleven other similar subjects were given no medication. All patients received outpatient nutritional rehabilitation and [cognitive-behavioral therapy](#) once per week. At 14 weeks, 6 patients in each group (55%) still had a diagnosis of a full eating disorder. Body mass index improved similarly for the two groups. At a follow-up examination at 12 to 18 months, rates of full remission were 54% in the [sertraline](#) group and 27% in the control group (not significantly different). The most frequently occurring side effects of [sertraline](#) were nausea, headache, and insomnia. No subject interrupted treatment because of side effects [39].

**4.5.2.A.4] Binging - Eating disorder****a) Overview**

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

Efficacy: Adult, Evidence is inconclusive

Recommendation: Adult, Class IIb

Strength of Evidence: Adult, Category B

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

**b) Summary:****Evidence**

A small study found [sertraline](#) to decrease the frequency of binges compared with placebo [40].

**c) Adult:**

1) [Sertraline](#) reduced the frequency of binges, global clinical severity scores, and BMI to a significantly greater extent than did placebo. In this double-blind study, 34 patients who met DSM-IV criteria for [binge eating disorder](#) and had binge episodes at least 3 times weekly for 6 months were randomized to 6-week treatment with either [sertraline](#) 50 mg or placebo; doses were adjusted based on response up to 200 mg daily. Estimated mean weight loss was 5.6 kg after [sertraline](#) compared with 2.4 kg after placebo. [Major depression](#) was an underlying condition in most of the study patients. Of the 18 patients treated with [sertraline](#), 11 had a lifetime diagnosis of [major depressive disorder](#) and 3 had a current diagnosis of the disorder. In the 16 placebo-treated patients, 7 had a lifetime diagnosis and 3 had a current diagnosis of [major depressive disorder](#) [40].

**4.5.2.A.5] Bipolar disorder, depressed phase; Adjunct****a) Overview**

FDA Approval: Adult, no; Pediatric, no

Efficacy: Adult, Evidence favors efficacy

Recommendation: Adult, Class IIb

Strength of Evidence: Adult, Category B

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

**b) Summary:**

**Evidence**

No significant difference between adjunctive [bupropion](#), [sertraline](#) or [venlafaxine](#) was revealed among response or remission rates in the treatment of acute [bipolar depression](#); however, the risk of switching into (hypo)mania was significantly higher with [venlafaxine](#) compared with [bupropion](#) and [sertraline](#) in a randomized, trial (N=174) [8]. During the 1-year continuation phase, no significant difference was observed in either response rates or switch rates among the [bupropion](#), [sertraline](#), and [venlafaxine](#) groups [9]. However, a post hoc analysis of patients who experienced treatment-emergent mania may have identified potential markers for (hypo)manic switch [10].

**c) Adult:**

**1) General Information**

**a)** The incidence of [bipolar disorder](#) is reported to occur in 1% to 3% of the population. Most importantly, bipolar patients spend a 3-fold greater time period in [depressive episodes](#) in comparison to (hypo)manic episodes and have a 10% to 20% lifetime risk of death by suicide [8]. Therefore, effective treatment of acute bipolar [depressive episode](#) is critical for reduction of morbidity and mortality in patients with [bipolar affective disorder](#). A lack of evidence on the use of second-generation antidepressants [9] for the treatment of acute bipolar [depressive episode](#) and the occurrence of mood switching from depression to mania (switching or treatment-emergent mania) [10] during adjunctive antidepressant treatment has added to the concern of effective treatment in this patient population. Though more recent evidence with newer agents has revealed a reduction in rates of treatment-emergent mania in comparison with tricyclic antidepressants, the incidence of treatment-emergent mania remains clinically significant (5% to 20%) [10]. In a randomized, double-blind, comparative study, there were no significant differences between adjunctive [bupropion](#), [sertraline](#), or [venlafaxine](#) among response or remission rates in the treatment of acute [bipolar depression](#), and the risk of (hypo)manic switch was significantly higher with [venlafaxine](#) compared with [bupropion](#) and [sertraline](#) [8]. During the 1-year continuation phase, no significant difference was observed in either response rates or switch rates among the [bupropion](#), [sertraline](#), and [venlafaxine](#) groups [9]. However, a post hoc analysis of patients who experienced treatment-emergent mania may have identified potential markers for (hypo)manic switch [10].

**2) Clinical Trials**

**a)** No significant difference between adjunctive [bupropion](#), [sertraline](#), or [venlafaxine](#) was revealed among response or remission rates in the treatment of acute [bipolar depression](#); however, the risk of switching into (hypo)mania was significantly higher with [venlafaxine](#) compared with [bupropion](#) and [sertraline](#) in a randomized trial (N=174). All patients were currently treated with at least 1 mood stabilizer or antimanic agent. Subjects were randomized to receive either adjunctive [bupropion](#)

75 to 450 mg/day (n=51), [sertraline](#) 50 to 200 mg/day (n=58), or [venlafaxine](#) 37.5 to 375 mg/day (n=65) for 10 weeks. Patients who displayed clinically relevant levels of mania at baseline were excluded from the study. Symptoms were assessed using the Inventory of Depression Symptomatology (IDS), the Young Mania Rating Scale (YMRS), and the Clinical Global Impression scale for [Bipolar Disorder](#) (CGI-BP). The outcome measures included antidepressant response (defined as either a 50% or greater improvement in IDS score or a decrease of at least 2 points in the CGI-BP depression score), antidepressant remission (defined as an IDS score less than 12 and/or a CGI-BP depression score of 1 at study endpoint), and antidepressant-related switch into mania or [hypomania](#) (defined as either an increase of 2 points on the CGI-BP manic severity score during any point of the trial, a CGI-BP manic severity score of 3 or more, or a YMRS score above 13 at any time point). At week 10, the response rates for [bupropion](#), [sertraline](#), and [venlafaxine](#) were 49%, 53%, and 51% and remission rates were 41%, 36%, and 34%, respectively. These differences were not significant between groups and controlling for [lithium](#) use did not alter the results. However, the risk of switching to mania or [hypomania](#) was highest with [venlafaxine](#). Based on at least a 2-point increase on the CGI-BP score, (hypo)manic switching occurred in 10%, 9%, and 29% of patients in the [bupropion](#), [sertraline](#), and [venlafaxine](#) groups, respectively. When these data were analyzed using survival analysis in order to control for the effect of withdrawals on the relative risk of switching, the overall difference between the 3 treatment groups was significant, and controlling for [lithium](#) demonstrated similar significant results. Post hoc analysis demonstrated that the switch effect was mainly due to the significant difference in the risk of switching-time between [venlafaxine](#) and [sertraline](#) and between [venlafaxine](#) and [bupropion](#), while there was no significant difference between [sertraline](#) and [bupropion](#). The risk was also demonstrated to be higher with [venlafaxine](#) when a more conservative YMRS score (greater than 13) was analyzed. By study endpoint, 4%, 7%, and 15% of patients switched into (hypo)mania in the [bupropion](#), [sertraline](#), and [venlafaxine](#) groups, respectively, and controlling for [lithium](#) did not change the results. The difference between [venlafaxine](#), [bupropion](#), and [sertraline](#) treatment groups remained significant when the combination of the CGI-BP severity of mania of at least 3 or YMRS greater than 13 criteria were used (p=0.03 without controlling for [lithium](#); p=0.02 when controlled for [lithium](#)). The incidence of switching in patients with rapid-cycling was significantly lower with [bupropion](#) compared with [venlafaxine](#) but there was no significant difference between [bupropion](#) and [sertraline](#) or between [sertraline](#) and [venlafaxine](#). The percentages of patients who discontinued the study prematurely for any reason were 31%, 41%, and 45% in the [bupropion](#), [sertraline](#), and [venlafaxine](#) groups, respectively. Withdrawal for adverse events did not vary between the 3 groups. Limitations of the study include no inclusion of a placebo group and lack of a power analysis [8]. During the 1-year continuation phase (n=59), no significant difference was observed in either response rates 62.5%, 68.8% and 71% or switch rates 29.2%, 31.3%, and 48.4% among the [bupropion](#) (n=15), [sertraline](#) (n=22), and [venlafaxine](#) (n=22) groups, respectively [9]. A post hoc analysis of patients who experienced treatment-emergent mania during adjunctive antidepressant treatment for bipolar [depressive episode](#) (even with minimal manic symptoms at baseline) had higher YMRS scores (some significant) on items of increased motor activity-energy, speech and thought content, which may serve as potential predictors for risk of (hypo)manic switching [10].

**4.5.2.A.6] Cerebrovascular accident, Post - Depression; Prophylaxis****a) Overview**

FDA Approval: Adult, no; **Pediatric, no**

Efficacy: Adult, Evidence is inconclusive

Recommendation: Adult, Class IIb

Strength of Evidence: Adult, Category B

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

**b) Summary:**

Evidence

[Sertraline](#) was more effective than placebo in the prevention of post-stroke depression [56].

**c) Adult:**

**1)** [Sertraline](#) treatment appeared to be more effective than placebo in the prevention of depression following [stroke](#). In a randomized, double-blind, placebo-controlled study, non-depressed, post-stroke patients received [sertraline](#) (n=70; initial, 50 mg/day for 2 weeks then titrated up to a maximum dose of 150 mg/day; mean dose, 62.9 mg/day) or placebo (n=67) for 12 months. The incidence rate of depression (assessed by the total score on the Hamilton Depression Scale (HAM-D)) in sertraline-treated patients was lower as compared with patients in the placebo group (8.2% vs 22.8%). The depression occurrence rate as measured by scores on the HAM-D subscale were also lower in the [sertraline](#) group as compared with placebo (11.5% vs 28). Fewer sertraline-treated patients had Clinical Global Impression (CGI) severity scores in the mild to severe range (score of at least 3), as compared with patients given placebo (18% vs 29.8%). [Sertraline](#) was well-tolerated and there were no significant differences between treatments in adverse events [56].

**4.5.2.A.7] Cerebrovascular accident, Post - Mood swings****a) Overview**

FDA Approval: Adult, no; **Pediatric, no**

Efficacy: Adult, Evidence is inconclusive

Recommendation: Adult, Class IIb

Strength of Evidence: Adult, Category B

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

**b) Summary:**

Evidence

In a small study (N=28), [sertraline](#) reduced emotional lability after a [stroke](#) [57].

**c) Adult:**

**1)** More patients treated with [sertraline](#) than placebo experienced a reduction in emotional lability. Twenty-eight patients who developed emotional lability after [stroke](#) were randomly



assigned to receive placebo or [sertraline](#) 50 mg/day for 8 weeks. At 8 weeks, a significant 93% of patients treated with [sertraline](#) versus 64% treated with placebo were improved using the Clinician's Interview-based impression of change and the emotionalism/lability of mood questions. Tearfulness was also diminished significantly after treatment with [sertraline](#) compared with placebo. Four patients did not complete the study; 2 patients receiving [sertraline](#) experienced an adverse effect, and 1 in each group had fatal [stroke](#) [57].

#### 4.5.2.A.8] [Clozapine](#) adverse reaction - [Obsessive-compulsive disorder](#)

##### a) Overview

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

Efficacy: Adult, Evidence is inconclusive

Recommendation: Adult, Class IIb

Strength of Evidence: Adult, Category C

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

##### b) Summary:

Evidence

In a single case, [sertraline](#) effectively treated [obsessive-compulsive behavior](#) induced by [clozapine](#) [42].

##### c) Adult:

1) Addition of [sertraline](#) to [clozapine](#) reduced [obsessive compulsive behavior](#) without adversely affecting the clinical response to or plasma concentrations of [clozapine](#). Although [clozapine](#) effectively reduced treatment-refractory [psychosis](#), the patient developed [obsessive compulsive behavior](#) manifested by hand washing that resulted in [skin excoriation](#). His treatment was switched to [risperidone](#) and [clomipramine](#) which were ineffective so treatment with [clozapine](#) was reinstituted along with [fluvoxamine](#). This treatment was effective but resulted in excessively high [clozapine](#) plasma concentrations which were likely due to competitive inhibition of cytochrome P450 isoenzymes by [fluvoxamine](#). Therefore, [fluvoxamine](#) was stopped and [sertraline](#) was initiated. On this regimen, his psychotic and obsessive-compulsive symptoms were well controlled [42].

#### 4.5.2.A.9] [Complication of hemodialysis](#) - [Hypotensive episode](#)

##### a) Overview

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

Efficacy: Adult, Evidence is inconclusive

Recommendation: Adult, Class III

Strength of Evidence: Adult, Category B

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

##### b) Summary:

Evidence

[Sertraline](#) reduced the severity of hypotension during and after [hemodialysis](#) sessions [52].

c) Adult:

1) [Sertraline](#) treatment raised the systolic and diastolic nadirs during [hemodialysis](#) sessions and increased systolic blood pressure (SBP) at the end of dialysis in patients with dialysis-induced hypotension. Of 12 patients selected for treatment, 3 were unable to tolerate [sertraline](#) at 100 mg/day. The remaining 9 were treated with 100 mg daily. Data from the 4 weeks before [sertraline](#) treatment were compared with data from a 4-week [sertraline](#) period. The [sertraline](#) period was begun 4 weeks after the start of [sertraline](#) treatment to achieve the full drug effect before data collection. Dry weights of the patients, [ultrafiltration](#) volumes, dialysate composition, dialysate temperature, hematocrit, and albumin did not change over the study. Predialysis SBP and diastolic blood pressure (DBP) were the same in the [sertraline](#) period as in the pre-sertraline period. However, the nadir of SBP significantly rose from an average of 77 mmHg in the pre-sertraline period to 87 mmHg in the [sertraline](#) period; the nadir of DBP significantly rose from 51 to 58 mmHg. Postdialysis SBP rose significantly from 90 to 100 mmHg. Postdialysis DBP did not change significantly (59 to 62 mmHg). The need for therapeutic interventions for hypotension significantly decreased from 1.3 per session to 0.44 per session [52].

4.5.2.A.10] Depression - [Myocardial infarction](#), Post

a) Overview

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

Efficacy: Adult, Evidence favors efficacy

Recommendation: Adult, Class IIb

Strength of Evidence: Adult, Category B

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

b) Summary:

Evidence

[Sertraline](#) relieved depression without causing adverse cardiac effects in patients with recent [myocardial infarction](#) [44].

Heart rate variability recovery following acute [myocardial infarction](#) was facilitated by [sertraline](#) [45].

c) Adult:

1) [Sertraline](#) improved depressive symptoms in patients with a recent [myocardial infarction](#) (MI) in an open study (N=26). Patients with a confirmed MI and depression received [sertraline](#) 50 mg daily beginning a mean of 30 days after the MI. At 16 weeks, 74% of patients had a positive response defined by a 50% reduction in the Hamilton rating for depression; the mean Hamilton rating decreased from 19.7 to 7.8. Fifteen (78.9%) of 19 patients who completed 16 weeks of treatment were judged to be "very much improved" or "depression completely resolved" by the Clinical Global Impression Scale. There were no significant changes in cardiac or bleeding parameters that were measured during the study [44].

2) Depressed, postmyocardial infarction (MI) patients treated with [sertraline](#) 50 mg daily had a steady increase in the standard deviation of 24-hour N-N intervals (SDNN) compared with

a matched placebo group. Thirty-eight depressed patients were entered into a randomized, double-blind, placebo-controlled trial. Eleven patients dropped out within 2 months (5 placebo, 6 [sertraline](#)) leaving 27 patients (16 males, average age 62 +/- 11 years) to complete the 22-week study. A nonrandomized reference group was used to compare "normal" rates of recovery and was composed of 11 age-matched, non-depressed, post-MI patients (9 males). All three groups had baseline measurements of heart rate variability (HRV), which is an independent predictor of mortality within the first year of an acute (MI), 2 weeks following the MI before [sertraline](#) or placebo was begun. HRV was determined using 24-hour [Holter monitoring](#) and by measuring the normal sinus-conducted N-N interbeat intervals, the average heart rate, and the standard deviation of all the 24-hour N-N intervals (SDNN). The HRV, as expressed by the SDNN, for the [sertraline](#) group increased by 5% compared with a 28% increase in the reference group and a 9% decrease in the placebo group. There was also a significant 26% decrease in the inventory to diagnose depression (IDD) score for the [sertraline](#) group compared with the placebo group [45].

#### 4.5.2.A.11] Drug-induced depressive state

##### a) Overview

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

Efficacy: Adult, Evidence is inconclusive

Recommendation: Adult, Class IIb

Strength of Evidence: Adult, Category C

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

##### b) Summary:

Evidence

[Sertraline](#) relieved depression caused by interferon-alfa therapy in a small study (N=10) [43].

##### c) Adult:

1) [Sertraline](#) relieved symptoms of interferon-alfa (IA)-induced depression without the necessity of discontinuation of IA therapy in a small study (n=10). Patients who were being treated with IA for [hepatitis C](#) and who met the DSM-IV criteria for substance (interferon-alfa)-induced [depressive disorder](#) were treated with [sertraline](#) 50 mg/day. At 2 or 4 weeks follow-up, all 10 patients reported marked improvement in depressed mood and irritability, with 7 reporting complete resolution of symptoms. Mild and transient side effects, such as nausea and headache, were reported in 5 patients. After 8 weeks, 1 patient experienced [erectile dysfunction](#), and his medication was changed to moclobemide [43].

#### 4.5.2.A.12] [Dysthymia](#)

##### a) Overview

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

Efficacy: Adult, Evidence favors efficacy

Recommendation: Adult, Class IIb

Strength of Evidence: Adult, Category B

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

**b) Summary:**

**Evidence**

[Sertraline](#) was more effective than placebo in improving psychiatric rating scores in patients with [dysthymic disorder](#) of greater than 5 years duration without a concomitant diagnosis of [major depressive disorder](#) and who were not taking any other psychotropic drugs in a randomized study (N=310) [46].

[Sertraline](#) alone or [sertraline](#) plus interpersonal psychotherapy (IPT) provided moderate improvement in mood in patients with [dysthymia](#) compared with IPT alone in a prospective, investigator-blinded, randomized clinical trial (n=586) [47].

**c) Adult:**

**1)** [Sertraline](#) was more effective than placebo in improving psychiatric rating scores in patients meeting the DSM-III-R criteria for [dysthymic disorder](#) of greater than 5 years duration without a concomitant diagnosis of [major depressive disorder](#) and who were not taking any other psychotropic drugs in a study (N=310). Patients were randomized to receive either [sertraline](#) 50 mg or placebo daily. Dose adjustments up to 200 mg daily were allowed during the 12-week treatment period. Based on intent-to-treat analysis, sertraline-treated patients had significantly greater reductions in Structured Interview Guide for the Hamilton Depression Rating Scale-Seasonal Affective Disorders Version (SIGH-SAD), Montgomery-Asberg Depression Rating Scale (MADRS), Clinical Global Impressions-Severity of Illness scale (CGI-S), and Hospital Anxiety and Depression Scale subscale for anxiety and depression (HAD-A and HAD-D). The proportion of patients achieving response, defined as reduction in SIGH-SAD or MADRS scores by 50%, or a CGI-Improvement (CGI-I) score of 1 or 2, was significantly higher in the [sertraline](#) group (51.9%, 53.2%, and 60.1% based on the 3 respective scales), compared with response rates in the placebo group (33.8%, 37.5%, and 39.5%, respectively). Remission (score of 8 or less on SIGH-SAD) was significantly higher with [sertraline](#) (33.8%) than with placebo (21.6%). Quality of life rating scores also improved significantly with [sertraline](#) compared with placebo [46].

**2)** [Sertraline](#) alone or [sertraline](#) plus interpersonal psychotherapy (IPT) provided moderate improvement in mood in patients with [dysthymia](#) compared with IPT alone in a randomized trial (N=586). Adults with [dysthymic disorder](#) with or without [major depressive disorder](#) as a chronic or acute episode were randomized to [sertraline](#) alone (group 1), [sertraline](#) plus IPT (group 2), or IPT alone (group 3). [Psychotic disorder](#) was an exclusion criteria. The initial dose of [sertraline](#) was 50 mg daily with dose adjustments, based on the efficacy index section of the Clinical Global Impression scale, at 1 to 2 week intervals up to maximum dose of 200 mg/day for 18 months. IPT consisted of 12 one-hour counseling sessions over 6 months. Concomitant medications including other antidepressants and/or anxiolytic/sedative medications were allowed in all 3 groups after the 6 months phase. The acute treatment phase was for 6 months followed by a longitudinal, uncontrolled 1 and 2 year phase. The primary endpoint was mood as measured by the Montgomery Asberg Depression Rating Scale (MADRS) at 6, 12, and 24 months. Retention rates were 83% at 6 months, 78.2% for group 1, 76.9% for group 2, and 67.5% for group 3 (p=0.02) at 2 years. Baseline MADRS scores were 24.9+/-6.5 for group 1, 26+/-6.3 for group 2, and 24.4+/-5.9 for group 3. At 6 months, the MADRS scores were 14.3 for group 1, 14.9 for group 2, and 16.8 for group 3. Response rates (40% or more reduction

in MADRS) were 59.7%, 57.5%, and 46.6%, respectively. Patient's assessment, as measured by Center for Epidemiologic Studies Depression Scale (CES-D) and Visual Analogue Scale (VAS), demonstrated no significant difference among groups in CES-D and VAS at 6 months. The number of patients who completed the 2-year follow-up was 525 (74%). At 1 year, the mean MADRS scores were 13.5 for group 1, 13.1 for group 2, and 15.5 for group 3. At year 2, the mean MADRS scores were 11.7, 12.3, and 14.3, respectively. At year 2, reductions in mean MADRS scores were 13.2+/-11 for group 1, 13.6+/-10.9 for group 2, and 10.2+/-11 for group 3 with significant differences between group 3 and both group 1 and group 2. During the first year of follow-up, 12.3% of group 1, 17.4% in group 2, and 28.2% in group 3 took other antidepressants, anxiolytic or sedative medications [47].

#### 4.5.2.A.13] **Fibromyalgia**

##### a) Overview

FDA Approval: Adult, no; **Pediatric, no**

Efficacy: Adult, Evidence favors efficacy

Recommendation: Adult, Class IIb

Strength of Evidence: Adult, Category B

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

##### b) Summary:

###### Evidence

A systematic review identified 12 randomized controlled studies of SSRIs, including 1 which studied [sertraline](#) 50 mg/day, in the treatment of [fibromyalgia](#). Improvement was seen in pain intensity, fatigue, sleep, depressiveness, and quality of life [3].

###### Guideline

SSRI medications, including [sertraline](#), are recommended in the treatment of [fibromyalgia](#), based on clinical evidence of improved pain, fatigue, depression, sleep, and quality of life [4].

#### 4.5.2.A.14] **Flashbacks**

##### a) Overview

FDA Approval: Adult, no; **Pediatric, no**

Efficacy: Adult, Evidence is inconclusive

Recommendation: Adult, Class IIb

Strength of Evidence: Adult, Category C

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

##### b) Summary:

###### Evidence

In a single patient, [sertraline](#) was effective for eliminating flashbacks associated with lysergic acid diethylamide (LSD) abuse [51].

##### c) Adult:

1j) [Sertraline](#) treatment, started at 25 mg daily and slowly titrated to a target dose of 100 mg daily, decreased and eventually eliminated lysergic acid diethylamide (LSD) flashbacks and depressive symptoms in a single patient with an 8-month history of LSD intake and daily flashbacks for 6 months after drug use. Mild exacerbations of the flashbacks were noted for 2 to 3 days after each dose increase but then subsided. This patient had no history of seizures or migraines. [Hallucinogen persisting perception disorder](#), commonly referred to as "flashbacks" is the re-experience at a later time of the original effects of the hallucinogenic drug. The hallucinogen, LSD, is believed to produce its acute hallucinatory effects through serotonergic mechanisms. [Sertraline](#) decreased the typical physiologic responses to serotonergic agonists as well as attenuated the subjective experience of LSD. [Sertraline](#) may promote tolerance to the remote effects of LSD which present as flashbacks [51].

#### 4.5.2.A.15] Generalized anxiety disorder

##### a) Overview

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

Efficacy: Adult, Evidence favors efficacy; Pediatric, Evidence is inconclusive

Recommendation: Adult, Class IIb; [Pediatric, Class IIb](#)

Strength of Evidence: Adult, Category B; Pediatric, Category B

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

##### b) Summary:

###### Evidence (Adult)

Sertraline-treated adults had significant decreases in the total Hamilton Rating Scale for Anxiety score compared with placebo, according to a 10-week, randomized, double-blind, flexible-dose study of 326 adults with moderate to severe primary [generalized anxiety disorder](#) [48].

###### Evidence (Pediatric)

[Sertraline](#) therapy in combination with [cognitive behavioral therapy](#) (CBT) was shown to be superior to [sertraline](#) therapy alone or CBT alone; while [sertraline](#) therapy alone or CBT alone were both superior to placebo in a randomized trial among children and adolescents with childhood anxiety (N=488) [49].

[Sertraline](#) reduced psychic and somatic symptoms in children with [generalized anxiety disorder](#) [50].

##### c) Adult:

1j) Sertraline-treated adult outpatients had significant decreases in the total Hamilton Rating Scale for Anxiety (HAM-A) score compared with placebo, according to a 10-week, randomized, double-blind, flexible-dose study of 326 evaluable adults with moderate to severe, primary [generalized anxiety disorder](#) (GAD). Patients included in the study were diagnosed with primary DSM-IV GAD, had a total HAM-A symptom score of 20 or greater, a score of 2 or greater on item 1 of the HAM-A ([anxious mood](#)), and a Covi Anxiety Scale total score higher than the Raskin Depression Scale score. There was no placebo run-in phase, but patients could not receive psychotropic drugs within 2 weeks of baseline (5 weeks for [fluoxetine](#)) or benzodiazepines within 30 days of baseline. Patients were randomized to receive



either placebo (n=162), or [sertraline](#) 25 mg/day (n=164) initially for 1 week with increases in 50-mg increments at weeks 2, 3, 4, and 7, up to a maximum of 200 mg/day. Decreases in dose were permitted at any time with only one subsequent increase thereafter. The mean daily dose of [sertraline](#) administered at 10 weeks was 149.1 mg +/- 59 mg. The mean age of patients was approximately 40 years, including 8.3% of patients over 60 years of age. In an intent-to-treat analysis of patients with at least 1 post-baseline measurement, the mean change in total HAM-A at 10 weeks compared with baseline was -12.71 +/- 7.17 in the [sertraline](#) group compared with -11.15 +/- 7.2, with least squares treatment effect between groups of -1.8 +/- 0.8. There were significant improvements in total HAM-A scores in sertraline-treated patients compared with placebo beginning at week 6 and lasting through week 10. An analysis of the HAM-A somatic subscale in sertraline-treated patients was not significantly different compared with placebo, but the HAM-A psychic subscale did demonstrate significant improvements. The response rate (at least 50% reduction in total HAM-A score) was a significant 59.2% in the [sertraline](#) group compared with 48.2% in placebo. Significant adverse events in the [sertraline](#) group (n=165) compared with placebo (n=163) included male sexual dysfunction (17.9% vs 0%), and a decrease or loss of libido (17.6% vs 2.4%). Diastolic blood pressure increases of 1.59 mmHg +/- 8.83 mmHg occurred in the [sertraline](#) group compared with decreases of 0.063 mmHg +/- 8.32 in the placebo group [48].

**d) Pediatric:**

**1) [Sertraline](#) therapy in combination with [cognitive behavioral therapy](#) (CBT) was shown to be superior to [sertraline](#) therapy alone or CBT alone; while [sertraline](#) therapy alone or CBT alone were both superior to placebo in a randomized, controlled trial among children and adolescents with childhood anxiety (n=488). In this multicenter trial, children from 7 to 17 years of age (mean age, 10.7 years; 74.2% younger than 13 years), with a primary diagnosis of [social phobia](#), separation or [generalized anxiety disorder](#) and substantial impairment were randomized in a 2:2:2:1 ratio to receive [sertraline](#) plus CBT (n=140), [sertraline](#) alone (n=133), CBT alone (n=139) or placebo (n=76). Subjects receiving [sertraline](#) plus CBT were aware they were receiving [sertraline](#), but subjects receiving [sertraline](#) alone and placebo therapy were not aware which therapy they were receiving. Independent evaluators completed outcome assessments. [Sertraline](#) and placebo were titrated on a fixed-flexible schedule beginning with 25 mg per day and adjusted upward in the absence of response and toxicity to 200 mg per day by week 8. CBT consisted of fourteen 60-minute sessions which included anxiety-management skills and behavioral exposure to anxiety-provoking situations. The mean daily dose of [sertraline](#) in the combination [sertraline](#)/CBT group was 133.7 +/- 59.8 mg and the mean daily dose for sertraline-only patients was 146 +/- 60.8 mg. The primary outcome measure was treatment response at week 12. Treatment response was assessed as improvement on the Clinical Global Impression-Improvement scale (a scale of 1 to 7 with lower scores indicating more improvement compared with baseline). The intention-to-treat population included all patients randomized. At week 12, a significant improvement in the Clinical Global Impression-Improvement scale of 1 or 2 (very much improved or much improved, respectively) was seen in 80.7% with [sertraline](#) in combination with CBT, 54.9% with [sertraline](#) only, and 59.7% with CBT only, compared with 23.7% with placebo. Pair-wise comparisons showed that combination therapy with [sertraline](#)/CBT was superior to either [sertraline](#) alone (odds ratio (OR), 3.4) or CBT alone (OR 2.8). There was no significant difference in treatment response between patients receiving [sertraline](#) alone or CBT alone (p=0.41). In the number needed to treat (NNT) analysis, treating 2 patients with combination therapy ([sertraline](#)/CBT) prevented one additional event; treating 3 patients with [sertraline](#) alone or CBT alone prevented 1 additional event. The incidence of adverse events (including suicidal and**

homicidal ideation) was not significantly greater in the [sertraline](#) group compared with the placebo group. There were no suicide attempts [49].

2) [Sertraline](#) was safe and efficacious in the treatment of [generalized anxiety disorder](#) in children and adolescents. After a 2- to 3-week evaluation period, 22 children (5 to 17 years of age) with a DSM-IV diagnosis of [generalized anxiety disorder](#) were randomly assigned to receive [sertraline](#) or placebo (double-blind) for 9 weeks. The [sertraline](#) dose was 25 mg/day for the first week and 50 mg/day thereafter. Significant treatment differences in favor of [sertraline](#) were evident from week 4 to the end of the study. By week 9, the somatic factor score of the Hamilton Anxiety Rating Scale, as well as the psychic factor score, was significantly better in the [sertraline](#) group than in the placebo group. Ten of 11 patients receiving [sertraline](#) were rated as improved, while only 1 of the placebo patients was rated as improved. Only 2 patients were rated as showing marked improvement. There was no depression-by-treatment interaction effect, indicating that the observed effects of [sertraline](#) were anxiolytic and separate from its antidepressive effects. No age effects on treatment were observed. Patients receiving [sertraline](#) reported less dizziness, nausea, and stomach pain than did those receiving placebo. Dry mouth, drowsiness, leg spasms, and restlessness occurred more frequently among those treated with [sertraline](#) than among those receiving placebo [50].

#### 4.5.2.A.16] [Myocardial infarction](#); Prophylaxis

##### a) Overview

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

Efficacy: Adult, Evidence favors efficacy

Recommendation: Adult, Class III

Strength of Evidence: Adult, Category B

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

##### b) Summary:

Evidence

[Sertraline](#) was associated with decreases in [platelet](#)/endothelial activation in depressed, post-acute coronary syndrome patients [53].

[Sertraline](#) may confer a protective effect against [first myocardial infarction](#) [54].

##### c) Adult:

1) [Sertraline](#) therapy was associated with a decrease in [platelet](#)/endothelial activation in patients experiencing [major depressive disorder](#) after [acute coronary syndrome](#) (ACS). In a randomized, placebo-controlled sub-study of the [Sertraline Antidepressant Heart Attack Randomized Trial](#) (SADHART) depressed, post- ACS patients (n=64) received [sertraline](#) 50 to 200 mg daily or placebo for 24 weeks. The use of [aspirin](#), anticoagulants, and ADP-receptor inhibitors was allowed throughout the treatment period. [Sertraline](#) therapy produced greater reductions in [platelet](#)/endothelial activation as compared with placebo and may offer further advantage for this patient population. Further studies are needed in order to establish clinical efficacy [53].

2) In a case-control study comprised of 653 cases of [first myocardial infarction](#) (MI) and 2990 control subjects, results indicated that SSRIs may confer a protective effect against first MI.

The subjects in this study were smokers, between the ages of 30 to 65 years, with a first MI hospitalized between September 1995 and December 1997. The four SSRIs investigated in this study were [fluoxetine](#), [fluvoxamine](#), [paroxetine](#), and [sertraline](#); doses taken by participants were not stated. The risk of patients who were taking SSRIs having a first MI compared with controls (after adjustment for potential confounders) was decreased 65% [54].

#### 4.5.2.A.17] Night eating syndrome

##### a) Overview

FDA Approval: Adult, no; **Pediatric, no**

Efficacy: Adult, Evidence favors efficacy

Recommendation: Adult, Class IIb

Strength of Evidence: Adult, Category B

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

##### b) Summary:

##### Evidence

Treatment with [sertraline](#) reduced the symptoms of night eating syndrome compared with placebo in adult outpatients in an 8-week, randomized study (N=34) [12].

##### c) Adult:

**1)** In an 8-week, randomized study (N=34), treatment with [sertraline](#) reduced the symptoms of night eating syndrome compared with placebo in adult outpatients. Patients meeting the standard criteria for night eating syndrome and with a body mass index of greater than 18 kg/m<sup>2</sup> were enrolled. Among other criteria, patients with severe depression, a lifetime diagnosis of [bipolar disorder](#) or any [psychotic disorder](#), or who lacked awareness of their night eating episodes were excluded. Study patients were randomly assigned [sertraline](#) 50 mg (n=17) or placebo (n=17) orally once daily for 8 weeks. [Sertraline](#) was adjusted up to a maximum dose of 200 mg/day (mean study dose, 126.5 mg/day) at visits conducted every other week. No other psychotropic medications were allowed during the study period. At each visit, patients completed the night eating symptom scale, the [Beck Depression Inventory](#), and the Quality of Life Enjoyment and Satisfaction Questionnaire, and a physician administered the Clinical Global Impression (CGI) improvement and severity scale, and the 17-item Hamilton Depression Rating scale. The primary outcome was the CGI-improvement scores, where patients achieving a CGI-improvement scale score of 2 (much improved) and 1 (very much improved) were considered to have responded and remitted, respectively. An intent-to-treat analysis revealed that 12 of 17 patients (71%) in the [sertraline](#) group responded and among them, 7 achieved remission. Three of 17 patients (18%) in the placebo group responded, and only 1 of the 3 responders achieved remission. In the [sertraline](#) group, the CGI severity scale decreased from 4.2 at baseline (moderate severity) to 2.2 at week 8 (borderline ill). In comparison, in the placebo group the CGI severity score decreased from 4.2 at baseline to 3.4 at week 8. Among secondary endpoints, the night eating symptom scores were reduced by 18.1 points (57%) and 5 points (16%) from baseline for the [sertraline](#) and placebo groups, respectively. Although a significant correlation between the change in night eating symptoms scores from baseline to week 2 and week 8 indicated that early improvement with [sertraline](#) was predictive of ultimate response, 50% of all [sertraline](#) responses, based on CGI improvement, occurred between weeks 4 and 8. The number of nocturnal ingestions

decreased from a baseline mean value of 8.3 +/- 8.5 per week to 1.6 +/- 2.6 per week at 8 weeks in the [sertraline](#) group compared with a decrease from the baseline mean of 6.4 +/- 4.9 per week to 5.5 +/- 4.9 per week at week 8 in the placebo group (-81% vs -14%). Compared with placebo, improvements also occurred for patients treated with [sertraline](#) in the number of awakenings, caloric intake after the evening meal, quality of life, and weight loss among overweight patients. Both groups had a modest level of depressive symptoms at baseline, and reductions in depressive symptoms during the study did not significantly correlate to change in night eating symptom scores. [Sertraline](#) was well-tolerated with only mild side effects that included dry mouth, fatigue, diminished libido, and sweating [12].

#### 4.5.2.A.18] Non-cardiac chest pain

##### a) Overview

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

Efficacy: Adult, Evidence is inconclusive

Recommendation: Adult, Class IIb

Strength of Evidence: Adult, Category B

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

##### b) Summary:

Evidence

A small study found [sertraline](#) to significantly reduce noncardiac chest pain [41].

##### c) Adult:

1) [Sertraline](#) significantly reduced pain scores compared with placebo in patients with chest pain determined as noncardiac based on normal [angiogram](#) and [stress test](#). In this double-blind study, 30 patients were randomized to either [sertraline](#) 50 mg or placebo, with dose adjustments up to 200 mg daily based on patient response. After 8 weeks of treatment, pain scores decreased significantly in the [sertraline](#) group compared with the placebo group. [Sertraline's](#) effect did not appear to be by improving a psychiatric disorder, since patients with psychiatric disease were excluded and no effect was seen on the [Beck Depression Inventory](#) in these patients. [Sertraline](#) was thought to act by reducing the perception of or sensitivity to pain [41].

#### 4.5.2.A.19] Premature ejaculation

##### a) Overview

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

Efficacy: Adult, Evidence is inconclusive

Recommendation: Adult, Class IIb

Strength of Evidence: Adult, Category B

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

##### b) Summary:

Evidence

[Sertraline](#) effectively increased time to ejaculation during a randomized, placebo-controlled trial (N=37) [59].

**c) Adult:**

**1)** Thirty-seven men were successfully treated with [sertraline](#) 50 mg daily for [premature ejaculation](#). During phase 1 of the study, patients were randomized to receive placebo (n=18) or [sertraline](#) (n=19) for 4 weeks. Patients then underwent a 4-week washout period and entered phase 2 which consisted of a 4-week crossover period. After phase 2, 29 patients went on to an extended open-label trial to evaluate the long-term effects of [sertraline](#) on [premature ejaculation](#) and the effects of [sertraline](#) withdrawal. Ejaculatory latency time for those treated with [sertraline](#) increased significantly compared with those in the placebo group, from a mean of 0.3 minutes to 3.2 minutes. Time-to-effect of [sertraline](#) was about 1 to 2 weeks. After withdrawal of the drug, efficacy was lost after 6 to 13 days [59].

**4.5.2.A.20] Respiratory obstruction**

**a) Overview**

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

Efficacy: Adult, Evidence is inconclusive

Recommendation: Adult, Class III

Strength of Evidence: Adult, Category C

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

**b) Summary:**

Evidence

Low doses of [sertraline](#) were effective in the treatment of patients with [obstructive airway disease](#) (N=7) [55].

**c) Adult:**

**1)** [Sertraline](#) 25 to 100 mg daily was effective in decreasing breathlessness and increasing exercise tolerance in 7 patients with mild-to-severe [obstructive lung disease](#). [Sertraline](#), however, had little effect on measures of [forced expiratory volume](#) at 1 second (FEV1). Only 3 of the 7 patients met criteria for a mood and/or anxiety disorder; however, most experienced anxiety during attacks of dyspnea. [Sertraline](#) may decrease the anxiety associated with breathing difficulties, thereby, increasing tolerance to dyspneic episodes. Since some of these patients did not have mood/anxiety disorders, [sertraline](#) may work on respiratory, rather than psychiatric symptoms. Serotonin participates in regulating respiration in the brain, possibly by decreasing patient sensitivity to carbon dioxide concentrations. Further studies are needed to confirm the efficacy and mechanism of action of [sertraline](#) on dyspnea [55].

**4.5.2.A.21] Schizophrenia**

**a) Overview**

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

Efficacy: Adult, Ineffective

Recommendation: Adult, Class III

Strength of Evidence: Adult, Category B

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

**b) Summary:**

Evidence

[Sertraline](#) had no effect on positive or negative symptoms of [schizophrenia](#) when added to an antipsychotic [58].

**c) Adult:**

**1j)** Addition of [sertraline](#) to [haloperidol](#) therapy had no effect on the positive or negative symptoms of [schizophrenia](#). All patients (N=36) enrolled in this trial had [chronic schizophrenia](#) for an average of 10 years and required institutional care. Patients were randomly assigned to placebo or [sertraline](#) 50 mg daily for 8 weeks. At study conclusion, there were no significant differences between treatments on the Positive and Negative Syndrome Scale, the Clinical Global Impression Scale, and the Simpson-Angus Extrapyramidal Effects Scale. Other studies have shown beneficial effects of adding a selective serotonin reuptake inhibitor to an antipsychotic. In this study, potential reasons for lack of efficacy include the long-term, severe disease course in the study population, the short duration of treatment, and the fixed, low-dose of [sertraline](#). Further studies are needed to clarify this important issue [58].

**4.5.2.A.22] Severe major depression with psychotic features; Adjunct**

**a) Overview**

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

Efficacy: Adult, Evidence favors efficacy

Recommendation: Adult, Class IIb

Strength of Evidence: Adult, Category B

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

**b) Summary:**

Evidence

In patients with unipolar [major depression](#) with psychotic features, treatment with [olanzapine](#) plus [sertraline](#) produced higher remission rates compared with [olanzapine](#) monotherapy in the 12-week randomized STOP-PD study (N=259) [11].

**4.6] Comparative Efficacy / Evaluation With Other Therapies**

**4.6.A] Amisulpride**

**4.6.A.1] Burning mouth syndrome**

**a)** Amisulpride, [sertraline](#), and [paroxetine](#) were all effective in reducing the symptoms of burning mouth syndrome (BMS), but response was achieved earlier with amisulpride than with the selective serotonin



reuptake inhibitors (SSRIs). In a randomized, single-blind study, 76 patients with BMS and without [major depression](#) were given amisulpride 50 milligrams (mg) per day, [paroxetine](#) 20 mg/day, or [sertraline](#) 50 mg/day for 8 weeks. Pain scores decreased significantly in all groups, as did depression (Hamilton Rating Scale for Depression) and anxiety (Hamilton Rating Scale for Anxiety), by week 8. The only difference among treatments was the shorter latency to response in the amisulpride group (22% of patients responding at 2 weeks with amisulpride vs 0% with [paroxetine](#) and 6% with [sertraline](#)) [531].

#### 4.6.A.2] [Dysthymia](#)

a) Although amisulpride and [sertraline](#) were equally effective for treatment of [dysthymia](#) at 12 weeks of treatment, measurable and patient-recognized improvement occurred significantly earlier with amisulpride than with [sertraline](#). In a 12-week, randomized, double-blind study, patients between the ages of 18 and 75 years who fulfilled DSM-IV criteria for [dysthymia](#), with or without [major depression](#), were given amisulpride (n=156) or [sertraline](#) (n=150), each drug at a starting dose of 50 milligrams (mg) per day. After 2 weeks the [sertraline](#) dose could be increased to 100 mg/day (27% were eventually increased to 100 mg/day). The median time to onset of partial response (corresponding to a decrease of 25% or more from baseline in the Hamilton Depression Rating Scale (HAMD) score) was significantly shorter with amisulpride: 11 days versus 15 days (p less than 0.0091). Percentages of patients achieving initial improvement by week 4 were 92% for amisulpride and 82% for [sertraline](#) (p less than 0.01). Patients reported perceiving improvement earlier with amisulpride: 8.4 days vs 10.6 days, p less than 0.0009. Full response (50% or greater improvement from baseline in HAMD score) also occurred earlier with amisulpride. By week 4, 63% of patients in the amisulpride group and 50% in the [sertraline](#) group showed full response (p less than 0.02); at week 8, corresponding values were 82% and 69% (p=0.009). By week 12, the percentage of responders did not differ for the 2 groups (84% in the amisulpride group vs 79% in the [sertraline](#) group). The percentage of patients reporting adverse events was about 45% for both groups but the adverse events were qualitatively different, with gastrointestinal symptoms being reported more often with [sertraline](#) and endocrine adverse events with amisulpride [532].

#### 4.6.B] [Amitriptyline](#)

##### 4.6.B.1] [Depression](#)

a) SUMMARY: Five clinical studies have reported similar efficacy between [amitriptyline](#) and [sertraline](#) in the treatment of depression [533][534][535][536][537]. [Sertraline](#) has had a higher incidence of gastrointestinal side effects, male sexual dysfunction, and insomnia while [amitriptyline](#) has been associated with anticholinergic effects, sedation, dizziness, and hypotension (Cohen et al, 1990)[535].

b) In an 8-week, double-blind, parallel-group study (n=385), [sertraline](#) and [amitriptyline](#) were comparable for treating [major depression](#); both active treatments were significantly better than placebo [533]. Patients were randomly assigned to receive placebo, [sertraline](#) 50 milligrams (mg), or [amitriptyline](#) 50 mg; titration of [sertraline](#) to 200 mg and [amitriptyline](#) to 150 mg was allowed in the protocol. Selected sections of Profile of Mood States (POMS) showed greater improvement in patients treated with [sertraline](#) than [amitriptyline](#); however, other patient rated assessments were similar between treatments. Significantly more patients reported adverse effects (71.8%) and dropped out of the study (15.3%) during treatment with [amitriptyline](#) than [sertraline](#). Due to differences in adverse effects, blinding may have been inadequate in this study. Long-term studies are needed to compare these agents.

c) In an 8-week, double-blind placebo-controlled parallel study of 379 patients with [major depression](#), [sertraline](#) 50 to 200 mg/day showed no significant difference in efficacy when compared to [amitriptyline](#) 50 to 150 mg/day. However, both drugs produced significant improvement over placebo. Patients were evaluated using the Hamilton Rating Scale for Depression (HAM-D) and Clinical Global Impressions (CGI) measurement [536]. Similar results were reported in 77 patients with [major depression](#) [537]. In this

8-week double-blind placebo-controlled trial, the investigators found that [sertraline](#) caused fewer adverse reactions than did [amitriptyline](#).

d) However, in another study, patients receiving [sertraline](#) had a significantly higher incidence of gastrointestinal side effects and male sexual dysfunction than either the [amitriptyline](#)- or placebo-treated group. The amitriptyline-treated group had a high incidence of anticholinergic effects, sedation and dizziness. In this double-blind study, 448 patients with [major depression](#) received [sertraline](#) (mean dose 145 milligrams), [amitriptyline](#) (mean dose 104 milligrams), or placebo. As measured by both the Hamilton Rating Scale and the Clinical Global Impressions Scale, both drug-treated groups showed significantly greater improvement than placebo [535].

e) In 241 elderly depressed patients, [amitriptyline](#) 50 to 150 milligrams daily or [sertraline](#) 50 to 200 milligrams daily showed no statistically significant differences in response. The incidence of side effects varied greatly. A higher proportion of amitriptyline-treated patients (38%) withdrew from the study due to side effects including somnolence, dry mouth, constipation and hypotension. This compared with a 28% incidence of treatment-withdrawal with [sertraline](#). Sertraline-treated patients had a higher frequency of gastrointestinal complaints and insomnia [534].

#### 4.6.C] [Bupropion](#)

##### 4.6.C.1] Depression

a) In a randomized, double-blind comparison trial between sustained-release [buPROPion](#) ([buPROPion](#) SR) and [sertraline](#), a greater incidence of sexual dysfunction was associated with sertraline-treated patients [545]. In the study, 248 patients diagnosed with moderate to severe [major depression](#) were randomly assigned to [buPROPion](#) SR or [sertraline](#) for 16 weeks. The initial dose of [buPROPion](#) SR was 100 milligrams/day (mg/day). If indicated, the dose was increased to 200 mg/day on day 4 and to 300 mg/day on day 7. The initial dose of [sertraline](#) was 50 mg/day and was increased to 100 mg/day on day 8, 150 mg/day on day 15, and 200 mg/day on day 22, if clinically indicated. A significantly greater number of patients treated with [sertraline](#) developed sexual dysfunction compared with [buPROPion](#) SR (men: 63% and 15%, respectively,  $p$  less than 0.001; women: 41% and 7%, respectively,  $p$  less than 0.0001). Sexual dysfunction included sexual desire disorder, [sexual arousal disorder](#), orgasm dysfunction, decreased satisfaction with sexual functioning, and worsened overall sexual functioning. Three [buPROPion](#) SR-treated patients and no sertraline-treated patients reported instances of [premature ejaculation](#); however, this difference was not statistically significant. A limitation of the study is the lack of a placebo-control group, which would help determine the extent of influence of the natural course of depression. This data does suggest, however, that [buPROPion](#) SR may be a more appropriate antidepressant than [sertraline](#) in patients for whom sexual dysfunction is of concern.

b) In an 8-week, double-blind trial, [sertraline](#) and [buPROPion](#) produced similar antidepressant effects while [buPROPion](#) produced fewer problems with sexual dysfunction [546]. Patients received [buPROPion](#) sustained release 150 to 400 milligrams (mg)/day ( $n=120$ ), [sertraline](#) 50 to 200 mg/day ( $n=119$ ), or placebo ( $n=121$ ). Doses were increased as clinically indicated. Mean doses were [buPROPion](#) SR 293 mg/day and [sertraline](#) 121 mg/day. Both active treatment groups responded better than the placebo group as measured by the Hamilton Rating Scale-Depression (responses: [buPROPion](#) SR 66%, [sertraline](#) 68%, placebo 47%,  $p=0.002$ ). At baseline, sexual desire disorder was reported by 39% of the [buPROPion](#) group, 43% of the [sertraline](#) group, and 46% of the placebo patients. At the end of 8 weeks this problem decreased to only 19% of [buPROPion](#) patients versus 31% receiving placebo ( $p$  less than 0.05). In comparison, 28% of [sertraline](#) patients still experienced the disorder (not significant as compared to placebo). More [sertraline](#) patients also experienced [orgasmic dysfunction](#) as compared to either [buPROPion](#) treated or placebo treated patients ( $p$  less than 0.001). Somnolence, insomnia, nausea, and diarrhea also occurred more often in the [sertraline](#) group than in the [buPROPion](#) group. Dry mouth occurred more often in the [buPROPion](#) group.

c) In a randomized, double-blind trial, **buPROPion** sustained release (SR) and **sertraline** were similarly effective in outpatients with moderate to severe **major depressive disorder** [547]. Patients received either **buPROPion** SR 100 to 300 milligrams (mg) daily in 2 doses (n=119) or **sertraline** 50 to 200 mg once daily (n=122) during a 16-week trial. Mean doses were **buPROPion** SR 238 mg/day and **sertraline** 114 mg/day. Patients improved similarly on several scales including the Hamilton Rating Scale for Depression, the Hamilton Rating Scale for Anxiety and the Clinical Global Impressions Scale for Severity of Illness and for Improvement. Nausea, diarrhea, somnolence and sweating were experienced more frequently in the **sertraline** group versus the **buPROPion** group (p less than 0.05). Orgasm delay and/or failure was also experienced more often in the **sertraline** group (p less than 0.001).

#### 4.6.D) **Citalopram Hydrobromide**

##### 4.6.D.1) **Major depressive disorder**

a) In a systematic review and metaanalysis in 15 randomized trials of patients aged 60 years or older with **major depressive disorder**, treatment with **duloxetine** (62%), **paroxetine** (48%), or **sertraline** (28%) was associated with a significantly greater likelihood of achieving a partial response (defined as 50% or greater reduction from baseline in depression score based on the Hamilton Depression Rating Scale, which is preferred, or the Montgomery-Asberg Depression Rating Scale) compared with placebo. **Venlafaxine** and **escitalopram** each had a nonsignificant 20% likelihood of a partial response, while **fluoxetine** (8%) and **citalopram** (7%) had the lowest benefit. As for dizziness, **duloxetine** had a significant 194% increased risk compared with placebo, while a nonsignificant risk was seen with **sertraline** (10% increase in risk) and **paroxetine** (47% increase risk) [16].

#### 4.6.E) **Clonazepam**

##### 4.6.E.1) **Social phobia, Refractory**

a) In a 12-week randomized trial of patients with generalized **social anxiety disorder** who remained symptomatic (Leibowitz Social Anxiety Scale (LSAS) score greater than 50) despite 10 weeks of initial **sertraline** monotherapy (N=181), treatment with **clonazepam** in addition to continued **sertraline** was associated a significantly higher response rate (LSAS score 50 or lower) of 56% and a significant decrease in the mean LSAS score (mean 26.5 point reduction) compared with continued **sertraline** plus placebo (a 36% response rate and mean LSAS point reduction of 16.5). In comparison, treatment with **venlafaxine** resulted in a response rate of 46% and a mean 17.6 point reduction in LSAS scores; neither outcome was significantly different from continued treatment with either **sertraline** plus placebo or **sertraline** plus **clonazepam**. Remission rates (LSAS score 30 or lower) between all 3 treatment groups were not significantly different (27%, **sertraline** plus **clonazepam**; 17% **sertraline** plus placebo; 19%, **venlafaxine**). Somnolence was more frequent among patients in the **sertraline** plus **clonazepam** group (32%) compared with the **venlafaxine** (15%) and **sertraline** plus placebo groups (23%) [549].

#### 4.6.F) **Desipramine**

##### 4.6.F.1) **Depression - Obsessive-compulsive disorder**

a) **Sertraline** was more effective than **desipramine** for reducing symptoms of **major depressive disorder** (MDD) and **obsessive compulsive disorder** (OCD). Eighty-five and 79 patients were randomly assigned to receive **desipramine** 50 milligrams (mg) per day or **sertraline** 50 mg per day for 12 weeks. The dosage of **sertraline** was titrated to a maximum of 200 mg/day; the maximum dosage of **desipramine** was 300 mg/day. At study end-point, the mean dosage of **sertraline** and **desipramine** was 160.1 mg/day and 193.5 mg/day, respectively. For the primary efficacy measures, Hamilton Rating Scale for Depression (HAM-D) and Yale-Brown Obsessive Compulsive Scale (Y-BOCS), **sertraline** was significantly better than **desipramine**

( $p=0.03$  and  $p=0.05$ ). Significantly more patients treated with [sertraline](#) than [desipramine](#) had a 40% or greater reduction in the Y-BOCS ( $p=0.01$ ); remission of depression defined as a score of 7 or less on the 17-item HAM-D was achieved by more patients in the [sertraline](#) than [desipramine](#) groups ( $p=0.04$ ). Discontinuation due to adverse effects occurred in significantly more patients treated with [desipramine](#) (26%) than [sertraline](#) (10%;  $p=0.009$ ). For patients with OCD and MDD, [sertraline](#) is an effective treatment [513].

#### 4.6.F.2] Premenstrual dysphoric disorder

a) [Sertraline](#) more effectively reduced symptoms and improved functioning in women with [premenstrual dysphoric disorder](#) (PMDD) than [desipramine](#) or placebo in a double blind study [514]. After a 3-month screening period, patients ( $n=189$ ) were randomly assigned to [sertraline](#) 50 milligrams (mg), [desipramine](#) 50 mg, or placebo daily; dosage increases of 50 mg at one month intervals to a maximum of 150 mg/day were allowed. Significantly more patients assigned to [desipramine](#) discontinued treatment primarily due to adverse effects (30 versus 13;  $p=0.002$ ). [Sertraline](#) resulted in a significantly greater decrease from baseline to endpoint in the Premenstrual Daily Symptom Report than [desipramine](#) or placebo ( $p$  less than 0.001). Similar results were obtained for the 17-item Hamilton Depression Rating Scale ( $p$  less than 0.001). Direct comparison of a [sertraline](#) and [desipramine](#) showed a more favorable response with the serotonergic agent.

b) In an open-label trial of 32 women with a history of severe premenstrual symptoms, [sertraline](#) and [desipramine](#) achieved similar reductions in depressive symptoms [515]. After 2 months treatment, 78% of [sertraline](#)-treated patients and 75% of [desipramine](#)-treated patients experienced at least a 50% score reduction on the Hamilton Rating Scale for Depression. However, more [sertraline](#)-treated patients (68%) reported a 50% or more reduction in premenstrual symptoms than [desipramine](#)-treated patients (33%). [Sertraline](#) was better tolerated than [desipramine](#) during the study, but this difference may not apply to long-term therapy. Long-term, placebo-controlled trials are needed to further assess the efficacy of these drugs in the treatment of [premenstrual syndrome](#).

#### 4.6.G] Duloxetine Hydrochloride

##### 4.6.G.1] Major depressive disorder

a) In a systematic review and metaanalysis in 15 randomized trials of patients aged 60 years or older with [major depressive disorder](#), treatment with [duloxetine](#) (62%), [paroxetine](#) (48%), or [sertraline](#) (28%) was associated with a significantly greater likelihood of achieving a partial response (defined as 50% or greater reduction from baseline in depression score based on the Hamilton Depression Rating Scale, which is preferred, or the Montgomery-Asberg Depression Rating Scale) compared with placebo. [Venlafaxine](#) and [escitalopram](#) each had a nonsignificant 20% likelihood of a partial response, while [fluoxetine](#) (8%) and [citalopram](#) (7%) had the lowest benefit. As for dizziness, [duloxetine](#) had a significant 194% increased risk compared with placebo, while a nonsignificant risk was seen with [sertraline](#) (10% increase in risk) and [paroxetine](#) (47% increase risk) [16].

#### 4.6.H] Escitalopram Oxalate

##### 4.6.H.1] Major depressive disorder

a) In a systematic review and metaanalysis in 15 randomized trials of patients aged 60 years or older with [major depressive disorder](#), treatment with [duloxetine](#) (62%), [paroxetine](#) (48%), or [sertraline](#) (28%) was associated with a significantly greater likelihood of achieving a partial response (defined as 50% or greater reduction from baseline in depression score based on the Hamilton Depression Rating Scale, which is preferred, or the Montgomery-Asberg Depression Rating Scale) compared with placebo. [Venlafaxine](#) and [escitalopram](#) each had a nonsignificant 20% likelihood of a partial response, while [fluoxetine](#) (8%)

and [citalopram](#) (7%) had the lowest benefit. As for dizziness, [duloxetine](#) had a significant 194% increased risk compared with placebo, while a nonsignificant risk was seen with [sertraline](#) (10% increase in risk) and [paroxetine](#) (47% increase risk) [16].

#### 4.6.1] [Fluoxetine](#)

##### 4.6.1.1] Depression

a) [Paroxetine](#), [fluoxetine](#), and [sertraline](#) were equally effective for the treatment of depression and for improving quality of life in patients in a primary care setting. In a 9-month, randomized, open-label trial (the ARTIST trial), depressed patients, whose symptoms warranted antidepressant treatment, according to their primary care physicians (PCP), were given [paroxetine](#) (n=180), [fluoxetine](#) (n=184) or [sertraline](#) (n=182). Starting doses were [paroxetine](#) 20 milligrams (mg), [fluoxetine](#) hydrochloride 20 mg, and [sertraline](#) 50 mg. The PCP could adjust the dose on the basis of clinical response and could switch the treatment to one of the other study drugs. Final average doses were 23.5 mg for [paroxetine](#), 23.4 mg for [fluoxetine](#), and 72.8 mg for [sertraline](#). All 3 groups showed substantial improvement in depressive symptoms and quality of life. Overall, the percentage of patients categorized as having [major depression](#) dropped from 74% at baseline to 32% at 3 months, and 26% at 9 months. No significant differences were evident among the 3 groups. When data from subgroups (patients with [major depression](#), patients who completed the trial on the drug initially assigned) were analyzed separately, still no differences among the drug treatments was evident. Patient satisfaction did not differ for the 3 groups. Changes in sexual function were small but tended to show improvement for all drug treatments. The drugs were associated with similar incidences of adverse effects and discontinuation rates [523].

b) An eight-week, double-blind, randomized study evaluated the efficacy and safety of [fluoxetine](#) vs [sertraline](#) in the treatment of [major depression](#) (DSM-III-R). One-hundred and eight out-patients with [major depression](#) entered into the study, but only 88 (48 [sertraline](#) and 40 [fluoxetine](#)) were evaluable. The final mean daily dose of [fluoxetine](#) was 28 milligrams (mg) and for [sertraline](#) 72 mg. Both treatment groups showed a statistically significant improvement from baseline at one week, and this was maintained until the end of treatment. No statistically significant differences were observed between the two treatment groups on the primary efficacy variables measured by Hamilton Rating Scale for Depression and Anxiety (HAM-D), Clinical Global Impression Scale (CGI), Montgomery Asberg Depression Rating Scale (MADRS), Leeds Sleep Score scale and Zung Anxiety Rating Scale. The incidence of adverse events was similar: 39.3% for [fluoxetine](#) and 40.4% for [sertraline](#). Most common were gastrointestinal (nausea and abdominal pain) and central nervous system (irritability, headache, somnolence, anorexia, agitation, anxiety and insomnia) effects. [Sertraline](#) was better tolerated than [fluoxetine](#) overall; 9.6% of [sertraline](#)-treated patients discontinued treatment, compared with 19.6% in the [fluoxetine](#)-treated group [524]. Investigation in a larger population is warranted to definitively establish the comparative efficacy and safety of the two drugs [524].

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

a) Both [fluoxetine](#) and [sertraline](#) were effective and well tolerated in the treatment of patients with [obsessive-compulsive disorder](#) (OCD). Patients received either [sertraline](#), 50 to 200 milligrams (mg) per day (mean 139.5 +/- 58.5 mg; N=76), or [fluoxetine](#), 20 to 80 mg/day (mean 56.7 +/- 23.0 mg; N=72), in a double-blind manner for 24 weeks. Group assignment was random and resulted in matched patient populations. Safety and efficacy measures were taken at the end of study weeks 1, 2, 4, 6, 8, 12, 16, 20, and 24 weeks or at the last assessment period if patients failed to complete the study. Primary efficacy measures included the Yale-Brown Obsessive-Compulsive Scale (Y-BOCS), the National Institute of Mental Health Global Obsessive-Compulsive Rating (NIHM-OC), and the Clinical Global Impression Severity and Improvement scales (CGI-S and CGI-I). Secondary measures included the Hamilton Rating Scale for Depression (HAM-D 21 item version) and the Clinical Anxiety Scale (CAS). By the end of the 24



week study, both medications were effective and there were no significant treatment differences between the two groups. All primary and secondary measures showed similar amounts of improvement. The time-course of improvement was also similar for both groups, with [sertraline](#) showing a statistically significant greater improvement, on some measures (Y-BOCS change score and global severity of illness score) during some of the early assessments (weeks 4, 8, 12), however this study was not sufficiently powered to reliably detect differences between the drug treatments during this time period. Adverse drug effects were described as mild to moderate for both drugs with no significant difference in incidence reported for [sertraline](#) or [fluoxetine](#) [525].

#### 4.6.I.3] Weight gain

a) Weight gain is a common complaint during antidepressant therapy, and weight gain was significantly greater with [paroxetine](#) than either [sertraline](#) or [fluoxetine](#) after 32 weeks of treatment. Patients meeting DSM-IV criteria for [major depressive disorder](#) were randomized to double-blind treatment with [sertraline](#) 50 milligrams (mg) daily (n=96) [fluoxetine](#) 20 mg daily (n=20), or [paroxetine](#) 20 mg daily (n=96) for 4 weeks. Patients responding to this dose continued for an additional 6 weeks, and those not responding had their doses titrated based on response up to a dose of 200 mg [sertraline](#), 60 mg [fluoxetine](#), and 60 mg [paroxetine](#), and then maintained at their optimal doses for 6 weeks. After this treatment phase, responders (Clinical Global Impressions-Improvement score of 1 or 2 for 2 consecutive weeks) continued for 16 additional weeks. The number of responders participating in the 16 additional weeks were similar for the 3 treatments: 48 [sertraline](#), 44 [fluoxetine](#), and 47 [paroxetine](#). However, among these responders, the mean increase in weight in the [paroxetine](#) group (3.6%) was significant compared to the mean increase with [sertraline](#) (1.0%) and mean decrease with [fluoxetine](#) (-0.2%). A gain of 7% or greater in weight occurred in 25.5% of [paroxetine](#) patients, 4.2% of [sertraline](#) patients, and 6.8% of [fluoxetine](#) patients; this difference was significant[526].

#### 4.6.J] Fluoxetine Hydrochloride

##### 4.6.J.1] Major depressive disorder

a) In a systematic review and metaanalysis in 15 randomized trials of patients aged 60 years or older with [major depressive disorder](#), treatment with [duloxetine](#) (62%), [paroxetine](#) (48%), or [sertraline](#) (28%) was associated with a significantly greater likelihood of achieving a partial response (defined as 50% or greater reduction from baseline in depression score based on the Hamilton Depression Rating Scale, which is preferred, or the Montgomery-Asberg Depression Rating Scale) compared with placebo. [Venlafaxine](#) and escitalopram each had a nonsignificant 20% likelihood of a partial response, while [fluoxetine](#) (8%) and [citalopram](#) (7%) had the lowest benefit. As for dizziness, [duloxetine](#) had a significant 194% increased risk compared with placebo, while a nonsignificant risk was seen with [sertraline](#) (10% increase in risk) and [paroxetine](#) (47% increase risk) [16].

#### 4.6.K] Fluvoxamine

##### 4.6.K.1] Depression

a) In a small study (n=64), the incidence of recurrent depression was similar between patients treated prophylactically with [sertraline](#) and [fluvoxamine](#). Sixty-four patients entered the study and received either [sertraline](#) 100 milligrams(mg)/day or [fluvoxamine](#) 200 mg/day for 2 years; increases in dose were allowed if depression recurred. During the study period, 7 sertraline-treated and 6 fluvoxamine-treated patients had a new episode of depression (p=0.88). Adverse effects were minor and transient for both treatments. Results of this study suggest that [sertraline](#) and [fluvoxamine](#) were effective for preventing recurrent depression episodes, but are limited by the absence of a placebo control group[529].



b) The pharmacology, pharmacokinetics, adverse effects, drug interactions, efficacy, and dosage of fluvoxamine (FVX), sertraline (SRT) and paroxetine (PRX) were compared in a comprehensive review [530]. All three agents have large volumes of distribution and are highly protein-bound. In comparison to fluoxetine, FVX, SRT, and PRX all have shorter elimination half-lives (approximately 24 hours) and are metabolized to clinically-inactive compounds. These agents, therefore, are less likely than fluoxetine to interact with other drugs. Nausea was the most commonly reported adverse effect for all three agents. Other reported adverse effects include sedation, headache, dry mouth, insomnia, sexual dysfunction, and constipation. FVX has been found to be superior to placebo and equivalent to imipramine, clomipramine, desipramine, mianserin, and maprotiline in the treatment of depression and both FVX and SRT have been shown to be superior to placebo in the treatment of obsessive-compulsive disorder (OCD). PRX has been found to be superior to placebo and equivalent to amitriptyline, imipramine, clomipramine, and doxepin in the treatment of depression while SRT has been found to be superior to placebo and equivalent to amitriptyline. Clinical experience has demonstrated all three drugs to be effective in the treatment of depression. They may be especially useful in elderly patients, in those who cannot tolerate alternate treatments, and in those who do not respond to adequate trials of other antidepressant therapies.

4.6.L] Imipramine

4.6.L.1] Depression

a) More than 50% of chronically depressed patients who were nonresponders to an antidepressant responded when switched to an antidepressant of another class. Patients who had completed a randomized, 12-week, double-blind trial with either sertraline or imipramine for treatment of chronic depression and had failed to respond were switched to the alternate treatment for 12 more weeks of double-blind treatment. Fifty-one patients were switched from imipramine to sertraline and 117 from sertraline to imipramine. Mean dosages at study end were 221 milligrams (mg) per day for imipramine and 163 mg/day for sertraline. Ten percent of those switched to sertraline and 25% of those switched to imipramine dropped out. The difference in dropout rate was mainly due to intolerable adverse effects of imipramine. Those who switched to imipramine experienced significant reductions in 3 adverse effects but significant increases in 8 adverse effects, whereas those who switched to sertraline had significant decreases in 6 adverse effects and significant increases in one:

	SERTRALINE TO IMIPRAMINE	IMIPRAMINE TO SERTRALINE
DECREASED INCIDENCE		
Diarrhea	Insomnia	Dry mouth
Abdominal Pain	Somnolence	
	Increased sweating	
	Constipation	
	Dizziness	
	Urinary complaints	
INCREASED INCIDENCE		
Increased sweating	Dry mouth	Insomnia
Constipation		
Dizziness		
Tremor		
Abnormal taste		
Increased appetite		
Urinary complaints		

b) The intent-to-treat response rates were 60% for sertraline and 44% for imipramine (p=0.03). Among completers, however, response rates were 63% and 55%, respectively (p=0.16). After averaging across the study weeks and adjusting for completion status, depression type, and baseline value, there were no

significant differences between groups in outcomes. The pattern of improvement over time did not differ for the 2 groups [518].

c) In a double-blind study of [major depression](#) with or without [dysthymia](#), response to [sertraline](#) was highest in women whereas response with [imipramine](#) was highest in men. Patients meeting DSM III-R criteria for chronic [major depression](#) (235 men and 400 women) were randomized to 12-week treatment with [sertraline](#) or [imipramine](#) in a 2:1 ratio. Both drugs were started at 50 milligrams (mg) daily and titrated to a maximum of 300 mg for [imipramine](#) and 200 mg for [sertraline](#). Although the overall response to [sertraline](#) was similar to [imipramine](#), a statistically significant gender and treatment interaction was observed. The highest response rates occurred in women taking [sertraline](#) and in men taking [imipramine](#). More women responded to [sertraline](#) (147/260; 57%) than to [imipramine](#) (61/133; 46%); and more men responded to [imipramine](#) (43/69; 62%) than to [sertraline](#) (73/161; 45%). Gender differences also occurred in the types of adverse events reported, and more women withdrew from the [imipramine](#) group than from the [sertraline](#) group; however, withdrawal rates by men were not significantly different for the 2 drugs. A significant interaction was also seen between menopausal status and treatment. Withdrawal from treatment was highest in premenopausal women taking [imipramine](#) and postmenopausal women taking [sertraline](#). The mechanism behind these gender differences is unknown, and may relate to interaction of female sex hormones and serotonin activity. [519]

#### 4.6.L.2] [Dysthymia](#)

a) [Sertraline](#) and [imipramine](#) are equally effective for the treatment of [dysthymia](#); however, [sertraline](#) is better tolerated. In a randomized trial, [sertraline](#) and [imipramine](#) were compared and evaluated in a group of 416 patients with [early-onset primary dysthymia](#). Outcome was based on response based on clinical evaluation (Hamilton Rate Scale for Depression, Montgomery- Asberg Depression Rating Scale, Hopkins [Symptom Checklist](#)) and patient-rated version of the Inventory of Depressive Symptoms. Improvement of scores of Clinical Global Impressions of 1 or 2 (very much or much improved) demonstrated response rates of 59% for [sertraline](#), 64% for [imipramine](#), and 44% for placebo. The mean dose of required for initial response was 89.5 milligrams (mg) for [sertraline](#) and 159.7 milligrams for [imipramine](#) [520].

b) Of the 416 patients described in the study above by Thase et al, 355 had completed the Tridimensional Personality Questionnaire before and after treatment, and the results revealed that temperament scores improved with improvement in [dysthymia](#). At baseline, temperament in dysthymic patients was abnormal, with higher mean harm avoidance score from the Tridimensional Personality Questionnaire than that reported for a community population. After 12 weeks of treatment, harm avoidance scores decreased significantly, with no significant differences between the [sertraline](#), [imipramine](#), and placebo group. Scores decreased for those achieving remission and those who did not; however, decreases were significantly greater among the remitters. Thus, improvement in temperament was mainly related to disease improvement regardless of treatment. The results revealed some gender and treatment effects, and further studies using multiple measures, rather than the single measure used in this study, would be needed to determine treatment effects on temperament and personality [521].

#### 4.6.L.3] [Mixed anxiety and depressive disorder](#)

a) [Imipramine](#) and [sertraline](#) were equally effective in the treatment of anxiety and depression in patients with comorbid [panic disorder](#) and [major depressive disorder](#). In an randomized, multicenter, double-blind study, patients with full Axis I [panic disorder](#) with concurrent [major depressive disorder](#) with a minimum of 4 panic attacks in the 4 weeks prior to screening and a baseline Montgomery-Asberg Depression Rating Scale (MADRS) score of at least 20 received either [sertraline](#) (n=138; 50 to 100 milligrams (mg), mean dose, 65.4 mg/day) or [imipramine](#) (n=69; 100 to 200 mg, mean dose 144.2 mg/day) for 26 weeks. [Sertraline](#) was given at an initial dose of 25 mg/day for 1 week, then titrated to 50 mg/day for 4 weeks, at which time the dose could be increased to 100 mg, if needed. The initial dose of [imipramine](#) was 25 mg/day, increased

at weekly intervals to 50 mg, 100 mg, and 150 mg. If needed, the dose could be increased again to 200 mg or reduced to 100 mg. Primary outcome measures were weekly panic attack frequency and MADRS score. [Sertraline](#) and [imipramine](#) produced similar improvements in the mean baseline (28.5 vs 28.7, respectively) to endpoint (11.1 vs 11.2, respectively) total MADRS score and in the mean baseline (7.1 vs 7, respectively) to endpoint (2.9 vs 2.3, respectively) weekly panic attack frequency. However, sertraline-treated patients reported significantly fewer adverse effects as compared with imipramine-treated patients (23% vs 42%, respectively;  $p=0.005$ ) and fewer discontinued treatment (11% vs 22%, respectively;  $p=0.04$ ). Nausea and diarrhea was more frequently reported with [sertraline](#) treatment, while dizziness, dry mouth, sweating, tremor, and constipation were more frequent with [imipramine](#) administration [517].

#### 4.6.M] Mianserin

##### 1) Adverse Effects

a) In a double-blind, placebo-controlled crossover study in elderly patients, [sertraline](#) doses of 100 to 200 mg daily did not affect cognitive or psychomotor performance on a number of psychometric tests. The addition of alcohol did not affect these results. Conversely, mianserin doses of 10 to 30 mg daily produced severe effects even at the lowest dose used and many subjects were withdrawn from the study [516].

#### 4.6.N] Mirtazapine

##### 4.6.N.1] Depression

a) The onset of response was faster with [mirtazapine](#) orally disintegrating tablets than with [sertraline](#) capsules ([sertraline](#) tablets were not assessed); changes from baseline Hamilton Depression Rating Scale (HAM-D) scores were observed with both drugs by day 4, however, and dose titration schedules differed between drug regimens [527].

#### 4.6.O] Nortriptyline

##### 4.6.O.1] Depression

a) [Sertraline](#) and [nortriptyline](#) were equally effective in treating depression in elderly outpatients; however, [sertraline](#) provided better response in those greater than 70 and in quality of life measures. In this double-blind study, 210 patients ages 60 years and older, and who met DSM III-R criteria for [major depression](#) had a Hamilton Depression Rating Scale (HAM-D) score of 18 or greater, were randomized to 12 weeks of [sertraline](#) or [nortriptyline](#). [Sertraline](#) was given as 50 milligrams (mg) daily titrated every 3 weeks if needed to 150 mg daily. [Nortriptyline](#) was given as 25 mg daily and titrated weekly as needed to 100 mg daily. At 12 weeks, improvements in HAM-D scores were similar for the 2 groups. Response (at least 50% reduction in baseline HAM-D scores) occurred in 55 of 72 (72.4%) [sertraline](#)-treated and in 43 of 70 (61.4%) [nortriptyline](#)-treated patients; this difference was not significant. However, HAM-D scores in patients older than 70 years old were higher than those of patients younger than 70 years after treatment with [nortriptyline](#), whereas [sertraline](#) decreased HAM-D scores equally well in both age groups. Scores measuring cognitive, functioning, energy, and quality of life improved significantly with [sertraline](#) compared to scores with [nortriptyline](#). [548]

#### 4.6.P] Paroxetine

##### 4.6.P.1] Burning mouth syndrome

a) Amisulpride, [sertraline](#), and [paroxetine](#) were all effective in reducing the symptoms of burning mouth syndrome (BMS), but response was achieved earlier with amisulpride than with the selective serotonin

reuptake inhibitors (SSRIs). In a randomized, single-blind study, 76 patients with BMS and without [major depression](#) were given amisulpride 50 milligrams (mg) per day, [paroxetine](#) 20 mg/day, or [sertraline](#) 50 mg/day for 8 weeks. Pain scores decreased significantly in all groups, as did depression (Hamilton Rating Scale for Depression) and anxiety (Hamilton Rating Scale for Anxiety), by week 8. The only difference among treatments was the shorter latency to response in the amisulpride group (22% of patients responding at 2 weeks with amisulpride vs 0% with [paroxetine](#) and 6% with [sertraline](#)) [538].

#### 4.6.P.2] Depression

a) [Paroxetine](#), [fluoxetine](#), and [sertraline](#) were equally effective for the treatment of depression and for improving quality of life in patients in a primary care setting. In a 9-month, randomized, open-label trial (the ARTIST trial), depressed patients, whose symptoms warranted antidepressant treatment, according to their primary care physicians (PCP), were given [paroxetine](#) (n=180), [fluoxetine](#) (n=184) or [sertraline](#) (n=182). Starting doses were [paroxetine](#) 20 milligrams (mg), [fluoxetine](#) hydrochloride 20 mg, and [sertraline](#) 50 mg. The PCP could adjust the dose on the basis of clinical response and could switch the treatment to one of the other study drugs. Final average doses were 23.5 mg for [paroxetine](#), 23.4 mg for [fluoxetine](#), and 72.8 mg for [sertraline](#). All 3 groups showed substantial improvement in depressive symptoms and quality of life. Overall, the percentage of patients categorized as having [major depression](#) dropped from 74% at baseline to 32% at 3 months, and 26% at 9 months. No significant differences were evident among the 3 groups. When data from subgroups (patients with [major depression](#), patients who completed the trial on the drug initially assigned) were analyzed separately, still no differences among the drug treatments was evident. Patient satisfaction did not differ for the 3 groups. Changes in sexual function were small but tended to show improvement for all drug treatments. The drugs were associated with similar incidences of adverse effects and discontinuation rates [539].

b) [Sertraline](#) and [paroxetine](#) were equally effective in treating [major depression](#), although side effects may be less with [sertraline](#). In a double-blind study, 353 outpatients meeting the DSM-III-R criteria for [major depression](#) and having a score of at least 21 on the Montgomery-Asberg Depression Rating Scale (MADRS) that did not improve at least 25% during a 1-week washout period were randomized to receive 24 weeks of treatment with either [sertraline](#) 50 milligrams (mg) or [paroxetine](#) 20 mg. Dose adjustments were allowed after 2 weeks based on response to a maximum of 150 mg [sertraline](#) and 40 mg [paroxetine](#). No significant differences were observed in the improvement of MADRS and Clinical Global Impression (CGI) scores between the [sertraline](#) and [paroxetine](#) group. Of the 176 patients taking [sertraline](#), 64% completed 24 weeks of treatment, and 65 % of 177 treated with [paroxetine](#) completed 24 weeks. Of those who completed therapy, remission (MADRS score less than 7) was achieved in 80.2% of the [sertraline](#) and in 73.7% of the [paroxetine](#)-treated patients. Quality of life measures improved with no significant differences between the two groups. Comparable improvements also occurred for the 2 groups in measures of personality. Both treatments were well-tolerated, with diarrhea reported significantly more often with [sertraline](#), and constipation, fatigue, decreased libido in women, and micturition problems significantly more common with [paroxetine](#). A significantly greater weight gain was observed with [paroxetine](#) (2.9 pound) compared with [sertraline](#) (1.3 pound) [540]

#### 4.6.P.3] Weight gain

a) Weight gain is a common complaint during antidepressant therapy, and weight gain was significantly greater with [paroxetine](#) than either [sertraline](#) or [fluoxetine](#) after 32 weeks of treatment. Patients meeting DSM-IV criteria for [major depressive disorder](#) were randomized to double-blind treatment with [sertraline](#) 50 milligrams (mg) daily (n=96) [fluoxetine](#) 20 mg daily (n=20), or [paroxetine](#) 20 mg daily (n=96) for 4 weeks. Patients responding to this dose continued for an additional 6 weeks, and those not responding had their doses titrated based on response up to a dose of 200 mg [sertraline](#), 60 mg [fluoxetine](#), and 60 mg [paroxetine](#), and then maintained at their optimal doses for 6 weeks. After this treatment phase, responders

(Clinical Global Impressions-Improvement score of 1 or 2 for 2 consecutive weeks) continued for 16 additional weeks. The number of responders participating in the 16 additional weeks were similar for the 3 treatments: 48 [sertraline](#), 44 [fluoxetine](#), and 47 [paroxetine](#). However, among these responders, the mean increase in weight in the [paroxetine](#) group (3.6%) was significant compared to the mean increase with [sertraline](#) (1.0%) and mean decrease with [fluoxetine](#) (-0.2%). A gain of 7% or greater in weight occurred in 25.5% of [paroxetine](#) patients, 4.2% of [sertraline](#) patients, and 6.8% of [fluoxetine](#) patients; this difference was significant [541].

#### 4.6.Q] [Paroxetine Hydrochloride](#)

##### 4.6.Q.1] [Major depressive disorder](#)

a) In a systematic review and metaanalysis in 15 randomized trials of patients aged 60 years or older with [major depressive disorder](#), treatment with [duloxetine](#) (62%), [paroxetine](#) (48%), or [sertraline](#) (28%) was associated with a significantly greater likelihood of achieving a partial response (defined as 50% or greater reduction from baseline in depression score based on the Hamilton Depression Rating Scale, which is preferred, or the Montgomery-Asberg Depression Rating Scale) compared with placebo. [Venlafaxine](#) and escitalopram each had a nonsignificant 20% likelihood of a partial response, while [fluoxetine](#) (8%) and [citalopram](#) (7%) had the lowest benefit. As for dizziness, [duloxetine](#) had a significant 194% increased risk compared with placebo, while a nonsignificant risk was seen with [sertraline](#) (10% increase in risk) and [paroxetine](#) (47% increase risk) [16].

#### 4.6.R] [Paroxetine Mesylate](#)

##### 4.6.R.1] [Major depressive disorder](#)

a) In a systematic review and metaanalysis in 15 randomized trials of patients aged 60 years or older with [major depressive disorder](#), treatment with [duloxetine](#) (62%), [paroxetine](#) (48%), or [sertraline](#) (28%) was associated with a significantly greater likelihood of achieving a partial response (defined as 50% or greater reduction from baseline in depression score based on the Hamilton Depression Rating Scale, which is preferred, or the Montgomery-Asberg Depression Rating Scale) compared with placebo. [Venlafaxine](#) and escitalopram each had a nonsignificant 20% likelihood of a partial response, while [fluoxetine](#) (8%) and [citalopram](#) (7%) had the lowest benefit. As for dizziness, [duloxetine](#) had a significant 194% increased risk compared with placebo, while a nonsignificant risk was seen with [sertraline](#) (10% increase in risk) and [paroxetine](#) (47% increase risk) [16].

#### 4.6.S] [Sildenafil](#)

##### 4.6.S.1] [Premature ejaculation](#)

a) According to a double-blind, randomized, cross-over study (n=31), as-needed [SILDENAFIL](#) was superior in the treatment of [premature ejaculation](#) compared with [CLOMIPRAMINE](#), [PAROXETINE](#), [SERTRALINE](#), and PAUSE-SQUEEZE technique. [Clomipramine](#), [paroxetine](#), and [sertraline](#) had generally similar efficacy and safety. [Paroxetine](#) exhibited improved efficacy and satisfaction over pause-squeeze, while efficacy and satisfaction were similar to pause-squeeze for [clomipramine](#) and [sertraline](#). Median intravaginal ejaculation latency time (IVELT) increased significantly to 4 minutes (min), 4 min, 3 min, 15 min, and 3 min from baseline 1 min for [clomipramine](#), [paroxetine](#), [sertraline](#), [sildenafil](#), and pause-squeeze, respectively (all p less than 0.0001). [Paroxetine](#) was superior to pause-squeeze with respect to IVELT (p=0.04) and sexual satisfaction (p=0.025). A significant positive correlation occurred between ejaculation latency and sexual satisfaction. No significant differences in adverse effects were found among the 4 drugs. Three patients dropped out due to side effects, including [sildenafil](#) (2) and [clomipramine](#) (1; also lack of efficacy in this patient). Three additional patients dropped out due to lack of efficacy related



to [clomipramine](#), [paroxetine](#), [sertraline](#), and/or pause-squeeze. Medications were administered as needed 3 to 5 hours before planned intercourse and not more than twice a week. Doses were [clomipramine](#) 25 milligrams (mg), [paroxetine](#) 20 mg, [sertraline](#) 50 mg, and [sildenafil](#) 50 mg [522].

#### 4.6.T] St John's Wort

##### 4.6.T.1] Depression

a) In a randomized, double-blind, 12-week study, there was no difference in improvement in depression scores between patients with [major depression](#) treated with [sertraline](#) and those treated with St. John's Wort (SJW). Eighty-seven subjects with [major depression](#) according to DSM-IV criteria and a score of 16 or greater on the Hamilton Rating Scale for Depression (HAMD) were randomized to receive [sertraline](#) 50 to 100 milligrams (mg) per day (n=43) or SJW 900 to 1800 mg/day (n=44). The Hypericum extract (SJW) was confirmed to have a hypericin content of 0.3%. Twenty-eight patients in the [sertraline](#) group and 29 in the SJW group completed the study. In the intent-to-treat analysis, baseline scores on the Ham-D were decreased by almost 50% for both groups at 12 weeks. Scores on the self-rated [Beck Depression Inventory](#) (BDI) declined similarly for the 2 groups. Mean reported adverse effects were significantly fewer at weeks 2 and 4 with SJW than with [sertraline](#). Thereafter, differences between the groups were not statistically significant. One serious adverse reaction occurred: a patient taking 1800 mg SJW per day developed acute mania and required hospitalization. One-third of the subjects of each group dropped out before completion of the study. From the St. John's Wort group, 4 withdrew because of side effects and 3 for lack of efficacy; from the [sertraline](#) group, 7 withdrew because of side effects and 1 for lack of efficacy [528].

#### 4.6.U] [Vardenafil Hydrochloride](#)

##### 4.6.U.1] [Premature ejaculation](#)

a) In a randomized, prospective, crossover study (n=72; mean age 38 +/- 5.7 years), both [vardenafil](#) and [sertraline](#) therapy were effective for the treatment of [premature ejaculation](#) (PE). After receipt of behavioral psychosexual therapy, all men with a PE grade score of 4 or greater (from Center for Marital and Sexual Health Questionnaire (CMASH)) and an intravaginal ejaculatory latency time (IELT) of less than 1.3 minutes (min) were eligible for the study. Forty nine men fulfilled study criteria and were randomized to receive 6 weeks of 'on-demand' [vardenafil](#) 10 milligrams (mg) at least 30 minutes before desired sexual intercourse (maximum 20 mg in 24 hours) or 'on-demand' [sertraline](#) 50 mg approximately 4 hours before desired sexual intercourse, followed by a 1-week washout phase and crossover design for an additional 6 weeks of therapy. The mean baseline initial CMASH score (PE grading) was 5.94 +/- 1.6 with a mean IELT for all patients of 0.59 min (range, 0.1 to 1.3 min). PE grading scores improved by 2.7 +/- 2.1 (p less than 0.01) and by 1.92 +/- 1.32 (p less than 0.01) in the [vardenafil](#) and [sertraline](#) groups, respectively. The measured IELT improved by 5.01 +/- 3.69 min (p less than 0.001) and by 3.2 +/- 1.89 min (p less than 0.001) in the [vardenafil](#) and [sertraline](#) groups, respectively. For all patients, partner satisfaction (measured with McCoy sex scale questionnaire) improved after therapy from 5.1 +/- 1.8 to 3.7 +/- 1.2 (p less than 0.01). Four patients discontinued therapy due to lack of efficacy (n=1 [vardenafil](#); n=3 [sertraline](#)) and 1 patient in the [vardenafil](#) group discontinued therapy due to adverse events. All other adverse events reported in both groups were mild to moderate in severity [550].

#### 4.6.V] [Venlafaxine](#)

##### 4.6.V.1] [Bipolar disorder, depressed phase](#)

a) There were no significant differences between [bupropion](#), [sertraline](#), and [venlafaxine](#) with regard to response or remission rates in the acute treatment of [bipolar depression](#), however, the risk of switching into [hypomania](#) or mania was significantly higher with [venlafaxine](#) compared with [bupropion](#) and



[sertraline](#) during a randomized, double-blind, double-dummy, comparative trial involving outpatients diagnosed with [bipolar depression](#). All patients were receiving at least one mood stabilizer with incomplete therapeutic response. Subjects were randomized to receive either adjunctive [bupropion](#) 75 to 450 milligrams (mg)/day (n=51), [sertraline](#) 50 to 200 mg/day (n=58), or [venlafaxine](#) 37.5 to 375 mg/day (n=65) for 10 weeks. Symptoms were assessed using the Inventory of Depression Symptomatology (IDS), the Young Mania Rating Scale (YMRS), and the Clinical Global Impression scale for [Bipolar Disorder](#) (CGI-BP). Primary outcome measurements included antidepressant response (defined as either a 50% or greater improvement in IDS score or a decrease of at least 2 points in the CGI-BP depression score), antidepressant remission (defined as an IDS score less than 12 and/or a CGI-BP depression score of 1 at study endpoint), and antidepressant-related switch into mania or [hypomania](#) (defined as either an increase of 2 points on the CGI-BP score during any point of the trial or a CGI-BP manic severity score of 3 or more or a YMRS score above 13 at any time point). Response rates at week 10 for [bupropion](#), [sertraline](#), and [venlafaxine](#) were 49%, 53%, and 51%, respectively, while remission rates were 41%, 36%, and 34%, respectively. Differences between the groups were not significant; however, a power analysis was not reported. Controlling for [lithium](#) use did not alter the results. Based on CGI-BP score, switching to mania or [hypomania](#) occurred more frequently with [venlafaxine](#) (29%) compared to [bupropion](#) (10%) and [sertraline](#) (9%; p less than 0.01 overall). During post hoc analysis, it was demonstrated that the switch effect was mainly due to the significant difference in the risk of switching time between [venlafaxine](#) and [sertraline](#) (p=0.01, adjusted for [lithium](#)) and [bupropion](#) (p less than 0.01, adjusted for [lithium](#)), while there was no significant difference between [sertraline](#) and [bupropion](#) (p=0.9). Based on YMRS score, switching occurred in 4%, 7%, and 15% of patients receiving [bupropion](#), [sertraline](#), and [venlafaxine](#), respectively (p=0.05 overall). The difference between the [venlafaxine](#) (31%) and [bupropion](#) (14%) and [sertraline](#) (16%) treatment groups remained significant when the combination of the CGI-BP severity of mania or YMRS criteria were used (p=0.03 without controlling for [lithium](#); p=0.02 when controlled for [lithium](#)). Post hoc analysis results again showed that the difference was driven by [venlafaxine](#). Based on combined criteria, the risk of switching in patients with a history of rapid cycling was also higher with [venlafaxine](#) (43%) compared to [bupropion](#) (14%) and [sertraline](#) (8%; p=0.02 overall). The percentages of patients who discontinued the study prematurely for any reason were 31%, 41%, and 45% in the [bupropion](#), [sertraline](#) and [venlafaxine](#) groups, respectively [8].

#### 4.6.V.2] Depression

a) An 8-week, randomized, double-blind, active-control study of outpatient adults with [major depressive disorder](#) demonstrated that rates of efficacy, safety, and tolerability of [sertraline](#) (n=82) were not significantly different than that of [venlafaxine](#) XR (n=76). Patients were randomized to receive capsules containing either [sertraline](#) 50 mg or [venlafaxine](#) XR 75 mg, which were flexibly dosed at 1 to 3 capsules/day. Primary outcome measure was the change in Quality of Life Enjoyment and Satisfaction Questionnaire (Q-LES-Q) total score from baseline (within the first week of treatment) to endpoint (8-weeks). Secondary outcome measures were the changes from baseline to endpoint in the scores of the 17-item Hamilton Rating Scale for Depression (HAM-D-17), the Clinical Global Impressions - Severity of Illness scale (CGI-S), the Clinical Global Impressions - Improvement scale (CGI-I), and the Hamilton Rating Scale for Anxiety (HAM-A). Response was defined as a score of 1 (very much improved) or 2 (much improved) on the CGI-I scale, or a reduction of HAM-D-17 score by at least 50%; remission was defined as a CGI-I score of 1 or 2 and a HAM-D-17 score of 7 or less. There were no significant differences between study groups with any outcome measures, including remission rates and response rates, or reported adverse effects during active treatment. The most common reported adverse effects during active treatment (10% or greater occurrence) were diarrhea, headache, insomnia, nausea and sexual side effects. The table below describes endpoint scores, response rates, and remission rates for the outcome measures [542]:

Endpoint Scores, Response Rates  
and Remission Rates for Outcome  
Measures

Measure/Sample	Sertraline (n=82)	Venlafaxine XR (n=76)
Q-LES-Q score, mean (SD)	0.69 (0.12)	0.67 (0.12)
HAM-D-17 score, mean (SD)	10.8 (6.4)	9.7 (6.4)
HAM-D-17 response rate, (N/N)	55%(45/82)	65% (49/76)
HAM-D-17 remission rate, (N/N)	38% (31/82)	49% (37/76)
CGI-S score, mean (SD)	2.6 (1.1)	2.4 (1.1)
CGI-I score, mean (SD)	2.3 (1.1)	2 (1.1)
HAM-A score, mean (SD)	9.1 (5.4)	8.2 (5.7)
CGI-I = Clinical Global Impressions-Improvement scale; CGI-S = Clinical Global Impressions-Severity of Illness scale; HAM-A = Hamilton Rating Scale for Anxiety; HAM-D-17 = 17-item Hamilton Rating Scale for Depression; Q-LES-Q = Quality of Life Enjoyment and Satisfaction Questionnaire; XR = extended-release		

**b)** In patients with [major depressive disorder](#), almost twice as many experienced a remission with [venlafaxine](#) therapy compared to [sertraline](#). In an 8-week, double-blind study, patients with a [major depressive disorder](#) randomly received [venlafaxine](#) 37.5 mg twice daily (n=75) or [sertraline](#) 50 mg daily (n=72). At the investigators' discretion, the [venlafaxine](#) could be increased to 75 mg twice daily or the [sertraline](#) increased to 50 mg twice daily on day 15. After 8 weeks, patients in both groups showed significant improvement on both the Hamilton Rating Scale for Depression (HAM-D) and the Montgomery- Asberg Depression Rating Scale (p less than 0.05). In the [venlafaxine](#) group 83% were responders compared with 68% in the [sertraline](#) group (p=0.05). Remission occurred in 68% of the [venlafaxine](#) group and in 45% of the [sertraline](#) group (p=0.008). The most common adverse events were nausea, headache, and sweating with [venlafaxine](#) and nausea, headache, and diarrhea with [sertraline](#) [543].

#### 4.6.V.3] Depression, Elderly

**a)** Treatment with [venlafaxine](#) had a lower tolerability, but was equally effective to [sertraline](#) therapy in elderly nursing home patients for the treatment of depression. In a randomized, double-blind study, fifty-two elderly patients (mean age, 82.5 years) with depression received either [sertraline](#) (initial, 25 milligrams (mg)/day, titrated to 100 mg/day) or immediate-release [venlafaxine](#) (initial, 18.75 mg/day, titrated to 150 mg/day) for 10 weeks. No significant differences were found in Hamilton Rating Scale for Depression (HAM-D) scores from baseline to endpoint between the two treatment groups. However, early termination and withdrawal rates due to serious adverse events were higher in venlafaxine-treated patients. Serious adverse events in the [venlafaxine](#) group included [urinary tract infection](#), cerebrovascular accident, [hypertension](#), decreased renal function, [rapid atrial fibrillation](#), [anemia](#), and [thrombocytopenia](#). [Delirium](#), [hyponatremia](#) and worsened [congestive heart failure](#) were observed in both treatment groups. From baseline to endpoint, heart rate increased in the [venlafaxine](#) group (74.6 bpm to 76.7 bpm, respectively) and decreased in the [sertraline](#) group (78.4 bpm to 70.9 bpm, respectively). The authors suggest that the lowered tolerability of [venlafaxine](#) may be related to noradrenergic uptake inhibition by this medication [544].

#### 4.6.W] Venlafaxine Hydrochloride

##### 4.6.W.1] Major depressive disorder

a) In a systematic review and metaanalysis in 15 randomized trials of patients aged 60 years or older with **major depressive disorder**, treatment with **duloxetine** (62%), **paroxetine** (48%), or **sertraline** (28%) was associated with a significantly greater likelihood of achieving a partial response (defined as 50% or greater reduction from baseline in depression score based on the Hamilton Depression Rating Scale, which is preferred, or the Montgomery-Asberg Depression Rating Scale) compared with placebo. **Venlafaxine** and **escitalopram** each had a nonsignificant 20% likelihood of a partial response, while **fluoxetine** (8%) and **citalopram** (7%) had the lowest benefit. As for dizziness, **duloxetine** had a significant 194% increased risk compared with placebo, while a nonsignificant risk was seen with **sertraline** (10% increase in risk) and **paroxetine** (47% increase risk) [16].

#### 4.6.W.2] **Social phobia, Refractory**

a) In a 12-week randomized trial of patients with generalized **social anxiety disorder** who remained symptomatic (Leibowitz Social Anxiety Scale (LSAS) score greater than 50) despite 10 weeks of initial **sertraline** monotherapy (N=181), treatment with **clonazepam** in addition to continued **sertraline** was associated a significantly higher response rate (LSAS score 50 or lower) of 56% and a significant decrease in the mean LSAS score (mean 26.5 point reduction) compared with continued **sertraline** plus placebo (a 36% response rate and mean LSAS point reduction of 16.5). In comparison, treatment with **venlafaxine** resulted in a response rate of 46% and a mean 17.6 point reduction in LSAS scores; neither outcome was significantly different from continued treatment with either **sertraline** plus placebo or **sertraline** plus **clonazepam**. Remission rates (LSAS score 30 or lower) between all 3 treatment groups were not significantly different (27%, **sertraline** plus **clonazepam**; 17% **sertraline** plus placebo; 19%, **venlafaxine**). Somnolence was more frequent among patients in the **sertraline** plus **clonazepam** group (32%) compared with the **venlafaxine** (15%) and **sertraline** plus placebo groups (23%) [549].

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