

DRUGDEX-EV 2565

MICROMEDEX

DRUGDEX® Evaluations
Database updated March 2017**VENLAFAXINE**

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0.0] Overview**1]) Class**

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

Antidepressant

2]) Dosing Information

- a])** [Venlafaxine](#) Hydrochloride

1]) Adult

a]) May convert from stable immediate-release dose to extended-release capsules or tablets based on nearest equivalent (mg/day) [5][6]

b]) Taper dose prior to discontinuation to minimize risk of withdrawal symptoms; reductions of 75 mg/day at intervals of 1 week have been used [4][5][6].

1]) Generalized anxiety disorder

a]) (Extended-release) Initial, 37.5 to 75 mg/day orally once daily; may increase dosage by 75 mg/day every 4 days to MAX 225 mg/day [5]

2]) Major depressive disorder

a]) (Immediate-release tablets) Outpatients, 75 mg/day orally (2 or 3 divided doses); may increase dosage by 75 mg/day every 4 days to MAX 225 mg/day [4]

b]) (Immediate-release tablets) Inpatients, 75 mg/day orally (2 to 3 divided doses); may increase dosage by 75 mg/day every 4 days to MAX 375 mg/day (3 divided doses) [4]

c) (Extended-release capsules and tablets) Initial, 37.5 to 75 mg/day orally once daily; may increase dosage by 75 mg/day every 4 days to MAX 225 mg/day [5][6]

3) Panic disorder, With or without agoraphobia

a) (Extended-release capsule) Initial, 37.5 mg/day orally for 7 days, then increase to 75 mg/day; dose may be further increased by up to 75 mg/day at weekly intervals to MAX 225 mg/day [5]

4) Social phobia

a) (Extended-release capsules and tablets) 75 mg/day orally once daily [5][6]

2) Pediatric

a) Safety and efficacy not established in pediatric patients [4][5][6]

3) Contraindications

a) Venlafaxine Hydrochloride

1) Concomitant use of MAOIs, including linezolid or IV methylene blue, within 7 days of venlafaxine discontinuation or use of venlafaxine within 14 days of discontinuing an MAOI; increased risk of serotonin syndrome [59][60][58]

2) Hypersensitivity to venlafaxine hydrochloride [59][60], desvenlafaxine [59], or to any excipients in the formulation [59][60]

4) Serious Adverse Effects

a) Venlafaxine Hydrochloride

1) Depression, Exacerbation

2) Gastrointestinal hemorrhage

3) Hemorrhage, Abnormal

4) Hepatitis

5) Hypomania

6) Hyponatremia

7) Mania

8) Neuroleptic malignant syndrome

9) Seizure

10) Serotonin syndrome

11) Suicidal thoughts

12) Suicide

5) Clinical Applications

a) Venlafaxine Hydrochloride

1) FDA Approved Indications

a) Generalized anxiety disorder

b) Major depressive disorder

c) Panic disorder, With or without agoraphobia

d) Social phobia

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

Venlafaxine

Venlafaxine HCl

Venlafaxine Hydrochloride

C) Physicochemical Properties

1) Venlafaxine Hydrochloride

a) Molecular Weight

1) Venlafaxine: 277 [436]; Venlafaxine hydrochloride: 313.87 [402][117]; O-desmethylvenlafaxine (ODV): 263 [436]

b) Partition Coefficient

1) Octanol-water: 0.43 (0.2 molar sodium chloride) [402][117]

c) pKa

1d) 9.4 [442]

d) Solubility

1d) Venlafaxine hydrochloride has a solubility of 572 mg/mL in water adjusted to an ionic strength of 0.2 molar with sodium chloride [402][117].

1.2] Storage and Stability

A) Venlafaxine Hydrochloride

1d) Preparation

a) Oral route

1d) Administer with food at approximately the same time each day [4][5][6].

2d) Swallow extended-release (XR) capsules and tablets whole with fluid. Do not divide, crush, chew, or place XR capsules or tablets in water. Alternatively, XR capsules may be administered by opening the capsule, sprinkling the contents on a spoonful of applesauce, and swallowing immediately without chewing. Follow with a glass of water [5][6].

B) Venlafaxine Hydrochloride

1d) Oral route

a) Capsule, Extended Release/Tablet

1d) Store at controlled room temperature, 20 to 25 degrees Celsius (68 to 77 degrees Fahrenheit) [4][5].

1.3] Adult Dosage

1.3.1] Normal Dosage

1.3.1.A] Important Note

d) Discontinue MAOIs intended to treat psychiatric disorders at least 14 days prior to the administration of venlafaxine. Allow at least 7 days to elapse between discontinuation of venlafaxine and initiation of MAOIs intended to treat psychiatric disorders [1].

d) Do not initiate venlafaxine in a patient receiving linezolid or IV methylene blue. If a patient is already receiving venlafaxine and treatment with linezolid or IV methylene blue is unavoidable, and the potential benefit of therapy outweighs the risk for serotonin syndrome, discontinue venlafaxine. Monitor for symptoms of serotonin syndrome for 7 days or for 24 hours after the last dose of linezolid or IV methylene blue, whichever comes first. Resume venlafaxine therapy 24 hours after the last dose of linezolid or IV methylene blue [1].

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

1.3.1.B] Venlafaxine Hydrochloride**1.3.1.B.1] Oral route****1.3.1.B.1.a] Generalized anxiety disorder****1)) Extended-Release Capsule**

a)) Initial dosage and titration: 37.5 to 75 mg/day orally once daily; may increase dosage by 75 mg/day every 4 days [5]

b)) Maximum dosage: 225 mg/day [5]

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

1.3.1.B.1.b] Major depressive disorder**1)) Immediate-Release**

a)) Initial dosage and titration: 75 mg/day orally in 2 or 3 divided doses; may increase dosage by 75 mg/day every 4 days [4]

b)) Maximum dosage (outpatients): 225 mg/day [4]

c)) Maximum dosage (inpatients): 375 mg/day in 3 divided doses [4]

2)) Extended-Release

a)) Initial dosage and titration: 37.5 to 75 mg/day orally once daily; may increase dosage by 75 mg/day every 4 days [5][6]

b)) Maximum dosage: 225 mg/day [5][6]

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

1.3.1.B.1.c] Panic disorder, With or without agoraphobia**1)) Extended-Release Capsule**

a)) Initial dosage: 37.5 mg/day orally once daily for 7 days then increase to 75 mg/day [5]

b)) Dosage titration: May further increase by up to 75 mg/day at weekly intervals [5]

c)) Maximum dosage: 225 mg/day [5]

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

1.3.1.B.1.d] Social phobia**1)) Extended-Release**

a)) Usual dosage: 75 mg/day orally once daily [5][6]

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

1.3.1.B.1.e] Conversion To Extended-Release

1J) May convert to extended-release capsules or tablets based on nearest equivalent (mg/day) of stable immediate-release dose [5][6]

1.3.1.B.1.f) Withdrawal Schedule

1J) Taper dose prior to discontinuation to minimize risk of withdrawal symptoms; reductions of 75 mg/day at intervals of 1 week have been used; individualization may be necessary [4][5][6].

1.3.2] Dosage in Renal Failure

A) Venlafaxine Hydrochloride

1J) Mild to moderate (GFR 10 to 70 mL/min): Decrease usual dosage by 25% to 50% [4][5][6]

1.3.3] Dosage in Hepatic Insufficiency

A) Venlafaxine Hydrochloride

1J) Mild to moderate: Decrease usual dosage by 50% or more [4][5]

1.3.4] Dosage in Geriatric Patients

A) Venlafaxine Hydrochloride

1J) No adjustment necessary [4][5][6]

1.3.5] Dosage Adjustment During Dialysis

A) Venlafaxine Hydrochloride

1J) **Hemodialysis:** Reduce total daily dosage by 50% [4][5][6]

1.3.6] Dosage in Other Disease States

A) Venlafaxine Hydrochloride

1J) **Pregnancy**

a) Third trimester: Consider tapering [4][5][6]

1.4] Pediatric Dosage

1.4.1] Normal Dosage

1.4.1.A] Important Note

J) Discontinue MAOIs intended to treat psychiatric disorders at least 14 days prior to the administration of venlafaxine. Allow at least 7 days to elapse between discontinuation of venlafaxine and initiation of MAOIs intended to treat psychiatric disorders [1].

J) Do not initiate venlafaxine in a patient receiving linezolid or IV methylene blue. If a patient is already receiving venlafaxine and treatment with linezolid or IV methylene blue is unavoidable, and the potential benefit of therapy outweighs the risk for serotonin syndrome, discontinue venlafaxine. Monitor for symptoms of serotonin syndrome for 7 days or for 24 hours after the

last dose of linezolid or IV methylene blue, whichever comes first. Resume venlafaxine therapy 24 hours after the last dose of linezolid or IV methylene blue [1].

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

1.4.1.B| Venlafaxine Hydrochloride

1.4.1.B.1| Oral route

a) Safety and efficacy have not been established in pediatric patients [4][5][6].

2.0| Pharmacokinetics

Onset and Duration

Drug Concentration Levels

ADME

2.1| Onset and Duration

A)| Onset

1)| Venlafaxine Hydrochloride

a)| Initial Response

1)| Depression, oral: 2 weeks to several months [426][427][4][5]

a)| Although some symptoms of major depression may improve within about 2 weeks [426][427], significant overall improvement may take several months or longer [4][5][426].

2.2| Drug Concentration Levels

A)| Venlafaxine Hydrochloride

1)| Therapeutic Drug Concentration

a)| Pregnancy

1)| Venlafaxine concentrations decreased during pregnancy when compared to the postpartum period in a study in 7 women receiving doses ranging from 37.5 to 225 mg as described in the table below. The median plasma concentration of venlafaxine was 65 mcg/L (1st trimester), 66 mcg/L (2nd trimester), and 25 mcg/L (3rd trimester) compared with 92 mcg/L postpartum. A nonsignificant decrease was seen in the median plasma concentration of O-desmethylvenlafaxine (active metabolite); 110 mcg/L (1st trimester), 100 mcg/L (2nd trimester) and 100 mcg/L (3rd trimester) compared with 210 mcg/L postpartum. Overall, the median metabolic ratio of the concentrations of O-desmethylvenlafaxine divided by venlafaxine changed significantly during pregnancy; 1.5 (1st trimester), 2 (2nd trimester) and 3.3 (3rd trimester) compared with 2.2 postpartum. The sum of O-desmethylvenlafaxine plus venlafaxine concentrations was below the therapeutic reference range of 100 to 400

mcg/L in 3 women during the first trimester, in 1 women during the second trimester, and in 2 women during the third trimester [431].

2j) Peak Concentration

a) **Venlafaxine** hydrochloride, oral, regular-release tablets: 53 ng/mL (25-mg dose); 167 to 225 ng/mL (75-mg dose); 393 ng/mL (150-mg dose) [428].

1j) Mean C_{max} for venlafaxine regular-release when 75 milligrams was administered every 12 hours was 225 nanograms/milliliter [5]

2j) Mean C_{max} values following administration of 25, 75, or 150 mg of the regular-release dosage form of venlafaxine hydrochloride to 18 healthy males every 8 hours for three days were 53, 167, and 393 nanograms/mL (0.19, 0.603, and 1.42 micromoles/L), respectively [428]. Venlafaxine exhibits linear pharmacokinetics over the dose range of 75 to 450 mg of venlafaxine per day [4][429].

b) **Venlafaxine** hydrochloride, oral, extended-release capsules: 150 ng/mL [5]

1j) The mean C_{max} value of venlafaxine following administration of 150 milligrams extended-release capsules every 24 hours was 150 nanograms/milliliter. Exposure to venlafaxine was similar between the regular- and extended-release formulations when equal daily doses were administered. The fluctuation in plasma concentrations was slightly lower with the extended-release capsules. Venlafaxine exhibits linear pharmacokinetics over the dose range of 75 to 450 mg of venlafaxine per day [5].

3j) Time to Peak Concentration

a) **Venlafaxine** hydrochloride, oral, regular-release tablets: 1 to 2 hours [5].

1j) Mean T_{max} for venlafaxine regular-release when 75 milligrams was administered every 12 hours was 2 hours [5]. The time to maximum concentration was not significantly different when venlafaxine was administered as a tablet or solution [430].

b) **Venlafaxine** hydrochloride, oral, extended-release capsules: 5.5 hours [5]

1j) The mean T_{max} value of venlafaxine following administration of 150 milligrams extended-release capsules every 24 hours was 5.5 hours. Exposure to venlafaxine was similar between the regular- and extended-release formulations when equal daily doses were administered. The fluctuation in plasma concentrations was slightly lower with the extended-release capsules. Venlafaxine exhibits linear pharmacokinetics over the dose range of 75 to 450 mg of venlafaxine per day [5].

2.3j ADME

2.3.1j Absorption

A) Venlafaxine Hydrochloride**1) Bioavailability****a) Oral, regular-release: 12.6% [432].**

1) About 92% of an oral dose is absorbed. Due to extensive first pass metabolism, only 12.6% is available in the systemic circulation [4][432].

2) The relative bioavailability was 100% in tablet form when compared to an oral solution [4]

3) Compared to healthy subjects, venlafaxine oral bioavailability increased 2- to 3-fold when administered orally to patients with Child-Pugh A and Child-Pugh B hepatic impairment [4].

b) Oral, extended release: 45% [5].

1) At least 92% of a single oral dose of venlafaxine is absorbed. The absolute bioavailability of venlafaxine is approximately 45% [5].

2) Compared to healthy subjects, venlafaxine oral bioavailability increased 2- to 3-fold when administered orally to patients with Child-Pugh A and Child-Pugh B hepatic impairment [5].

2) Effects of Food**a) No effect on systemic bioavailability [4][5].**

1) Food had no effect on the absorption or bioavailability of venlafaxine or its active metabolite, O-desmethylvenlafaxine (ODV) [4][5].

2.3.2] Distribution**A) Distribution Sites****1) Venlafaxine Hydrochloride****a) Protein Binding**

1) 27% to 30% [4][5][433].

a) Venlafaxine and O-desmethylvenlafaxine, the major active metabolite, are approximately 27% to 30% protein-bound, respectively [4][5][433].

B) Distribution Kinetics**1) Venlafaxine Hydrochloride****a) Volume of Distribution**

1)) 7.5 L/kg [4][5].

a)) The steady state volume of distribution is 7.5 and 5.7 L/kg for venlafaxine and O-desmethylvenlafaxine, respectively [4][5].

2.3.3] Metabolism

A)) Metabolism Sites and Kinetics

1)) Venlafaxine Hydrochloride

a)) Liver, extensive [4][5][430][433].

1)) Venlafaxine is metabolized via the CYP2D6 isoenzyme [5][432].

2)) Following absorption, venlafaxine undergoes extensive first-pass metabolism in the liver, primarily to the active metabolite, O-desmethylvenlafaxine (ODV), but also to N-desmethylvenlafaxine, N,O-didesmethylvenlafaxine, and other minor metabolites. The formation of ODV is catalyzed by the isoenzyme CYP2D6 [5][430][433].

B)) Metabolites

1)) Venlafaxine Hydrochloride

a)) O-desmethylvenlafaxine, active [4][5][430][433].

1)) O-desmethylvenlafaxine is the only major active metabolite of venlafaxine hydrochloride [4][5].

b)) N-desmethylvenlafaxine, active [5][433].

1)) This metabolite is less active than O-desmethylvenlafaxine [5][433].

c)) N,O-didesmethylvenlafaxine, active [5][433].

1)) This metabolite is less active than O-desmethylvenlafaxine [5][433].

2.3.4] Excretion

A)) Kidney

1)) Venlafaxine Hydrochloride

a)) Renal Clearance (rate)

1)) 0.074 to 0.079 L/hr/kg [430].

b)) Renal Excretion (%)

1) 87% [4][5].

a) Within 48 hours, approximately 87% of a venlafaxine dose is recovered in the urine as either unchanged venlafaxine (5%), unconjugated O-desmethylvenlafaxine (ODV, 29%), conjugated ODV (26%), or other minor inactive metabolites (27%). Renal elimination of venlafaxine and its metabolites is the primary route of excretion [4][5].

b) After single oral doses of venlafaxine 80 to 100 mg, approximately 1 to 10% is excreted in the urine as unchanged drug. About 30% is excreted in the urine as O-desmethylvenlafaxine, the active metabolite. Another 6% to 19% and 1%, respectively, is excreted in the urine as N,O-didesmethylvenlafaxine and N-desmethylvenlafaxine [433].

B) Feces

1) Venlafaxine Hydrochloride

a) 2% [435][436][428]

1) Within 35 days, approximately 2% of a venlafaxine dose is excreted in the feces [435][436][428].

C) Total Body Clearance

1) Venlafaxine Hydrochloride

a) 1.3 L/hr/kg [4][5].

1) Mean steady-state plasma clearance of venlafaxine and its major metabolite, O-desmethylvenlafaxine is 1.3 and 0.4 liters/hour/kilogram, respectively [4][5].

2) After oral administration of venlafaxine to renally impaired patients (GFR of 10 to 70 milliliters/minute), clearance was decreased by approximately 24% when compared to normal subjects. Clearance of O-desmethylvenlafaxine remained unchanged in patients with renal impairment compared to normal subjects [4][5].

3) After oral administration of venlafaxine to patients requiring dialysis, the clearance of venlafaxine and O-desmethylvenlafaxine was reduced by approximately 57% and 56%, respectively, compared to normal subjects [4][5].

4) After oral administration of venlafaxine to 9 patients with hepatic cirrhosis, clearance of venlafaxine and O-desmethylvenlafaxine was decreased by approximately 50% and 30%, respectively. Three patients with more severe cirrhosis had an approximate 90% decrease in venlafaxine clearance compared to normal subjects [4][5].

5) After oral and intravenous administration of venlafaxine to Child-Pugh A (n=8) and Child-Pugh B (n=11) hepatically impaired patients, oral clearance of venlafaxine

was decreased by more than 50% when compared to normal subjects (n=21). Clearance of O-desmethylvenlafaxine was similar to that for normal subjects [4][5].

2.3.5] Elimination Half-life

A) Parent Compound

1) Venlafaxine Hydrochloride

a) ELIMINATION HALF-LIFE

1) 5 hours [4][5].

a) The mean steady state elimination half-life of venlafaxine is 5 hours [4][5]. The elimination half-life is independent of the dose [433].

b) After oral administration of venlafaxine to 9 patients with hepatic cirrhosis, elimination half-life of venlafaxine was increased by approximately 30% [4][5].

c) After oral and intravenous administration of venlafaxine to Child-Pugh A (n=8) and Child-Pugh B (n=11) hepatically impaired patients, oral elimination half-life of venlafaxine was approximately twice as long as compared to normal subjects (n=21) [4][5].

d) After oral administration of venlafaxine to renally impaired patients (GFR of 10 to 70 milliliters/minute), elimination half-life of venlafaxine was prolonged by approximately 50% when compared to normal subjects [4][5].

e) After oral administration of venlafaxine to patients requiring dialysis, the elimination half-life of venlafaxine was prolonged by approximately 180% when compared to normal subjects [4][5].

B) Metabolites

1) Venlafaxine Hydrochloride

a) O-desmethylvenlafaxine, 11 hours [4][5].

b) After oral administration of venlafaxine to 9 patients with hepatic cirrhosis, elimination half-life of O-desvenlafaxine was increased by approximately 60% [4][5].

c) After oral and intravenous administration of venlafaxine to Child-Pugh A (n=8) and Child-Pugh B (n=11) hepatically impaired patients, oral elimination half-life of O-desvenlafaxine was prolonged by approximately 40% as compared to normal subjects (n=21) [4][5].

d) After oral administration of venlafaxine to renally impaired patients (GFR of 10 to 70 milliliters/minute), elimination half-life of O-desvenlafaxine was prolonged by approximately 40% when compared to normal subjects [4][5].

e) After oral administration of [venlafaxine](#) to patients requiring dialysis, the elimination half-life of O-desvenlafaxine was prolonged by approximately 142% when compared to normal subjects [4][5].

2.3.6] Extracorporeal Elimination

A) [Hemodialysis](#)

1) [Venlafaxine](#) Hydrochloride

a) Dialyzable: No[437]

3.0] Cautions

[Contraindications](#)

[Precautions](#)

[Adverse Reactions](#)

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

[Drug Interactions](#)

3.0.A] Black Box WARNING

Venlafaxine Hydrochloride

Oral (Capsule, Extended Release)

Antidepressants increased the risk of suicidal thoughts and behavior in children, adolescents, and young adults in short-term studies. These studies did not show an increase in the risk of suicidal thoughts and behavior with antidepressant use in patients over age 24; there was a reduction in risk with antidepressant use in patients aged 65 and older [56].

In patients of all ages who are started on antidepressant therapy monitor closely for clinical worsening and emergence of suicidal thoughts and behaviors. Advise families and caregivers of the need for close observation and communication with the prescriber [56].

Oral (Tablet; Tablet, Extended Release)

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 venlafaxine 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. Venlafaxine is not approved for use in pediatric patients [57][58].

3.1] Contraindications

A) Venlafaxine Hydrochloride

- 1) Concomitant use of MAOIs, including [linezolid](#) or IV methylene blue, within 7 days of [venlafaxine](#) discontinuation or use of [venlafaxine](#) within 14 days of discontinuing an MAOI; increased risk of [serotonin syndrome](#) [59][60][58]
- 2) Hypersensitivity to [venlafaxine](#) hydrochloride [59][60], desvenlafaxine [59], or to any excipients in the formulation [59][60]

3.2] Precautions

A) Venlafaxine Hydrochloride

- 1) Black box warning: [Suicidal ideation](#) and behavior or worsening depression has been reported, especially in children, adolescents, and young adults during first few months of therapy or following changes in dosage; close monitoring recommended [59][60][58]
- 2) Beers Criteria: Use with caution in elderly patients as SIADH or [hyponatremia](#) may occur or be exacerbated. Monitor sodium levels when starting or changing doses [2].
- 3) Abrupt withdrawal: May lead to serious discontinuation symptoms; monitoring and gradual dose reduction recommended [59][60][58]
- 4) Cardiovascular: Uncontrolled [hypertension](#) may be exacerbated [61][58]
- 5) Cardiovascular: Heart rate increases have occurred; use caution in patients with comorbidities affected by increased heart rate (eg, [hyperthyroidism](#), [heart failure](#), recent [myocardial infarction](#)) [59][60][58]
- 6) Cardiovascular: Sustained [hypertension](#) has occurred in both pediatric (off-label use) and adult patients; may require dose reduction or discontinuation [60][58]; monitoring recommended [59]
- 7) Concomitant use: Avoid alcohol during treatment [59]
- 8) Concomitant use: Weight loss agents, such as [phentermine](#), are not recommended [59][60][58]
- 9) Endocrine and metabolic: Reduced growth rate may occur, especially in children younger than 12 years [59]
- 10) Endocrine and metabolic: [Hyponatremia](#) has occurred, often associated with SIADH; risk factors include advanced age, concomitant use with diuretics, and volume depletion; discontinuation may be required [59]
- 11) Endocrine and metabolic: Weight reduction of 5% or more has been reported in adult patients [59]
- 12) Endocrine and metabolic: Anorexia (treatment-emergent) may occur [59]
- 13) Endocrine and metabolic: Clinically relevant increases in [serum cholesterol](#) have occurred; monitoring recommended [59]

- 14)) Hematologic: Abnormal bleeding, including [gastrointestinal hemorrhage](#) and life-threatening hemorrhages, has been reported [59][60][58]
- 15)) Hepatic: [Hepatic impairment](#), including [cirrhosis](#), can lead to decreased [venlafaxine](#) clearance; lower dose may be required [59][60][58]
- 16)) Neurologic: [Serotonin syndrome](#) has been reported, especially with concurrent use of other serotonergic drugs (eg, triptans, tricyclic antidepressants, [fentanyl](#), [lithium](#), [tramadol](#), [buspirone](#), tryptophan, [amphetamines](#), St John's wort), MAOIs (including methylene blue IV and [linezolid](#)), and other drugs that impair serotonin metabolism; monitoring recommended and discontinue if suspected [62][60][58]
- 17)) Neurologic: Use caution in patients with history of seizures; discontinuation may be required [59][60][58]
- 18)) Neurologic: Insomnia and nervousness may occur [59]
- 19)) Ophthalmic: Use caution in patients with history of or at risk for [narrow-angle glaucoma](#) or increased intraocular pressure due to risk of mydriasis [60][58]
- 20)) Ophthalmic: [Angle-closure glaucoma](#) may worsen in patients with narrow angles who do have patent [iridectomy](#) [59]
- 21)) Psychiatric: Use caution in patients with history of mania because of risk of activation of mania/[hypomania](#) [59][60][58]
- 22)) Psychiatric: Use caution in patients with [bipolar disorder](#) because of risk of precipitation of a mixed/[manic episode](#); rule out disorder prior to initiating therapy [59][60][58]
- 23)) Renal: [Renal impairment](#) (GFR 10 to 70 mL/min) can lead to decreased [venlafaxine](#) clearance; lower dose may be required [59][60][6]
- 24)) Respiratory: [Interstitial lung disease](#) and [eosinophilic pneumonia](#) have been rarely reported [60][58]; prompt medical evaluation recommended if signs and symptoms develop; discontinuation may be required [59]

3.3] Adverse Reactions

3.3.1] Cardiovascular Effects

3.3.1.A] [Venlafaxine](#) Hydrochloride

3.3.1.A.1] [Heart failure](#)

- a)) Two cases of [interstitial pneumonia](#) with [heart failure](#) have been reported following the use of [venlafaxine](#). In one case, withdrawal of [venlafaxine](#) (initial, 75 mg/day; 35 mg/day after one month) in combination with steroid treatment led to a complete recovery in a 21-year-old woman. However, in the other case, a 62-year-old man ([venlafaxine](#) dose not provided) progressed to multiple-organ failure and died despite attempts at treatment [66].

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

- a)) Incidence: 3% to 13%[4][5]
b)) Immediate-Release

1J) In a dose-comparison study of [venlafaxine](#), a mean increase in supine diastolic blood pressure (SDBP) of 7.2 mmHg occurred at week 6 in patients receiving 375 mg of [venlafaxine](#) daily. There were essentially no changes observed in patients receiving 75 and 225 mg daily. There was a mean decrease in SDBP of 2.2 mmHg in patients receiving placebo [4].

2J) Sustained increases in blood pressure have been reported in patients receiving therapeutic doses of immediate-release [venlafaxine](#). Premarketing studies have shown an incidence of sustained increased supine diastolic blood pressure of 3% for [venlafaxine](#) doses less than 100 mg/day, 5% for doses between 101 and 200 mg/day, 7% for doses between 201 and 300 mg/day, and 13% for doses greater than 300 mg/day. Most of the blood pressure increases were between 10 and 15 mmHg; however, sustained increases such as these may have serious consequences. There have also been cases of elevated blood pressure during postmarketing use that required immediate treatment. It is recommended that preexisting [hypertension](#) be controlled before treatment with [venlafaxine](#) and that blood pressure is routinely monitored during treatment. Additionally, dose reduction or discontinuation of therapy should be considered in patients who experience a sustained increase in blood pressure while receiving [venlafaxine](#) [4][5].

3J) Meta-analysis of controlled clinical studies revealed a crude incidence of sustained elevation in supine diastolic blood pressure (SDBP) of 4.8% (p=0.015) for [venlafaxine](#), 4.7% for [imipramine](#), and 2.1% for placebo; this information was obtained during controlled clinical trials. During the continuation phase, 21 of 467 patients (4.5%) developed an elevated SDBP (p=0.0503) [67].

cJ) Extended-Release

1J) In premarketing studies, sustained [hypertension](#) occurred with the following frequency in patients on [venlafaxine](#) extended-release [5]:

Studies #	Dose Range	Percent of patients with sustained HTN *	Mean change in SDBP
Venlafaxine extended-release (greater than 75 mg/day)	Placebo		
Major depressive disorder	75 to 375 mg/day	3% (19/705)	+ 3.56 mmHg
Generalized anxiety disorder	37.5 to 225 mg/day	0.5% (5/101)	+ 1.68 and + 1.28 mmHg ##
Social anxiety disorder	75 to 225 mg/day	0.6% (5/771)	+ 1.34 and + 1.96 mmHg **
Panic disorder	75 to 225 mg/day	0.9% (9/973)	+ 0.16 mmHg
Key: # = patients were on extended-release venlafaxine;			
* sustained hypertension			
(HTN) = defined as			
treatment-emergent supine			
diastolic blood pressure 90			
mmHg or greater and 10			
mmHg or greater above			
baseline for 3 consecutive			
on-therapy visits; mg/day			
= milligrams/day; SDBP			
= supine diastolic blood			
pressure; ## = up to 8			
weeks and up to 6 months,			
respectively; ** = up to 12			
weeks and up to 6 months,			
respectively			

Studies #	Discontinuation Rate due to sustained HTN ##	Range of SDBP
Major depressive disorder	0.7% (5/705)	12 to 16 mmHg
Generalized anxiety disorder	0.7% (10/1381) *	12 to 25 mmHg
1.3% (7/535) **	8 to 28 mmHg **	
Social anxiety disorder	0.6% (5/771) ***	1 to 24 mmHg *
Panic disorder	0.5% (5/1001) ***	7 to 19 mmHg *

Key: # = patients were on extended-release venlafaxine; ## sustained hypertension (HTN) = defined as treatment-emergent supine diastolic blood pressure 90 mmHg or greater and 10 mmHg or greater above baseline for 3 consecutive on-therapy visits; * = up to 8 weeks; ** = up to 6 months; *** = up to 12 weeks

Across all clinical trials in [major depressive disorder](#), [generalized anxiety disorder](#), [social anxiety disorder](#), and [panic disorder](#), 1.4% of patients treated with extended-release [venlafaxine](#) experienced an increase in supine diastolic blood pressure of 15 mmHg or more compared with 0.9% of patients receiving placebo. Additionally, 1% of patients treated with extended-release [venlafaxine](#) experienced an increase in supine diastolic blood pressure of 20 mmHg or more compared with 0.3% of patients receiving placebo [5].

3.3.1.A.3] Increased heart rate

a) Immediate-release

1) During clinical trials, [venlafaxine](#) hydrochloride treatment (averaged over all dose groups) was associated with a mean increase in pulse rate of approximately 3 beats/minute. There was no change for placebo. In a study with [venlafaxine](#) doses ranging from 200 to 375 mg/day and where the mean daily dose was 300 mg, the mean increase in pulse rate was approximately 2 beats per minute compared with a mean decrease of approximately 1 beat per minute for placebo [4].

2) When ECGs from 769 patients treated with [venlafaxine](#) and 450 patients with placebo during controlled clinical trials were analyzed, the mean increase in heart rate from baseline was 4 beats per minute in the [venlafaxine](#) group. In a flexible-dose study, the mean heart rate increase was 8.5 beats per minute in patients receiving [venlafaxine](#) at doses ranging from 200 to 375 mg/day (mean dose greater than 300 mg/day) compared with 1.7 beats per minute for placebo. Disease states that may put patients at risk for complications from increased heart rate include [hyperthyroidism](#), [heart failure](#), or recent [myocardial infarction](#), particularly with doses greater than 200 mg/day [4].

b) Extended-Release

1) Treatment with extended-release [venlafaxine](#) was associated with a mean increase in pulse rate during [major depressive disorder](#), [generalized anxiety disorder](#) (GAD), [social anxiety disorder](#), and [panic disorder](#) clinical trials [5]. The mean final on-therapy increase in pulse rate is summarized below:

Trial	Duration	Mean Change In PulseVenlafaxine Extended-Release	Mean Ch PulsePlac
Major Depressive Disorder	up to 12 weeks	+ 2 beats/minute	+ 1 beat/
Generalized Anxiety Disorder	up to 8 weeks	+ 2 beats/minute	+ less tha
Social Anxiety Disorder	up to 12 weeks	+ 3 beats/minute	+ 1 beat/
Panic Disorder	up to 12 weeks	+ 1 beat/minute	decrease minute

2j) When [electrocardiograms](#) were analyzed, extended-release [venlafaxine](#) was associated with an increase in heart rate during clinical trials [5]. Results are summarized below:

Trial	Number of Patients With Analyzed ECGs(venlafaxine extended-release/placebo)	Mean Change In Heart Rate From BaselineVenlafaxine Extended-Release	Mean Heart Baselin
Major Depressive Disorder	495 (275/220)	+ 4 beats/minute	+ 1 be
Generalized Anxiety Disorder	908 (610/298)	+ 3 beats/minute	no cha
Social Anxiety Disorder	1127 (593/534)	+ 5 beats/minute	no cha
Panic Disorder	1056 (661/395)	+ 3 beat/minute	decrea beat/m

3.3.1.A.4] Palpitations

a) Incidence: 3% [5]

b) Palpitations have been reported in 3% of [venlafaxine](#) extended-release treated patients (n=819) compared with 1% of placebo-treated patients (n=695) in short-term clinical trials involving patients with [social anxiety disorder](#) [5].

c) Palpitations were reported in 3 of 66 patients receiving [venlafaxine](#) 75 to 375 mg/day in one study; however, a causal relationship was not established [68].

3.3.1.A.5] Prolonged QT interval

a) Compared with baseline, the corrected QT interval increased in [venlafaxine](#) extended-release treated patients and decreased in placebo-treated patients. Studies excluded patients with a recent history of [myocardial infarction](#) or unstable [heart disease](#). The duration of the studies ranged from 8 to 12 weeks. The following table provides the change from baseline in corrected QT interval in [venlafaxine](#) extended-release relative to placebo-treated patients [5]:

Studies	Mean change from baseline in QTc interval	
Venlafaxine ER	Placebo	
Major depressive disorder (n=495)	+ 4.7 msec	- 1.9 msec
Generalized anxiety disorder (n=908)	no difference from placebo	---
Social anxiety disorder (n=1127)	+ 3.4 msec	- 1.6 msec
Panic disorder (n=1056)	+ 1.5 msec	- 0.7 msec
Key: ER = extended-release; msec = millisecond		

b) A 60-year-old woman receiving 150 mg of [venlafaxine](#) daily for depression developed QT-interval prolongation. She presented to the emergency department with a blood pressure of 180/110 mmHg in

both arms and mild dyspnea. An ECG showed sinus rhythm and a corrected QT (QTc) interval of 582 milliseconds. She was given [atenolol](#) plus [amlodipine](#) for the [hypertension](#), [venlafaxine](#) administration was stopped, and she was hospitalized for further evaluation. Her CBC, electrolytes, and [thyroid function tests](#) were all within normal limits. Prior to hospitalization, she was not on any other medications besides [venlafaxine](#) and she denied consumption of grapefruit juice or any changes in her diet. She also denied a family history of [long-QT syndrome](#) or sudden death. A 24-hour ECG recorded multifocal [premature ventricular complexes](#) and [couplets](#) and a transthoracic echocardiographic study showed mild left ventricular [concentric hypertrophy](#). Over the next several days, the QTc interval gradually decreased before stabilizing at 430 milliseconds [70].

3.3.1.A.6] Summary

a) [Hypertension](#), palpitations, and vasodilation, primarily hot flashes, have been experienced in patients on [venlafaxine](#) during clinical trials [4][5]. The corrected QT interval increased from baseline for [venlafaxine](#) extended-release treated patients compared with decreased in placebo-treated patients. The mean heart rate increase was 8.5 beats per minute in patients receiving [venlafaxine](#) at doses ranging from 200 to 375 mg/day (mean dose greater than 300 mg/day) compared with 1.7 beats per minute for placebo [4][5]. Also, a case of QT interval prolongation has been reported in a 60-year-old woman receiving [venlafaxine](#) for depression [70]. Two cases of [interstitial pneumonia](#) with [heart failure](#) have been reported following the use of [venlafaxine](#) [66].

3.3.1.A.7] Takotsubo cardiomyopathy

a) In a prospective cohort study of 110 patients with [takotsubo cardiomyopathy](#) (TTC), 6 patients were taking [venlafaxine](#) (n=5) or desvenlafaxine (n=1) at time of onset of TTC. Among patients who took [venlafaxine](#), 2 patients were prescribed relatively high doses (375 mg and 300 mg daily), 1 patient took a single overdose (2100 mg), and 2 patients took lower doses (37.5 mg and 100 mg daily). The desvenlafaxine patient took 100 mg daily. Common risk factors for TTC, being a postmenopausal female or having an antecedent stressor, were absent in 4 of the 6 cases. QT-interval prolongation occurred in all 6 patients by day 2; 1 patient developed [torsade de pointes](#) on day 6. Segmental [left ventricular dysfunction](#) was present acutely in all patients, and wall motion abnormalities subsequently recovered. The patient taking [venlafaxine](#) 37.5 mg daily continued the medication. The other patients switched to an SSRI. There were no TTC recurrences during the follow-up period of 3 to 36 weeks. The authors suggest that the increased catecholamine levels induced by [venlafaxine](#) and desvenlafaxine (a metabolite of [venlafaxine](#)) may have contributed to patients experiencing TTC [71].

3.3.1.A.8] Vasodilatation

- a) Incidence: 2% to 5.6% [4][69]
- b) During a dose-comparison trial involving 358 patients, the incidence of vasodilatation was 0% for placebo compared with 4.5%, 5.6%, and 2.3% for immediate-release [venlafaxine](#) 75, 225, and 375 mg/day, respectively [4].
- c) Vasodilation, primarily hot flashes, occurred in 3% to 4% of patients who received extended-release [venlafaxine](#) compared with 2% of patients who received placebo during clinical trials [5].

3.3.2] Dermatologic Effects

3.3.2.A] [Venlafaxine](#) Hydrochloride

3.3.2.A.1] Acquired palmoplantar [keratoderma](#)

a) A 57-year-old male smoker acquired palmoplantar [keratoderma](#) (psoriasiform) and subungual [hyperkeratosis](#) approximately 4 months after starting [venlafaxine](#) for depression. The palms and soles showed evidence of severe [hyperkeratosis](#) with an inflammatory red border. The epidermis had psoriasiform changes, and the upper dermis had superficial lymphocytic and eosinophilic infiltrate on histopathological specimens. Massive subungual [hyperkeratosis](#) with paronychia was noted on all 20 nails. Mycological cultures from skin and nails were negative. No improvement was noted after topical treatment with 10% urea, [salicylic acid](#), caryolysin, and oral retinoids. Within 4 to 5 weeks of stopping [venlafaxine](#), palm and sole [keratoderma](#) slowly resolved and dramatic improvement of the nails occurred [96].

3.3.2.A.2] [Alopecia](#)

a) A 50-year-old woman experienced hair loss while being treated for depression with [venlafaxine](#). The woman was otherwise healthy and took no other medications. The initial [venlafaxine](#) dose of 75 mg per day was raised to 150 mg/day after 2 weeks. Two weeks later she began to notice hair loss. Although the treatment relieved her depression, the woman discontinued [venlafaxine](#) after 3 months, and her hair loss stopped completely 1 month later. In another episode of depression 10 months later, she restarted [venlafaxine](#) and began noticing hair loss 10 days after achieving the dose of 150 mg/day. She discontinued [venlafaxine](#) and attained complete remission with [sertraline](#) 50 mg/day without hair loss [97].

3.3.2.A.3] Subungual [hyperkeratosis](#)

a) A 57-year-old male smoker acquired palmoplantar [keratoderma](#) (psoriasiform) and subungual [hyperkeratosis](#) approximately 4 months after starting [venlafaxine](#) for depression. The palms and soles showed evidence of severe [hyperkeratosis](#) with an inflammatory red border. The epidermis had psoriasiform changes, and the upper dermis had superficial lymphocytic and eosinophilic infiltrate on histopathological specimens. Massive subungual [hyperkeratosis](#) with paronychia was noted on all 20 nails. Mycological cultures from skin and nails were negative. No improvement was noted after topical treatment with 10% urea, [salicylic acid](#), caryolysin, and oral retinoids. Within 4 to 5 weeks of stopping [venlafaxine](#), palm and sole [keratoderma](#) slowly resolved and dramatic improvement of the nails occurred [96].

3.3.2.A.4] Sweating symptom

- a) Incidence: 6.7% to 25% [4][5]
- b) During 4- to 8-week trials of [venlafaxine](#) hydrochloride (dose ranging from 75 to 375 mg/day), the incidence of sweating in patients receiving [venlafaxine](#) (n=1033) was 12% compared with 3% in patients receiving placebo (n=609) [4].
- c) During a dose-comparison trial involving 358 patients, the incidence of sweating was 5.4% for placebo compared with 6.7%, 12.4%, and 19.3% for immediate-release [venlafaxine](#) 75, 225, and 375 mg/day, respectively [4].
- d) During clinical trials, sweating occurred in 10% to 14% of patients who received extended-release [venlafaxine](#) compared with 2% to 3% of patients who received placebo [69].

The table below provides the incidence rates of anorexia during clinical trials of extended-release [venlafaxine](#) [5]:

Studies	Incidence of Sweating
Venlafaxine ER	Placebo
Major depressive disorder (n=642)	14%
Generalized anxiety disorder (n=1936)	10%

Social anxiety disorder (n=1514)	13%
Panic disorder (n=1663)	10%
Key: ER = extended-release	

- e) At 9 and 14 weeks, diaphoresis and pruritus occurred in 2 elderly women who were receiving venlafaxine extended-release (XR) for depression. The first patient was taking venlafaxine XR 225 mg/day and noted profuse night sweats, increased daytime sweating, and generalized itching without rash. Gradual tapering of venlafaxine XR to 75 mg/day resulted in resolution of symptoms without addition of allergy medications. The second patient noted profuse, generalized sweating and itching without rash while taking venlafaxine XR 75 mg/day. Gradual discontinuation of venlafaxine XR was effective in resolving her symptoms. The medication history, physical examination, and environmental factors in the home revealed no other potential cause for these symptoms [98].
- f) Profuse sweating has been reported in 2 patients following oral venlafaxine therapy for the treatment of depression. Symptoms resolved following discontinuation of the venlafaxine [99][100]. The patient was restarted on venlafaxine therapy, 75 mg twice daily, with the addition of benztropine, 0.5 mg twice daily. The diaphoresis did not recur, and the venlafaxine was increased to 75 mg 3 times daily with no subsequent side effects.
- g) A study reported a 25% incidence of increased sweating in patients receiving venlafaxine 75 to 375 mg/day, compared with no increased sweating in patients receiving placebo [89].

3.3.3] Endocrine/Metabolic Effects

3.3.3.A] Venlafaxine Hydrochloride

3.3.3.A.1] Height / growth finding

- a) Pediatric patients, especially patients younger than 12 years, who received venlafaxine grew less than pediatric patients who received placebo. Pediatric patients (6 to 17 years of age) who received venlafaxine extended-release (n=122), on average, grew 0.3 cm compared with 1 cm for placebo-treated patients (n=132) (p=0.041), during an 8-week generalized anxiety disorder study. Pediatric patients on venlafaxine extended-release (n=146), on average, grew 0.8 cm compared with 0.7 cm for placebo-treated patients (n=147), during an 8-week major depressive disorder study. Height increases were less than expected based on data from age- and sex-matched peers, in a 6-month, open-label study [69].

3.3.3.A.2] Hot sweats

- a) A 52-year-old menopausal woman experienced hot flashes while being treated for depression with venlafaxine. The woman had been taking conjugated estrogens for 8 years, subsequent to total hysterectomy and bilateral salpingo-oophorectomy. Although she experienced hot flashes immediately after surgery, she became asymptomatic after beginning treatment with estrogens. After 2 weeks of therapy with extended-release venlafaxine 75 mg per day, the woman reported transient nausea, dry mouth, and a return of hot flashes. After 5 weeks of therapy, the hot flashes were occurring daily and were rated moderate to severe. After 7 weeks, the severity and frequency of hot flashes were reduced (mild to moderate, every 2 to 3 days). Her dose was then increased to 150 mg/day to increase the antidepressant response. The woman had 5 days of daily hot flashes, after which the frequency declined to every 2 to 3 days. Venlafaxine has been used to treat hot flashes [78].

3.3.3.A.3] Hyponatremia

- a) Summary

1j) **Hyponatremia** has been reported with the use of SSRIs and serotonin **norepinephrine** reuptake inhibitors (SNRIs) and is most often the result of the SIADH. Serum sodium levels lower than 110 mmol/L have been reported. Patients at greater risk of developing **hyponatremia** with SSRIs and SNRIs include the elderly and patients receiving diuretics or who are volume depleted. Symptoms of **hyponatremia** include headache, difficulty concentrating, **memory impairment**, confusion, weakness, and unsteadiness which may or may not lead to falls. Signs associated with more severe cases include hallucination, syncope, seizure, coma, respiratory arrest, and death. Discontinuation of **venlafaxine** therapy should be considered and appropriate medical intervention should be instituted in patients with symptomatic **hyponatremia** [4][5].

b) Literature Reports

1j) **Hyponatremia** was reported in 15 patients following therapeutic use of **venlafaxine**. The average onset of the **hyponatremia** was 9 days after initiation of **venlafaxine** therapy and the serum sodium concentrations ranged from 116 to 130 mEq/L (116 to 130 mmol/L) (normal, 135 to 145 mEq/L (135 to 145 mmol/L)) [80].

2j) A 70-year-old woman developed **hyponatremia** (125 mmol/L) while taking **venlafaxine**. **Hyponatremia** resolved with discontinuation of **venlafaxine** and fluid restriction. She had previously developed SIADH while taking **mirtazapine** [81].

3j) A 76-year-old woman developed **hyponatremia** (serum sodium level of 118 mEq/L (118 mmol/L)) following oral **venlafaxine** 75 mg daily. The **venlafaxine** was discontinued and the patient's serum sodium level returned to baseline 3 days later following fluid restriction, infusion of normal saline, and **furosemide** administration [82].

3.3.3.A.4) Serum cholesterol raised

a) Incidence: 5.3% [4][5]

b) Clinically relevant increases in **serum cholesterol** were reported in 5.3% of **venlafaxine** immediate-release treated patients compared with 0% of patients who received placebo during 12-month extension trials. Clinically relevant was defined as a final or an average on-therapy increase in **serum cholesterol** of 50 mg/dL (1.3 mmol/L) or greater from baseline and to a final value or an average value of 261 mg/dL (6.75 mmol/L) or greater. Significant increases in mean **serum cholesterol** have been reported in patients receiving **venlafaxine** immediate-release tablets (3 to 9.1 mg/dL (80 to 235 mcmmol/L)) and **venlafaxine** extended-release capsules (1 to 11.4 mg/dL (26 to 295 mcmmol/L)) during multiple clinical trials. Periodic monitoring is recommended during long-term treatment [4][5][79].

c) Treatment with extended-release **venlafaxine** was associated with increases in **serum cholesterol** concentrations during premarketing placebo-controlled trials [5]. Results are summarized below:

Trials	Duration	Mean Change in Serum Cholesterol (Venlafaxine Extended-Release)	Mean Change Cholesterol (P
Major Depressive Disorder	up to 12 weeks	+1.5 mg/dL (+39 mcmmol/L)	-7.4 mg/dL (-1
Generalized Anxiety Disorder	up to 8 weeks	+1 mg/dL (+26 mcmmol/L)	-4.9 mg/dL (-1
up to 6 months	+2.3 mg/dL (+59 mcmmol/L)	-7.7 mg/dL (-199 mcmmol/L)	
Social Anxiety Disorder	up to 12 weeks	+7.9 mg/dL (+204 mcmmol/L)	-2.9 mg/dL (-7
up to 6 months	+5.6 mg/dL (+145 mcmmol/L)	-4.2 mg/dL (-109 mcmmol/L)	

Panic Disorder

up to 12 weeks

+5.8 mg/dL (+150 mcmmol/L) -3.7 mg/dL (-9 L)

3.3.3.A.5] Serum triglycerides raised

a) Treatment with extended-release **venlafaxine** was associated with increases in fasting serum **triglyceride** concentrations during premarketing placebo-controlled trials [5]. Results are summarized below:

Trials	Duration	Mean Change in Serum Triglycerides (Venlafaxine Extended-Release)	Mean Change in Triglycerides (
Social Anxiety Disorder up to 6 months	up to 12 weeks +11.8 mg/dL (+133 mcmmol/L)	+8.2 mg/dL (+93 mcmmol/L) +1.8 mg/dL (+20 mcmmol/L)	+0.4 mg/dL (+
Panic Disorder up to 6 months	up to 12 weeks +9.3 mg/dL (+105 mcmmol/L)	+5.9 mg/dL (+67 mcmmol/L) -0.3 mg/dL (-3 mcmmol/L)	+0.9 mg/dL (+

3.3.3.A.6] Syndrome of inappropriate antidiuretic hormone secretion**a) Summary**

1) SIADH has occurred in patients who received **venlafaxine**. Patients at risk include the elderly, volume-depleted, or those taking diuretics [4][5].

b) Literature Reports

1) Approximately 8 months after starting **venlafaxine**, a 92-year-old woman developed the SIADH. From the time **venlafaxine** was started, the serum sodium gradually fell from 133 to 124 mEq/L (133 to 124 mmol/L); the antidiuretic hormone concentration was in the low-normal range; and a simultaneous **urine osmolality** of 508 milliosmoles (mOsm)/kg was high compared with a low serum osmolality of 255 mOsm/kg. **Venlafaxine** was stopped, and the serum sodium increased to the normal range within one month. Due to the temporal relationship and similar reports to other SSRIs, the SIADH was probably caused by **venlafaxine** [83].

2) A 65-year-old man developed the SIADH, possibly due to **venlafaxine** 75 mg daily added the previous week. At hospital admission, he complained of dizziness; abnormal laboratory values included a serum sodium of 114 mmol/L, serum osmolality 248 milliosmoles/liter (mOsm/L), urinary sodium excretion 239 mmol/24 hours, and **urine osmolality** of 640 mOsm/L. **Venlafaxine** was stopped, and the patient was treated with a restricted fluid intake of 1500 mL/24 hours. When the fluid restriction was stopped, the serum sodium concentration and osmolality remained normal. Medical causes for SIADH were ruled out; thus, the authors attributed the SIADH to **venlafaxine**. It is recommended that patients treated with an SSRI, who develop symptoms of weakness, lethargy, headache, anorexia, weight gain, confusion, or constipation, have serum sodium measured [84].

3.3.3.A.7] Weight loss

a) Incidence: 3% to 47% [4][5][79]

b) Adults

1J) Treatment with immediate-release [venlafaxine](#) for several weeks in adults was associated with a loss of 5% or more of body weight in 6% of patients receiving [venlafaxine](#) compared with 3% and 1% in patients receiving another antidepressant or placebo, respectively. The weight loss appeared to be dose-dependent and discontinuation for weight loss was uncommon [4].

2J) During short-term [major depressive disorder](#) trials, weight loss of 5% or more of body weight occurred in 7% and 2% of patients treated with [venlafaxine](#) extended-release and placebo, respectively, and the discontinuation rate due to weight loss was 0.1%. During 6-month, [generalized anxiety disorder](#) (GAD) studies, weight loss of 7% or more occurred in 3% of [venlafaxine](#) extended-release treated patients compared with 1% in placebo patients. The discontinuation rate due to weight loss during the GAD studies with a duration of up to 8 weeks was 0.3% for patients receiving [venlafaxine](#) extended-release. During 6-month, [social anxiety disorder](#) studies, weight loss of 7% or more occurred in 4% of [venlafaxine](#) extended-release treated patients compared with 1% in placebo patients. Additionally, 3% and 2% of patients receiving [venlafaxine](#) extended-release and placebo, respectively, sustained a loss of 7% or more of body weight during up to 12 weeks of treatment in [panic disorder](#) trials. No patients discontinued treatment due to weight loss in either the [social anxiety disorder](#) or [panic disorder](#) trials [5].

cJ) Pediatrics

1J) Results of a pooled analysis of four 8-week, double-blind, placebo-controlled, flexible-dose trials for [major depressive disorder](#) and [generalized anxiety disorder](#) involving pediatric patients (ages 6 to 17 years) indicate that a weight loss of at least 3.5% occurred in 18% of [venlafaxine](#) extended-release treated patients compared with 3.6% of placebo treated patients (p less than 0.001). On average, 0.45 kg (n=333) was lost in the [venlafaxine](#) extended-release group compared with an average weight gain of 0.77 kg (n=333) in the placebo group. Children less than 12 years old were at a greater risk for weight loss than adolescents older than 12 years, when data (the difference between observed weight gain and expected weight gain) from an open-label study were evaluated [69].

2J) Pediatric patients enrolled in a 16-week, double-blind, trial for [social anxiety disorder](#) and who received [venlafaxine](#) extended-release lost an average of 0.75 kg compared with an average gain of 0.76 kg in patients receiving placebo. A weight loss of at least 3.5% of body weight was experienced by 47% of patients receiving [venlafaxine](#) extended-release compared with 14% of patients receiving placebo (p less than 0.001) [69].

3J) Children less than 12 years old were at a greater risk for weight loss than adolescents older than 12 years, when data (the difference between observed weight gain and expected weight gain) from an open-label [major depressive disorder](#) study were evaluated [69].

3.3.4J Gastrointestinal Effects

3.3.4.AJ [Venlafaxine](#) Hydrochloride

3.3.4.A.1J Constipation

aJ) Incidence: 8% to 15% [4][5]

bJ) During 4- to 8-week trials of [venlafaxine](#) hydrochloride (dose ranging from 75 to 375 mg/day), the incidence of constipation in patients receiving [venlafaxine](#) (n=1033) was 15% compared with 7% in patients receiving placebo (n=609) [4].

c) Constipation occurred in 8% to 10% of patients who received extended-release [venlafaxine](#) compared with 3% to 5% of patients who received placebo during clinical trials [69].

The table below provides the incidence rates of constipation during clinical trials of extended-release [venlafaxine](#) [5]:

Studies	Percent of patients with constipation
Venlafaxine ER	Placebo
Major depressive disorder (n=642)	8%
Generalized anxiety disorder (n=1936)	10%
Social anxiety disorder (n=1514)	9%
Panic disorder (n=1663)	9%
Key: ER = extended-release	

3.3.4.A.2] Diarrhea

a) Incidence: 8% [4][5].

b) During 4- to 8-week trials of [venlafaxine](#) hydrochloride (dose ranging from 75 to 375 mg/day), the incidence of diarrhea in patients receiving [venlafaxine](#) (n=1033) was 8% compared with 7% in patients receiving placebo (n=609) [4].

c) Diarrhea occurred in 8% of patients who received extended-release [venlafaxine](#) (n=819) compared with 6% of patients who received placebo (n=695) during [social anxiety disorder](#) clinical trials [5].

3.3.4.A.3] Gastrointestinal hemorrhage

a) Incidence: rare [4][69]

b) In case reports and epidemiological studies, drugs which interfere with serotonin reuptake (eg, SSRIs, serotonin [norepinephrine](#) reuptake inhibitors (SNRIs)) have been associated with an increased incidence of [gastrointestinal hemorrhage](#). [Gastrointestinal hemorrhage](#) has been reported rarely (defined as occurring in fewer than 1 in 1000 patients) in the premarketing evaluation of patients receiving [venlafaxine](#) hydrochloride. Additionally, hemorrhage, including [gastrointestinal bleeding](#), has been temporally associated with [venlafaxine](#) hydrochloride in postmarketing reports, although a causal relationship has not been definitively established. Because the risk of bleeding may be increased by the concomitant use of drugs that affect coagulation (eg, NSAIDs, [aspirin](#), [warfarin](#)), use caution when these agents are coadministered with [venlafaxine](#) hydrochloride. Additionally, patients receiving concurrent [warfarin](#) therapy should be monitored when [venlafaxine](#) is started or discontinued [4][69].

3.3.4.A.4] Grinding teeth

a) A 50-year-old man with [bipolar disorder](#) experienced [bruxism](#) following a dose increase of [venlafaxine](#). He was initially prescribed [venlafaxine](#) 37.5 mg twice daily, which was increased 1 week later to 75 mg twice daily. After 5 weeks of treatment, the patient reported anxiety, tremor, insomnia, and clenching and [grinding of teeth](#) day and night. The patient also described awakening with sore jaws and teeth. [Bruxism](#) ceased within 1 to 2 days after the initiation of oral [gabapentin](#) 300 mg at night for insomnia and anxiety [85].

3.3.4.A.5] Loss of appetite

a) Incidence: 8% to 22% [4][5]

b) During 4- to 8-week trials of [venlafaxine](#) hydrochloride (dose ranging from 75 to 375 mg/day), the incidence of anorexia in patients receiving [venlafaxine](#) (n=1033) was 11% compared with 2% in patients receiving placebo (n=609) [4].

c) During a dose-comparison trial involving 358 patients, the incidence of anorexia was 2.2% for placebo compared with 14.6%, 13.5%, and 17% for immediate-release [venlafaxine](#) 75, 225, and 375 mg/day, respectively [4].

The table below provides the incidence rates of anorexia during clinical trials of extended-release [venlafaxine](#) [5]:

Studies	Percent of patients with anorexia
Venlafaxine ER	Placebo
Major depressive disorder (n=642)	8%
Generalized anxiety disorder (n=1936)	8%
Social anxiety disorder (n=1514)	17%*
Panic disorder (n=1663)	8%*

Key: ER = extended-release; * mostly described as decreased appetite and loss of appetite

The discontinuation rate for [venlafaxine](#) extended-release due to anorexia was 1% in [major depressive disorder](#) studies, 0.9% in [generalized anxiety disorder](#) studies of up to 8 weeks, 0.6% in [social anxiety disorder](#) studies of up to 12 weeks, and 0.4% in [panic disorder](#) studies of up to 12 weeks [5].

d) Pediatrics

1) The incidence of anorexia in pediatric patients (aged 6 to 17 years) during clinical trials for [generalized anxiety disorder](#) and [major depressive disorder](#) was 10% and 3% in patients who were treated with [venlafaxine](#) extended-release and placebo, respectively. None of the patients in these trials discontinued therapy due to anorexia or weight loss. During the [social anxiety disorder](#) trials in patients aged 8 to 17 years, the incidence of anorexia was 22% and 3% in patients who were treated with [venlafaxine](#) extended-release and placebo, respectively. The discontinuation rates of [venlafaxine](#) extended-release and placebo due to anorexia were 0.7% and 0%, respectively, while the discontinuation rates due to weight loss were 0.7% for both [venlafaxine](#) extended-release and placebo [5].

3.3.4.A.6] Nausea

a) Incidence: 21% to 58% [4][5]

b) During 4- to 8-week trials of [venlafaxine](#) hydrochloride (dose ranging from 75 to 375 mg/day), the incidence of nausea in patients receiving [venlafaxine](#) (n=1033) was 37% compared with 11% in patients receiving placebo (n=609) [4].

c) During a dose-comparison trial involving 358 patients, the incidence of nausea was 14.1% for placebo compared with 32.6%, 38.2%, and 58% for immediate-release [venlafaxine](#) 75, 225, and 375 mg/day, respectively. Over a 6-week period, there was evidence of adaptation to nausea with continued therapy [4].

The table below provides the incidence rates of nausea during clinical trials of extended-release [venlafaxine](#) [5]:

Studies	Percent of patients with nausea
Venlafaxine ER	Placebo
Major depressive disorder (n=642)	31%
Generalized anxiety disorder (n=1936)	35%
Social anxiety disorder (n=1514)	31%
Panic disorder (n=1663)	21%
Key: ER = extended-release	

- d) The discontinuation rate due to nausea for [venlafaxine](#) extended-release was 2% to 8% compared with 0% to less than 1% for placebo-treated patients [5].
- e) Although [venlafaxine](#) is a highly effective antidepressant, up to one-third of patients develop nausea. In many 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, [cisapride](#) administered for a few weeks reduced nausea and vomiting which allowed continued treatment with [venlafaxine](#). Other alternatives to reduce nausea include: (1) administration of [venlafaxine](#) with food, (2) administration of [venlafaxine](#) 37.5 mg twice daily for a few days, or (3) counseling patients about possible nausea with reassurance that it will decrease over time [86]. 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 [87].

3.3.4.A.7] Summary

- a) Adverse effects which commonly occurred during clinical trials of [venlafaxine](#) and [venlafaxine](#) extended-release included constipation, dry mouth, nausea, vomiting, anorexia, and diarrhea. Cases of [gastrointestinal hemorrhage](#) have been reported rarely (defined as occurring in fewer than 1 in 1000 patients) in the premarketing evaluation of patients receiving [venlafaxine](#) hydrochloride. Additionally, hemorrhage, including [gastrointestinal bleeding](#), has been associated with [venlafaxine](#) in postmarketing reports, although a causal relationship has not been definitively established [4][5].

3.3.4.A.8] Vomiting

- a) Incidence: 3% to 7.9% [4][5]
- b) During 4- to 8-week trials of [venlafaxine](#) hydrochloride (dose ranging from 75 to 375 mg/day), the incidence of vomiting in patients receiving [venlafaxine](#) (n=1033) was 6% compared with 2% in patients receiving placebo (n=609) [4].
- c) During a dose-comparison trial involving 358 patients, the incidence of vomiting was 1.1% for placebo compared with 7.9%, 3.4%, and 6.8% for immediate-release [venlafaxine](#) 75, 225, and 375 mg/day, respectively [4].

The table below provides the incidence rates of vomiting during clinical trials of extended-release [venlafaxine](#) [5]:

Studies	Percent of patients with vomiting
Venlafaxine ER	Placebo
Major depressive disorder (n=642)	4%
Generalized anxiety disorder (n=1936)	5%
Social anxiety disorder (n=1514)	3%
Key: ER = extended-release	

- d) 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 [87]. Vomiting usually occurs with higher doses and subsides with continued treatment [73][74][88][89].

3.3.4.A.9] Xerostomia

- a) Incidence: 12% to 22% [4][5]
- b) During 4- to 8-week trials of [venlafaxine](#) hydrochloride (dose ranging from 75 to 375 mg/day), the incidence of dry mouth in patients receiving [venlafaxine](#) (n=1033) was 22% compared with 11% in patients receiving placebo (n=609) [4].

c) Dry mouth occurred in 12% to 17% of patients who received extended-release [venlafaxine](#) compared with 4% to 6% of patients who received placebo during clinical trials [69].

The table below provides the incidence rates of dry mouth during clinical trials of extended-release [venlafaxine](#) [5]:

Studies	Percent of patients with dry mouth
Venlafaxine ER	Placebo
Major depressive disorder (n=642)	12%
Generalized anxiety disorder (n=1936)	16%
Social anxiety disorder (n=1514)	17%
Panic disorder (n=1663)	12%
Key: ER = extended-release	

3.3.5] Hematologic Effects

3.3.5.A] [Venlafaxine](#) Hydrochloride

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

a) Approximately 3 weeks after discontinuing mianserin therapy and 5 days after beginning [venlafaxine](#) therapy, a 70-year-old woman developed [agranulocytosis](#) (granulocyte count, 58/mcL; total WBC count, 2900). The patient completely recovered following the discontinuation of [venlafaxine](#). It was not clear as to which agent was responsible for the [agranulocytosis](#) [65].

3.3.5.A.2] [Ecchymosis](#)

a) Incidence: 1% or greater [4][5]

b) Ecchymosis has been reported frequently (defined as occurring on one or more occasions in at least 1 in 100 patients) in the premarketing evaluation of patients receiving [venlafaxine](#) hydrochloride. Because the risk of bleeding may be increased by the concomitant use of drugs that affect coagulation (eg, NSAIDs, [aspirin](#), [warfarin](#)), use caution when these agents are coadministered with [venlafaxine](#) hydrochloride. Additionally, patients receiving concurrent [warfarin](#) therapy should be monitored when [venlafaxine](#) hydrochloride is started or discontinued [4][5].

3.3.5.A.3] [Hemorrhage, Abnormal](#)

a) General Information

1) Increased risk of [gastrointestinal bleeding](#) due to interference with serotonin reuptake [4][59].

2) Bleeding events include ecchymoses, [hematomas](#), [epistaxis](#), [petechiae](#), [gastrointestinal bleeding](#), and life-threatening hemorrhages [4][59].

3) Risk may be increased by the concomitant use of drugs that affect coagulation (eg, NSAIDs, [aspirin](#), [warfarin](#)) [4][59].

b) Prevention and Management

1) Use caution when coadministering drugs that affect coagulation with [venlafaxine](#) [4][59].

2) Monitor patients receiving concurrent [warfarin](#) therapy when [venlafaxine](#) is started or discontinued [4][59].

3) Consider discontinuation of [venlafaxine](#) at least 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. As a high-dose antidepressant, [venlafaxine](#) may require discontinuation more than 2 weeks prior to surgery. Restart therapy as soon as possible when there is no longer perioperative bleeding risk [63].

4) Use of an antidepressant agent that is less likely to or does not increase the clinical risk of bleeding (eg, [bupropion](#), [mirtazapine](#)) may be considered [63].

5) Take into account the type of surgery, type of antidepressant, risk of suicide, severity of depression, risk factors for bleeding, and potential for discontinuation syndrome when determining management plan [63]

c) Adult Clinical Trials

1) [Facelift surgery](#), [CABG](#) surgery (oral route): No significant relationship between serotonergic antidepressant use and a risk of perioperative bleeding in 4 studies (review article) [63]

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) [63]

d) Adult Case Reports

1) Easy and spontaneous bruising 1 week after initiating treatment and resolving 10 days after discontinuing treatment was reported in a 19-year-old woman [64].

3.3.6] Hepatic Effects

3.3.6.A] [Venlafaxine](#) Hydrochloride

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

a) [Cholestatic hepatitis](#) was reported in a 39-year-old white woman who was treated with [venlafaxine](#) for depression. She had no history of chronic or metabolic liver disease, [blood transfusion](#), or alcohol consumption. Six years after starting treatment, the [venlafaxine](#) dose was increased from 75 to 150 mg/day. Approximately 3 months after the dose increase, she developed a transient episode of [acute hepatitis](#). Liver biopsy showed centrilobular accentuated [cholestatic hepatitis](#). Her medications, including mizolastine which was started less than a month earlier for allergic rhinoconjunctivitis, were discontinued and her symptoms rapidly improved. Two months following discontinuation, [venlafaxine](#) 75 mg/day was restarted and was well tolerated. Approximately 2.5 years after restarting treatment, the [venlafaxine](#) dose was increased stepwise to 300 mg/day for severe depression. Two months after the dose increase, the patient presented to the hospital with severe nausea, icterus, vomiting, and [pruritus](#); AST was 1033 units/L, [ALT](#) was 2063 units/L, [alkaline phosphatase](#) was 274 units/L, gamma-glutamyltransferase was 284 units/L, and [bilirubin](#) was 4.6 mg/dL (79 mcmol/L). Viral and [autoimmune hepatitis](#) were excluded. Liver biopsy showed [cholestatic hepatitis](#) predominantly involving zone 3 of hepatic acini and a mixed portal inflammatory infiltrate with eosinophils. The patient was discharged 10 days after discontinuing [venlafaxine](#) and was readmitted 1 week after discharge with persistent nausea and vomiting and elevated liver function tests. She received [methylprednisolone](#) 50 mg/day for 7 days followed by gradual tapering. Within

4 days, liver function tests improved to near normal levels, and the patient was asymptomatic at discharge the next day [90].

b) A 78-year-old man with a past history of [Parkinson disease](#) and a [major depression](#) episode developed icteric [acute hepatitis](#) after taking [venlafaxine](#) for almost 2 months. Liver function returned to normal after [venlafaxine](#) therapy was progressively discontinued [91].

c) [Venlafaxine](#) 150 mg/day for 6 months was associated with [acute hepatitis](#) in a 44-year-old woman. Liver function tests (LFTs) were normal before [venlafaxine](#) was started. Due to severe asthenia, LFTs were repeated with the following results: ALT 1082 units/L and AST 661 units/L. [Serologic tests](#) for [hepatitis](#) were negative, and abdominal [ultrasonography](#) was normal; however, a liver biopsy was consistent with drug-induced [hepatotoxicity](#). Four months after [venlafaxine](#) was stopped, LFTs returned to normal. This patient received lormetazepam and [trazodone](#) before [venlafaxine](#) was initiated; these medications were continued after [venlafaxine](#) was stopped [92].

3.3.8] Musculoskeletal Effects

3.3.8.A] [Venlafaxine](#) Hydrochloride

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

a) A 43-year-old man with [idiopathic Parkinson disease](#) and [bronchiectasis](#) developed [serotonin syndrome](#) with resulting [rhabdomyolysis](#) and [acute renal failure](#) 2 weeks after initiating [venlafaxine](#) for depression. Other medications the patient was taking included [carbidopa](#) 25 mg/[levodopa](#) 100 mg 3 times daily, [amantadine](#) 100 mg twice a day, [benzhexol](#) 2 mg daily, and [ropinirole](#) 0.5 mg 3 times daily. His medical history included probable [neuroleptic malignant syndrome](#) 6 months earlier after a trial of a phenothiazine for agitation and restlessness. The patient presented with fever (41.2 degrees C), [dysphagia](#), and agitated [delirium](#), and he had become progressively drowsy over the previous 2 days. On physical examination, the patient had [high blood pressure](#) (135/90 mmHg), [tachycardia](#) (heart rate of 120 beats/minute), diaphoresis, flushing, dilated pupils, hypertonic muscles, and sustained clonus. No other recent medication changes had been made other than the addition of [venlafaxine](#). On admission, laboratory results revealed [metabolic acidosis](#), a serum [creatinine](#) level of 205 mcmol/L, an AST level of 358 units/L, a CPK level of 3600 international units/L, an INR of 1.5, and myoglobinuria. Shortly after admission, the patient developed hypotension, went into shock, and was transferred to the ICU for supportive care where he received 3 inotropic agents and mechanical ventilation. [Venlafaxine](#) was stopped and [midazolam](#) and broad spectrum antibiotics were started. The diagnoses of [rhabdomyolysis](#) and [acute renal failure](#) were made on day 3 when the CPK level peaked at 170,800 international units/L, urine output dropped, and serum [creatinine](#) increased. With regular [hemodialysis](#), normalization of renal function and CPK occurred in 2 weeks. The patient made a slow recovery that was complicated by multiple episodes of [pneumonia](#) requiring ventilatory support. He was discharged from the ICU on day 96. The patient was determined to have experienced [serotonin syndrome](#) related to [venlafaxine](#) therapy, although considerable weight was given to [neuroleptic malignant syndrome](#) as the possible cause of the [rhabdomyolysis](#) and [renal failure](#) [101].

b) A 38-year-old man developed [rhabdomyolysis](#) after ingesting [venlafaxine](#) and [lamotrigine](#) [102].

3.3.9] Neurologic Effects

3.3.9.A] [Venlafaxine](#) Hydrochloride

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

a) Adult Case Report

1J) A 69-year-old man with mild [dementia](#), [hypertension](#), and [diabetes mellitus](#) developed moderate [akathisia](#) within 3 months of [venlafaxine](#) extended-release 150 mg initiation to treat depression. Maintenance therapies included [metoprolol](#), [glipizide](#), [metformin](#), [aspirin](#), and [divalproex](#) sodium. The patient had residual [hemiparesis](#) on his right side associated with a [stroke](#) suffered 5 years before. At presentation, the patient had an 8- and 2-week history of progressive restlessness and agitation, respectively. Hyperkinetic movements in his extremities ceased during sleep; no tremors or other parkinsonian features were noted. [Akathisia](#) symptoms resolved within 3 days of [venlafaxine](#) discontinuation, with the patient's Barnes [Akathisia](#) Rating Scale score dropping from 6 (out of a possible 9) to 1 [76].

3.3.9.A.2] Asthenia

aJ) Incidence: 8% to 19% [4][5]

bJ) Immediate-Release

1J) During 4- to 8-week trials of [venlafaxine](#) hydrochloride (dose ranging from 75 to 375 mg/day), the incidence of asthenia in patients receiving [venlafaxine](#) (n=1033) was 12% compared with 6% in patients receiving placebo (n=609) [4].

2J) During a dose-comparison trial involving 358 patients, the incidence of asthenia was 3.3% for placebo compared with 16.9%, 14.6%, and 14.8% for immediate-release [venlafaxine](#) 75, 225, and 375 mg/day, respectively [4].

cJ) Extended-Release

1J) Asthenia led to discontinuation in 1% to 3% of patients who received extended release [venlafaxine](#) and 0% to less than 1% of patients who received placebo during clinical trials. The table below provides the incidence rates of asthenia during clinical trials of extended-release [venlafaxine](#) [5]:

Studies	Percent of patients with asthenia
Venlafaxine ER	Placebo
Major depressive disorder (n=642)	8%
Generalized anxiety disorder (n=1936)	12%
Social anxiety disorder (n=1514)	19%
Panic disorder (n=1663)	10%
Key: ER = extended-release	

3.3.9.A.3] Dizziness

aJ) Incidence: 11% to 23.9% [4][5]

bJ) Immediate-Release

1J) Dizziness is a relatively common side effect with [venlafaxine](#), usually occurring at higher doses. Adaptation to dizziness was apparent over a 6-week period of continued therapy [4] [73][74].

2J) During 4- to 8-week trials of [venlafaxine](#) hydrochloride (dose ranging from 75 to 375 mg/day), the incidence of dizziness in patients receiving [venlafaxine](#) (n=1033) was 19% compared with 7% in patients receiving placebo (n=609) [4].

3j) During a dose-comparison trial involving 358 patients, the incidence of dizziness was 4.3% for placebo compared with 19.1%, 22.5%, and 23.9% for immediate-release [venlafaxine](#) 75, 225, and 375 mg/day, respectively [4].

c) Extended-Release

1j) The table below provides the incidence rates of dizziness associated with extended-release [venlafaxine](#) during placebo-controlled clinical trials [5]:

Studies	Percent of patients with dizziness
Venlafaxine ER	Placebo
Major depressive disorder (n=642)	20%
Generalized anxiety disorder (n=1936)	16%
Social anxiety disorder (n=1514)	16%
Panic disorder (n=1663)	11%
Key: ER = extended-release	

3.3.9.A.4] Dream disorder

a) Incidence: 3% to 7% [4][5]

b) During 4- to 8-week trials of [venlafaxine](#) hydrochloride (dose ranging from 75 to 375 mg/day), the incidence of abnormal dreams in patients receiving [venlafaxine](#) (n=1033) was 4% compared with 3% in patients receiving placebo (n=609) [4].

c) The table below provides the incidence rates of abnormal dreams, primarily described as "vivid dreams," "nightmares," and "increased dreaming," during clinical trials of extended-release [venlafaxine](#) [5]:

Studies	Percent of patients with abnormal dreams	
Venlafaxine ER	Placebo	
Major depressive disorder (n=642)	7%	2%
Generalized anxiety disorder (n=1936)	3%	2%
Social anxiety disorder (n=1514)	3%	less than 1%
Key: ER = extended-release		

3.3.9.A.5] Headache

a) Incidence: 25% to 38% [4][5]

b) During 4- to 8-week trials of [venlafaxine](#) hydrochloride (dose ranging from 75 to 375 mg/day), the incidence of headache in patients receiving [venlafaxine](#) (n=1033) was 25% compared with 24% in patients receiving placebo (n=609) [4].

c) In short-term clinical trials involving patients with [social anxiety disorder](#) (n=1514), 38% of extended-release [venlafaxine](#) treated patients and 34% of placebo-treated patients experienced headache [5].

d) Headache and fatigue are frequently reported side effects and have occurred with higher single doses of [venlafaxine](#); these effects may be due to its serotonergic activity [73][74].

3.3.9.A.6] Insomnia

a) Incidence: 14% to 24% [4][69]

b) Immediate-Release

1J) During 4- to 8-week trials of [venlafaxine](#) hydrochloride (dose ranging from 75 to 375 mg/day), the incidence of insomnia in patients receiving [venlafaxine](#) (n=1033) was 18% compared with 10% in patients receiving placebo (n=609). Insomnia led to drug discontinuation in 3% of patients receiving [venlafaxine](#) during phase 2 and phase 3 depression studies [4].

2J) During a dose-comparison trial involving 358 patients, the incidence of insomnia was 9.8% for placebo compared with 22.5%, 20.2%, and 13.6% for immediate-release [venlafaxine](#) 75, 225, and 375 mg/day, respectively [4].

cJ) Extended-Release

1J) The table below provides the incidence rates of insomnia during clinical trials of extended-release [venlafaxine](#) [5]:

Studies	Percent of patients with insomnia
Venlafaxine ER	Placebo
Major depressive disorder (n=642)	17%
Generalized anxiety disorder (n=1936)	15%
Social anxiety disorder (n=1514)	24%
Panic disorder (n=1663)	17%

Key: ER = extended-release

The discontinuation rates due to insomnia were 1% to 3% of patients on extended-release [venlafaxine](#) compared with less than 1% of patients on placebo during clinical trials [5].

3.3.9.A.7] Paresthesia

aJ) Adult Case Reports

1J) A 32-year-old man with a history of [major depressive disorder](#) developed paresthesias with use of [venlafaxine](#) extended-release 150 mg/day. Following dose titration over 2 weeks from 37.5 mg/day to 150 mg/day, tingling, numbness, and itching began in both arms and spread to his left leg. No rash or discoloration was seen in the affected areas, and the patient denied illicit drug use. Symptoms resolved 3 to 5 days after the dose was reduced to 75 mg/day but reemerged upon rechallenge at the 150 mg/day dose. The dose was reduced again and the paresthesias did not return for the remaining 8 months of [venlafaxine](#) extended-release treatment at a reduced 75 mg/day dose [77].

3.3.9.A.8] Restless legs syndrome

aJ) 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) [72].

3.3.9.A.9] Seizure

aJ) Incidence: 0.3% [4][5]

b))General Information

1)) Seizures have occurred when [venlafaxine](#) and MAOI therapy were started or stopped within close proximity of each other (MAOI started after a recent discontinuation of [venlafaxine](#) or [venlafaxine](#) started after a recent discontinuation of an MAOI) [4][5].

c)) Prevention and Management

1)) Use cautiously in patients with a history of seizures [4][5].

2)) Discontinue if a patient experiences a seizure [4][5].

d)) Adult Clinical Trials

1)) Depression (oral route): 0.3% patients receiving immediate-release [venlafaxine](#) (n=3082); extended-release [venlafaxine](#), 1 seizure occurred out of a total of 3906 patients [4][5].

2)) Depression (oral route): A significant increase in the risk of [epilepsy](#)/seizure was reported with [venlafaxine](#) (more than 2.8 times higher) when compared with periods of no treatment in the first 5 years of follow-up [75].

3.3.9.A.10) Somnolence

a)) Incidence: 14% to 26% [4][5]

b)) During 4- to 8-week trials of [venlafaxine](#) hydrochloride (dose ranging from 75 to 375 mg/day), the incidence of somnolence in patients receiving [venlafaxine](#) (n=1033) was 23% compared with 9% in patients receiving placebo (n=609) [4].

c)) During a dose-comparison trial involving 358 patients, the incidence of somnolence was 4.3% for placebo compared with 16.9%, 18%, and 26.1% for immediate-release [venlafaxine](#) 75, 225, and 375 mg/day, respectively [4].

d)) The table below provides the incidence rates of somnolence during clinical trials of extended-release [venlafaxine](#) [5]:

Studies	Percent of patients with somnolence
Venlafaxine ER	Placebo
Major depressive disorder (n=642)	17%
Generalized anxiety disorder (n=1936)	14%
Social anxiety disorder (n=1514)	20%
Panic disorder (n=1663)	12%
Key: ER = extended-release	

e)) The discontinuation rates due to somnolence were 0% to 3% in patients who received extended-release [venlafaxine](#) compared with 0% to less than 1% of patients who received placebo during clinical trials [5].

3.3.9.A.11) Summary

a)) Asthenia, dizziness, headache, insomnia, drowsiness, tremor, and abnormal dreams have commonly been experienced in patients who received [venlafaxine](#) during clinical trials [4][5]. Serious side effects that have occurred during the use of [venlafaxine](#) include seizures and [serotonin syndrome](#). Features resembling [neuroleptic malignant syndrome](#) have occurred when [venlafaxine](#) and MAOI therapy were started or stopped within close proximity of each other (MAOI started after a recent discontinuation of [venlafaxine](#) or [venlafaxine](#) started after a recent discontinuation of an MAOI) [4][5].

3.3.9.A.12] Tremor

- a) Incidence: 1.1% to 10.2% [4][69]
- b) During 4- to 8-week trials of [venlafaxine](#) hydrochloride (dose ranging from 75 to 375 mg/day), the incidence of tremor in patients receiving [venlafaxine](#) (n=1033) was 5% compared with 1% in patients receiving placebo (n=609) [4].
- c) During a dose-comparison trial involving 358 patients, the incidence of tremor was 0% for placebo compared with 1.1%, 2.2%, and 10.2% for immediate-release [venlafaxine](#) 75, 225, and 375 mg/day, respectively [4].
- d) The table below provides the incidence rates of tremor during clinical trials of extended-release [venlafaxine](#) [5]:

Studies	Percent of patients with tremor	
Venlafaxine ER	Placebo	
Major depressive disorder (n=642)	5%	2%
Generalized anxiety disorder (n=1936)	4%	less than 1%
Social anxiety disorder (n=1514)	2%	2%
Panic disorder (n=1663)	5%	2%
Key: ER = extended-release		

3.3.10] Ophthalmic Effects**3.3.10.A] [Venlafaxine](#) Hydrochloride****3.3.10.A.1] [Angle-closure glaucoma](#)****a) General Information**

- 1) Pupillary dilation occurs following use of many antidepressant drugs and may trigger an angle closure attack in patients with anatomically narrow angles who do not have a patent [iridectomy](#) [59].

b) Adult Case Report

- 1) Bilateral [acute angle closure glaucoma](#) was reported in a 45-year-old woman with [bipolar disorder](#), taking [venlafaxine](#) extended-release 75 mg/day, [chlorpromazine](#) (up to 150 mg daily), sodium [valproate](#) (1500 mg/day), and slow-release [lithium](#) (450 mg/day). After 3 days of [venlafaxine](#) treatment, she manifested retro-orbital pain, nausea and vomiting, and subsequent swelling and drooping of the left upper eyelid with a dilated and fixed pupil. She was treated with [timolol](#), IV [mannitol](#), topical [apraclonidine](#) hydrochloride, [latanoprost](#), and [pilocarpine](#) eye drops. Laser [iridotomy](#) was done repeatedly until successful, and [venlafaxine](#) was discontinued. After 8 days of [venlafaxine](#) treatment, she developed similar symptoms in the right eye. After 8 weeks, her intraocular pressures were normal without ophthalmic treatment [93].

3.3.10.A.2] Blurred vision

- a) Incidence: 4% to 6% [5][4]
- b) Adult Clinical Trials

- 1) Major depressive disorder (oral route): 6% vs 2% with placebo [4].

2j) The table below provides the incidence rates of abnormal vision during clinical trials of extended-release [venlafaxine](#) [5]:

Studies	Venlafaxine ER	Placebo
Major depressive disorder (n=642)	4%*	less than
Generalized anxiety disorder (n=1936)	5%*	less than
Social anxiety disorder (n=1514)	4%**	2%
Key: ER = extended-release; * mostly described as blurred vision and difficulty focusing eyes; ** mostly described as blurred vision		

3.3.10.A.3] [Disorder of accommodation](#)

a) Incidence: 5.6% to 9.1% [4]

b) Adult Clinical Trials

1) [Major depressive disorder](#) (oral route): 9.1%, 7.9%, and 5.6% for immediate-release [venlafaxine](#) 75, 225, and 375 mg/day, respectively, vs 0% with placebo[4]

3.3.12] Psychiatric Effects

3.3.12.A] [Venlafaxine Hydrochloride](#)

3.3.12.A.1] Aggressive behavior

a) Pediatric Clinical Trials

1) Various indications (Off-labels usages; oral route): Significantly increased risk of aggressive behavior by 179% with antidepressant use ([duloxetine](#), [fluoxetine](#), [paroxetine](#), [sertraline](#), or [venlafaxine](#)) in a systematic review and meta-analysis of clinical study reports (11 trials in 1231 children and adolescents) [104].

3.3.12.A.2] Anxiety

a) Incidence: 5% to 11.2% [4][5]

b) During 4- to 8-week trials of [venlafaxine](#) hydrochloride (dose ranging from 75 to 375 mg/day), the incidence of anxiety in patients receiving [venlafaxine](#) (n=1033) was 6% compared with 3% in patients receiving placebo (n=609). Anxiety led to drug discontinuation in 2% of patients receiving [venlafaxine](#) during phase 2 and phase 3 depression studies [4].

c) During a dose-comparison trial involving 358 patients, the incidence of anxiety was 4.3% for placebo compared with 11.2%, 4.5%, and 2.3% for immediate-release [venlafaxine](#) 75, 225, and 375 mg/day, respectively [4].

d) Anxiety was experienced in 5% of extended-release venlafaxine-treated patients and 4% of placebo-treated patients during clinical trials in patients with [social anxiety disorder](#) (n=1514) [5].

3.3.12.A.3] Depression, Exacerbation

a) Incidence: rare [4][5]

b) Adult and pediatric patients being treated with antidepressants for [major depressive disorder](#) who experience symptoms of anxiety, agitation, panic attacks, insomnia, irritability, hostility, aggressiveness, impulsivity, [akathisia](#) (psychomotor restlessness), [hypomania](#), mania, or other unusual behavior changes may be at risk of worsening of their depression, especially during early

antidepressant treatment and when the dose is adjusted. Symptoms such as these indicate the need for very close monitoring and possible changes in the medication. This same concern applies to treating patients with other psychiatric and nonpsychiatric disorders. If these symptoms are observed, therapy should be reevaluated and it may be necessary to discontinue medications when symptoms are severe, sudden in onset, or were not part of the patient's initial symptoms. Patients and their caregivers should be provided with the Medication Guide that is available for this drug [4][5][109].

3.3.12.A.4] Feeling nervous

a) Incidence: 4% to 21.3% [4][5]

b) During 4- to 8-week trials of [venlafaxine](#) hydrochloride (dose ranging from 75 to 375 mg/day), the incidence of nervousness in patients receiving [venlafaxine](#) (n=1033) was 13% compared with 6% in patients receiving placebo (n=609). Nervousness led to drug discontinuation in 2% of patients receiving [venlafaxine](#) during phase 2 and phase 3 depression studies [4].

c) During a dose-comparison trial involving 358 patients, the incidence of anxiety was 4.3% for placebo compared with 21.3%, 13.5%, and 12.5% for immediate-release [venlafaxine](#) 75, 225, and 375 mg/day, respectively [4].

d) The table below provides the incidence rates of nervousness during clinical trials of extended-release [venlafaxine](#) [5]:

Studies	Percent of patients with nervousness
Venlafaxine ER	Placebo
Major depressive disorder (n=642)	10%
Generalized anxiety disorder (n=1936)	6%
Social anxiety disorder (n=1514)	10%
Panic Disorder (n=1663)	4%

Key: ER = extended-release

The discontinuation rates due to nervousness were 0.1% to 3% of patients who received extended-release [venlafaxine](#) during clinical trials [5].

3.3.12.A.5] Hallucinations

a) In a case report, a 17-year-old male exhibited visual and tactile hallucinations following a dose increase of [venlafaxine](#) for the treatment of anxiety, depression, and comorbid migraine headaches. The patient had a family history of anxiety (maternal) and a personal history of DSM-IV moderate, [single-episode major depressive disorder](#), [social phobia](#), and [generalized anxiety disorder](#). He also had a history of drug reactions, which included [delirium](#) following [anesthesia](#), and visual and tactile hallucinations following [promethazine](#) administration. His cognition and other psychiatric systems were normal. Upon presentation, he had a 6- to 7-month escalation of depression and anxiety, and several months of worsening migraine headaches which coincided with his anxiety. Concomitant drugs included [lamotrigine](#), [eletriptan](#) (once a week), [hydrocodone/acetaminophen](#) (maximum once daily), [ibuprofen](#), and [diphenhydramine](#) (once nightly). Despite a 2-week treatment with immediate-release [venlafaxine](#) 37.5 mg once daily, the patient's symptoms persisted and [venlafaxine](#) was increased to 37.5 mg twice daily. The following day, after the morning dose, he experienced visual and tactile hallucinations of crawling bugs and became disoriented 1 hour later. The patient's symptoms of disorientation and hallucinations were consistent with [delirium](#). [Venlafaxine](#) treatment was suspended until the next morning. On the second day, the patient was instructed to take an additional one-half tablet in the evening. The following day, after the morning dose, the patient again experienced visual and tactile hallucinations and within 30 to 60 minutes became extremely disoriented and was unable to recognize his family. Upon admission to the emergency department, the patient's symptoms resolved

overnight 16 to 20 hours following his last [venlafaxine](#) dose. The patient opted to permanently discontinue antidepressant therapy and his anxiety improved with [cognitive-behavioral therapy](#) [105].

3.3.12.A.6] Hypomania

a) During phase 2 and phase 3 trials with immediate-release [venlafaxine](#), mania or [hypomania](#) occurred in 0.5% of venlafaxine-treated patients. During [major depressive disorder](#) trials, mania or [hypomania](#) occurred in 0.3% of patients receiving [venlafaxine](#) extended-release compared with 0% of placebo-treated patients. The incidence rates of mania or [hypomania](#) during [generalized anxiety disorder](#) studies was 0% and 0.2% for [venlafaxine](#) extended-release and placebo, respectively, while the rates reported during [social anxiety disorder](#) trials were 0.2% and 0%, respectively. During [panic disorder](#) trials, the incidence of mania or [hypomania](#) was 0.1% and 0% in patients receiving [venlafaxine](#) extended-release and placebo, respectively. [Venlafaxine](#) should be used cautiously in patients with a history of mania [4][5].

b) Two women with [bipolar affective disorder](#) developed [hypomania](#) after starting [venlafaxine](#). The first patient had been unresponsive to several different antidepressants during a 2-year period of depression. [Venlafaxine](#) 75 mg titrated to 225 mg daily resulted in [hypomania](#) within 12 days; [hypomania](#) was difficult to control despite discontinuation of [venlafaxine](#). After beginning [venlafaxine](#) 75 mg titrated to 150 mg, the second patient became hypomanic in 8 weeks. [Hypomania](#) resolved 1 week after stopping [venlafaxine](#). Over 20 months, 5 cases of mania associated with [venlafaxine](#) were reported to the United Kingdom's Committee on Safety of Medicines. Based on these reports, the authors recommend cautious use of [venlafaxine](#) in patients with [bipolar disorder](#) [110].

3.3.12.A.7] Mania

a) During phase 2 and phase 3 trials with immediate-release [venlafaxine](#), mania or [hypomania](#) occurred in 0.5% of venlafaxine-treated patients. During [major depressive disorder](#) trials, mania or [hypomania](#) occurred in 0.3% of patients receiving [venlafaxine](#) extended-release compared with 0% of placebo-treated patients. The incidence rates of mania or [hypomania](#) during [generalized anxiety disorder](#) studies was 0% and 0.2% for [venlafaxine](#) extended-release and placebo, respectively, while the rates reported during [social anxiety disorder](#) trials were 0.2% and 0%, respectively. During [panic disorder](#) trials, the incidence of mania or [hypomania](#) was 0.1% and 0% in patients receiving [venlafaxine](#) extended-release and placebo, respectively. [Venlafaxine](#) should be used cautiously in patients with a history of mania [4][5].

b) A 17-year-old female diagnosed with severe [major depressive disorder](#) per DSM-IV criteria experienced venlafaxine-induced mania. She had no past or family history of psychiatric illness. She started [venlafaxine](#) 37.5 mg/day, which was then gradually increased to 150 mg/day over a 2-week period. Four weeks into [venlafaxine](#) treatment, she became irritable, showed pervasive elated moods, increased energy levels, increased speech output, decreased need for sleep, increased goal-directed activity, racing thoughts, expansive thoughts, disruptive and disinhibited behavior which warranted hospital admission, and she met DSM-IV criteria for mania. [Venlafaxine](#) was discontinued but no improvement was seen over the next 4 days. Thus, [risperidone](#) 1 mg/day and [valproate](#) 750 mg/day (subsequently increased to 1500 mg/day) were initiated. The patient reached a euthymic state over the next 8 weeks. [Risperidone](#) was discontinued over the next 4 weeks and the patient remained euthymic during the last 6 months of [valproate](#) treatment. Since the patient had no risk factors for bipolarity and the switch to mania occurred within 4 weeks of [venlafaxine](#) treatment, the authors suspected venlafaxine-induced mania [106].

c) Three patients with no history of mania or [hypomania](#) developed mania when they were treated for depression with [venlafaxine](#) in doses of 100 to 237.5 mg per day for 1 to 3 months [107].

d) A 63-year-old man with [bipolar disorder](#) developed mania 6 days after [venlafaxine](#) was increased to 75 mg twice daily. He was receiving [divalproex](#) sodium 500 mg 3 times daily and [nefazodone](#) but depressive symptoms had not improved after 8 months of treatment with [nefazodone](#). [Venlafaxine](#) was initiated with titration to 75 mg twice daily over 3 weeks. Behavioral symptoms included verbal agitation, hyperactivity, grandiose ideas, thoughts of persecution, irritability, lack of trust, and inappropriate sexual behavior. Treatment consisted of [fluphenazine](#) 10 mg at bedtime and an increase in the [divalproex](#) sodium dose. Two weeks after stopping [venlafaxine](#), manic symptoms resolved but mild psychotic symptoms persisted for 8 weeks. This patient had been hospitalized several times for [manic behavior](#), and this episode may have been related to the natural progression of the [bipolar disorder](#). However, the close temporal relationship to initiation and discontinuation of [venlafaxine](#) suggests that [venlafaxine](#) may have caused or contributed to development of this [manic episode](#) [108].

3.3.12.A.8] [Paranoid delusion](#)

a) [Paranoid delusion](#) developed in an 85-year-old Caucasian man following administration of [venlafaxine](#) for depression. Seventy-two hours after an augmentation in the patient's [venlafaxine](#) dose from 75 mg daily to 150 mg daily for increasing depression, he began having [paranoid ideations](#) of being poisoned and abused. The paranoia continued despite a reduction in the dose to 75 mg/day. [Venlafaxine](#) was withdrawn and symptoms resolved within 48 hours. Treatment with [venlafaxine](#) was reinitiated a week later and paranoia returned within 48 hours. These symptoms resolved again with the withdrawal of the drug. [Sertraline](#) therapy was initiated and no further symptoms of paranoia were observed (Iraqi, 2003).

3.3.12.A.9] [Suicidal thoughts](#)

a) General Information

1) 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 [4][5]:

2) Most events were reported within the first 6 months after start of therapy [103].

b) Prevention and Management

1) Adult and pediatric patients being treated with antidepressants for [major depressive disorder](#) who experience symptoms of anxiety, agitation, panic attacks, insomnia, irritability, hostility, aggressiveness, impulsivity, [akathisia](#) (psychomotor restlessness), [hypomania](#), mania, or other unusual behavior changes may be at risk of [suicidal ideation](#) and behavior (suicidality), especially during early antidepressant treatment and when the dose is adjusted. Symptoms such as these indicate the need for very close monitoring and possible changes in the medication. This same concern applies to treating patients with other psychiatric and nonpsychiatric disorders. If these symptoms are observed, therapy should be reevaluated and it may be necessary to discontinue medications when symptoms are severe, sudden in onset, or were not part of the patient's initial symptoms. Patients and their caregivers should be provided with the Medication Guide that is available for this drug [4][5].

c) Adult Clinical Trials

1) Various indications (oral route): Suicide attempts, 5.87/1000 person-years with [venlafaxine](#) (n=35,732; 18,900 person-years) vs 5.14/1000 person-years with no treatment (n=30,321; 16,528 person-years) in a population-based cohort study consisting of 287,543 adults receiving antidepressant therapy over a 9-year period [103].

d) Pediatric Clinical Trials

1) Various indications (Off-label usages; oral route): Significantly increased risk of suicidality by 139% and suicide events by 124% with antidepressant use ([duloxetine](#), [fluoxetine](#), [paroxetine](#), [sertraline](#), or [venlafaxine](#)) in a systematic review and meta-analysis of clinical study reports (11 trials in 1231 children and adolescents) [104].

3.3.12.A.10] Suicide**a) General Information**

1) Most events were reported within the first 6 months after start of therapy [103].

b) Adult Clinical Trials

1) Various indications (oral route): Suicide, 0.79/1000 person-years with [venlafaxine](#) (n=35,732; 18,900 person-years) vs 0.73/1000 person-years with no treatment (n=30,321; 16,528 person-years) in a population-based cohort study consisting of 287,543 adults receiving antidepressant therapy over a 9-year period; suicide attempts, 5.87/1000 person-years vs 5.14/1000 person-years [103].

c) Pediatric Clinical Trials

1) Various indications (Off-label usages; 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) [104].

3.3.12.A.11] Summary

a) Anxiety, mania/[hypomania](#), nervousness, and [suicidal ideation](#)/worsening of depression (rare) have been experienced with [venlafaxine](#). Anxiety, nervousness, and insomnia led to discontinuation of [venlafaxine](#) during clinical trials. Adult and pediatric patients being treated with antidepressants for [major depressive disorder](#) who experience symptoms of anxiety, agitation, panic attacks, insomnia, irritability, hostility, aggressiveness, impulsivity, [akathisia](#) (psychomotor restlessness), [hypomania](#), mania, or other unusual behavior changes may be at risk of worsening of their depression and/or suicidality, especially during early antidepressant treatment and when the dose is adjusted. Symptoms such as these indicate the need for very close monitoring and possible changes in the medication [4]. Two women with [bipolar affective disorder](#) developed [hypomania](#) after starting [venlafaxine](#) [110].

3.3.13] Renal Effects**3.3.13.A] Venlafaxine Hydrochloride****3.3.13.A.1] Difficulty passing urine**

a) Incidence: 2% [4]

b) During 4- to 8-week trials of [venlafaxine](#) hydrochloride (dose ranging from 75 to 375 mg/day), the incidence of impaired urination in patients receiving [venlafaxine](#) (n=1033) was 2% compared with less than 1% in patients receiving placebo (n=609) [4].

3.3.13.A.2] Finding of frequency of urination

- a) Incidence: 3% [4]
- b) During 4- to 8-week trials of [venlafaxine](#) hydrochloride (dose ranging from 75 to 375 mg/day), the incidence of urinary frequency in patients receiving [venlafaxine](#) (n=1033) was 3% compared with 2% in patients receiving placebo (n=609) [4].

3.3.14] Reproductive Effects

3.3.14.A] [Venlafaxine](#) Hydrochloride

3.3.14.A.1] Abnormal ejaculation

- a) Incidence: 2.2% to 19% [4][5]
- b) During 4- to 8-week trials of [venlafaxine](#) hydrochloride (dose ranging from 75 to 375 mg/day), the incidence of abnormal ejaculation/orgasm in male patients receiving [venlafaxine](#) was 12% compared with less than 1% in patients receiving placebo [4].
- c) During a dose-comparison trial involving 358 patients, the incidence of abnormal ejaculation/orgasm was 0% for placebo compared with 4.5%, 2.2%, and 12.5% for immediate-release [venlafaxine](#) 75, 225, and 375 mg/day, respectively [4].
- d) The table below provides the incidence rates of abnormal ejaculation in males on [venlafaxine](#) extended-release or placebo during clinical trials [5]:

Studies	Percent of males with abnormal ejaculation	
Venlafaxine ER	Placebo	
Major depressive disorder *	16%	less than 1%
Generalized anxiety disorder (n=745) **	11%	less than 1%
Social anxiety disorder (n=811) **	19%	less than 1%
Panic disorder (n=573) ***	8%	less than 1%
Key: ER = extended-release; * = mostly delayed ejaculation; ** = includes delayed ejaculation and anorgasmia ; *** = includes delayed or retarded ejaculation and anorgasmia		

3.3.14.A.2] [Erectile dysfunction](#)

- a) Incidence: 2.1% to 6% [4][5]
- b) During 4- to 8-week trials of [venlafaxine](#) hydrochloride (dose ranging from 75 to 375 mg/day), the incidence of impotence in male patients receiving [venlafaxine](#) was 6% compared with less than 1% in patients receiving placebo [4].
- c) During a dose-comparison trial involving 219 male patients, the incidence of impotence was 0% for placebo compared with 5.8%, 2.1%, and 3.6% for immediate-release [venlafaxine](#) 75, 225, and 375 mg/day, respectively [4].
- d) The table below provides the incidence rates of [impotence in males](#) on [venlafaxine](#) extended-release or placebo during clinical trials [5]:

Studies	Percent of males with impotence
---------	---------------------------------

Venlafaxine ER	Placebo	
Major depressive disorder	4%	less than 1%
Generalized anxiety disorder (n=745)	5%	less than 1%
Social anxiety disorder (n=811)	6%	less than 1%
Panic disorder (n=573)	4%	less than 1%
Key: ER = extended-release		

3.3.14.A.3] Orgasm disorder

a) Incidence: 2% to 5% [4][5][79][88]

b) During 4- to 8-week trials of [venlafaxine](#) hydrochloride (dose ranging from 75 to 375 mg/day), the incidence of orgasm disturbance in female patients receiving [venlafaxine](#) was 2% compared with less than 1% in patients receiving placebo [4].

c) The table below provides the incidence rates of [anorgasmia](#), delayed orgasm, or [abnormal orgasm](#) in females on [venlafaxine](#) extended-release or placebo during clinical trials [5]:

Studies	Percent of females with anorgasmia , delayed orgasm, or abnormal orgasm	
Venlafaxine ER	Placebo	
Major depressive disorder *	3%	less than 1%
Generalized anxiety disorder (n=1191) **	2%	0%
Social anxiety disorder (n=703) ***	5%	less than 1%
Panic disorder (n=1090) *	2%	less than 1%
Key: ER = extended-release; * = mostly delayed orgasm or anorgasmia ; ** = includes delayed orgasm, abnormal orgasm and anorgasmia ; *** = includes abnormal orgasm and anorgasmia		

3.3.14.A.4] Priapism

a) A 16-year-old boy developed [priapism](#) while being treated with [venlafaxine](#) (37.5 mg/day, titrated to 150 mg/day) for depression. [Priapism](#) occurred on 4 occasions with sexual intercourse. He had no problem with libido, erection, or ejaculation; however, after ejaculation, his erection persisted for 3 or more hours. The [priapism](#) resolved after micturition. He stopped taking [venlafaxine](#) and experienced only 1 more episode of [priapism](#), approximately 3 weeks after discontinuing the drug [111].

3.3.14.A.5] Reduced libido

a) Incidence: 1.1% to 8% [4][5]

b) During 4- to 8-week trials of [venlafaxine](#) hydrochloride (dose ranging from 75 to 375 mg/day), the incidence of reduced libido in patients receiving [venlafaxine](#) (n=1033) was 2% compared with less than 1% in patients receiving placebo (n=609) [4].

c) During a dose-comparison trial involving 358 patients, the incidence of reduced libido was 1.1% for placebo compared with 2.2%, 1.1%, and 5.7% for immediate-release [venlafaxine](#) 75, 225, and 375 mg/day, respectively [4].

d) The table below provides the incidence rates of decreased libido during clinical trials of extended-release [venlafaxine](#) [5]:

Studies	Incidence of Decreased Libido	
Venlafaxine ER	Placebo	
Major depressive disorder (n=642)	3%	less than 1%
Generalized anxiety disorder (n=1936)	4%	2%

Social anxiety disorder (n=1514)	8%	2%
Panic disorder (n=1663)	4%	2%
Key: ER = extended-release		

3.3.15] Respiratory Effects

3.3.15.A] Venlafaxine Hydrochloride

3.3.15.A.1] Dyspnea

a) Postmarketing

- 1) Has been reported [1]

3.3.15.A.2] Interstitial lung disease

a) Postmarketing

- 1) Has been reported [1]

3.3.15.A.3] Interstitial pneumonia

a) Two cases of [interstitial pneumonia](#) with [heart failure](#) have been reported following the use of [venlafaxine](#). In one case, withdrawal of [venlafaxine](#) (initial, 75 mg/day; 35 mg/day after one month) in combination with steroid treatment led to a complete recovery in a 21-year-old woman. However, in the other case, a 62-year-old man ([venlafaxine](#) dose not provided) progressed to multiple-organ failure and died despite attempts at treatment [66]. The possibility of [interstitial pneumonia](#) should be considered in patients receiving [venlafaxine](#) who display progressive dyspnea, [cough](#), or chest discomfort. In these cases, prompt medical evaluation is necessary and discontinuation of [venlafaxine](#) should be considered [4][5].

3.3.15.A.4] Simple pulmonary eosinophilia

a) [Acute eosinophilic pneumonia](#) developed in a man treated with [venlafaxine](#) for 17 days. On admission, he had a respiratory rate of 30 breaths per minute. Examination revealed bibasilar crackles and rales; the [oxygen saturation](#) was 89.4%. The WBC count was elevated with 32.5% bands and 1% eosinophils. [Bronchoalveolar lavage](#) (BAL) revealed 25% eosinophils; transbronchial biopsies showed accumulation of eosinophils and neutrophils within alveolar vessels. He received [clarithromycin](#) 500 mg twice daily for 7 days and [methylprednisolone](#) 1 g IV daily for 3 days followed by tapering doses of [prednisone](#) for 4 weeks. He showed gradual improvement, and the chest [radiograph](#) showed marked clearing within 5 days of beginning corticosteroids. All potential infectious causes were excluded with appropriate stains and cultures. This patient had many classic features of [acute eosinophilic pneumonia](#) that resolved rapidly after starting corticosteroids [95]. The possibility of [eosinophilic pneumonia](#) should be considered in patients receiving [venlafaxine](#) who display progressive dyspnea, [cough](#), or chest discomfort. In these cases, prompt medical evaluation is necessary and discontinuation of [venlafaxine](#) should be considered [4][5].

3.3.15.A.5] Yawning

a) Incidence: 3% to 8% [4][5]

b) A dose increase of [venlafaxine](#) extended release (XR) led to excessive yawning in a patient who was being treated for depression. A 24-year-old man, who had no previous history of medical or psychiatric disorders, suffered for 8 weeks from [dysphoric mood](#), difficulty in concentration, loss of interest, and [suicidal ideation](#). He was subsequently diagnosed with a first episode of [major depressive](#)

disorder and prescribed [venlafaxine](#) XR 75 mg/day for 4 weeks. Due to an inadequate response, [venlafaxine](#) XR was increased to 150 mg/day and the patient's depressive symptoms improved after 2 weeks of the dose increase. Excessive yawning not associated with drowsiness was noted 7 days after the [venlafaxine](#) dose increase. The patient experienced 50 or more occurrences of yawning per day, frequently in the morning, that interfered with his normal daily activities and interpersonal interactions. The [venlafaxine](#) XR dose was reduced to 75 mg/day per the patient's request, and the yawning completely disappeared 3 days after the dose decrease with no further recurrence of depressive symptoms. Study authors hypothesized that, although the mechanism of excessive yawning was not clear, noradrenergic and dopaminergic mechanisms may play a role in the relationship between yawning and [venlafaxine](#) dosage, and the yawning side effect appeared to be dose-dependent [94].

c) During 4- to 8-week trials of [venlafaxine](#) hydrochloride (dose ranging from 75 to 375 mg/day), the incidence of yawning in patients receiving [venlafaxine](#) (n=1033) was 3% compared with less than 1% in patients receiving placebo (n=609) [4].

d) During a dose-comparison trial involving 358 patients, the incidence of yawning was 0% for placebo compared with 4.5%, 5.6%, and 8% for immediate-release [venlafaxine](#) 75, 225, and 375 mg/day, respectively [4].

e) The table below provides the incidence rates of yawning during clinical trials of extended-release [venlafaxine](#) [5]:

Studies	Venlafaxine ER	Placebo
Major depressive disorder (n=642)	3%	0%
Generalized anxiety disorder (n=1936)	3%	less than 1%
Social anxiety disorder (n=1514)	5%	less than 1%
Key: ER = extended-release		

3.3.16] Other

3.3.16.A] [Venlafaxine](#) Hydrochloride

3.3.16.A.1] [Angioedema](#)

a) In postmarketing evaluations, [angioedema](#) has been reported in patients who received [venlafaxine](#); however, causality could not be established [60].

3.3.16.A.2] [Neuroleptic malignant syndrome](#)

a) [Neuroleptic malignant syndrome](#) developed 12 hours after adding [venlafaxine](#) 75 mg daily to [trifluoperazine](#) 1 mg 3 times daily. [Trifluoperazine](#) had been used for 10 years without adverse effects. The patient presented with profound anxiety, malaise, rigidity, tremor, and severe diaphoresis. On examination, the blood pressure was between 130/80 mmHg and 165/100 mmHg. His pulse was 163 beats per minute, temperature 38.3 degrees C, and respiratory rate 25 breaths/minute. All laboratory parameters were within normal limits except the CPK concentration (11,320 international units/L) and WBC count (23.5 x 10(9)/L). Treatment consisted of a single dose of [dantrolene](#) 70 mg followed by [bromocriptine](#) 15 mg twice daily for 48 hours. Vital signs were normal 24 hours after admission, and [trifluoperazine](#) was restarted without problems [115].

3.3.16.A.3] [Serotonin syndrome](#)

a) [Serotonin syndrome](#), including life-threatening cases, or [neuroleptic malignant syndrome](#) (NMS)-like reactions have been reported with the use of [venlafaxine](#) 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 [60][61].

b) A 43-year-old man with [idiopathic Parkinson disease](#) and [bronchiectasis](#) developed [serotonin syndrome](#) with resulting [rhabdomyolysis](#) and [acute renal failure](#) 2 weeks after initiating [venlafaxine](#) for depression. Other medications the patient was taking included [carbidopa](#) 25 mg/[levodopa](#) 100 mg 3 times daily, [amantadine](#) 100 mg twice a day, benzhexol 2 mg daily, and [ropinirole](#) 0.5 mg 3 times daily. His medical history included probable [neuroleptic malignant syndrome](#) 6 months earlier after a trial of a phenothiazine for agitation and restlessness. The patient presented with fever (41.2 degrees C), [dysphagia](#), and agitated [delirium](#), and he had become progressively drowsy over the previous 2 days. On physical examination, the patient had [high blood pressure](#) (135/90 mmHg), [tachycardia](#) (heart rate of 120 beats/minute), diaphoresis, flushing, dilated pupils, hypertonic muscles, and sustained clonus. No other recent medication changes had been made other than the addition of [venlafaxine](#). On admission, laboratory results revealed [metabolic acidosis](#), a serum [creatinine](#) level of 205 mcmol/L, an AST level of 358 units/L, a CPK level of 3600 international units/L, an INR of 1.5, and myoglobinuria. Shortly after admission, the patient developed hypotension, went into shock, and was transferred to the ICU for supportive care where he received 3 inotropic agents and mechanical ventilation. [Venlafaxine](#) was stopped and [midazolam](#) and broad spectrum antibiotics were started. The diagnoses of [rhabdomyolysis](#) and [acute renal failure](#) were made on day 3 when the CPK level peaked at 170,800 international units/L, urine output dropped, and serum [creatinine](#) increased. With regular [hemodialysis](#), normalization of renal function and CPK occurred in 2 weeks. The patient made a slow recovery that was complicated by multiple episodes of [pneumonia](#) requiring ventilatory support. He was discharged from the ICU on day 96. The patient was determined to have experienced [serotonin syndrome](#) related to [venlafaxine](#) therapy, although considerable weight was given to [neuroleptic malignant syndrome](#) as the possible cause of the [rhabdomyolysis](#) and [renal failure](#) [101].

c) Despite compliance with the recommended 2-week washout period, 3 patients were diagnosed with [serotonin syndrome](#) after switching from [phenelzine](#) to [venlafaxine](#). Fourteen days after stopping treatment with [phenelzine](#), a 25-year-old woman started [venlafaxine](#) 37.5 mg/day. Following initiation of [venlafaxine](#), the woman experienced agitation, erythema, twitching in her legs, shakiness, sweating, [tachycardia](#), tachypnea, fever, and [increased blood pressure](#). The woman was treated in the emergency department with IV fluids and returned to baseline 3 hours later with no residual problems. A 49-year-old woman also started [venlafaxine](#) 14 days after discontinuation of [phenelzine](#) and experienced dizziness, weakness, chills, and palpitations. The woman's symptoms subsided 3 hours later without treatment. Fourteen days after terminating [phenelzine](#) therapy, a 33-year-old man started [venlafaxine](#) and experienced sweating, chest tightness, anxiety, and emesis. Symptoms subsided without medical treatment. A 29-year-old woman started [venlafaxine](#) 6 days after terminating [phenelzine](#) treatment. Fifteen minutes after ingestion of [venlafaxine](#), the woman experienced shakiness, stomach pain, facial flushing, crying, diaphoresis, agitation, muscle tremors, fever, and [tachycardia](#). The woman was successfully treated with [ciproheptadine](#) and [lorazepam](#) and had no residual problems. A longer waiting period may be necessary for those patients who [transition](#) from an MAOI to [venlafaxine](#) [112].

d) A 44-year-old woman experienced [serotonin syndrome](#) after accidentally ingesting two 15-mg [phenelzine](#) tablets and two 75-mg [venlafaxine](#) tablets. The woman became nauseated and anxious 30 minutes after ingesting the medications. Forty-five minutes later she experienced lower extremity shaking and increased respirations. The woman was taken to the hospital and upon arrival had an

elevated blood pressure, heart rate, respiratory rate, and temperature. The patient also experienced agitation, muscle rigidity, sedation, and decreased responsiveness. The patient was given 50 g of charcoal with sorbitol, hydration therapy, benzodiazepines for muscle rigidity, and [sodium bicarbonate](#) to protect renal function. After 6 days of supportive measures, the woman showed improvements and, an additional 6 days later, was discharged from the hospital with no apparent long-term complications [113].

e) A 60-year-old woman presented to the emergency department obtunded, tachycardic, hyperthermic, hyperreflexic, diaphoretic, weak, and confused following unintentional ingestion of a single dose of [venlafaxine](#) while on maintenance [tranylcypromine](#) therapy. The patient recovered following supportive treatment [114].

3.3.16.A.4] Withdrawal sign or symptom

a) Withdrawal symptoms, such as agitation, anorexia, anxiety, confusion, impaired coordination and balance, diarrhea, dizziness, dry mouth, [dysphoric mood](#), fasciculation, fatigue, flu-like symptoms, headaches, [hypomania](#), insomnia, nausea, nervousness, nightmares, [sensory disturbances](#) (including shock-like electrical sensations), somnolence, sweating, tremor, vertigo, and vomiting, have occurred with abrupt discontinuation or dose reduction of [venlafaxine](#) at various doses. The frequency of these effects increased with increased dose level and with longer duration of therapy [60][5].

b) A 45-year-old man and a 36-year-old woman reported electric shock-like sensations of the head shortly after stopping or taking reduced doses of extended-release (ER) [venlafaxine](#). The man experienced severe sensations of shock in his head and radiating to his back and arms on 2 occasions after his [venlafaxine](#) ER dose was tapered from 150 mg at bedtime and 150 mg twice daily to 75 mg at bedtime and 150 mg at bedtime, respectively. The female patient was taking [venlafaxine](#) ER 75 mg 3 times daily and also reported sensations of electric shocks in her head when trying to stop the medication on several occasions. Her dose was tapered to 37.5 mg 3 times a day with no symptoms, but she experienced shocks and "tracers" (after-images of objects in her field of vision) when the medicine was withdrawn. For both patients, the sensations resolved on the sixth day after the last dose of medication [116].

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: B2

a) Drugs which have been taken by only a limited number of pregnant women and women of childbearing age, without an increase in the frequency of malformation or other direct or indirect harmful effects on the human fetus having been observed. Studies in animals are inadequate or may be lacking, but available data show no evidence of an increased occurrence of fetal damage.

See Drug Consult reference: PREGNANCY RISK CATEGORIES

3) Crosses Placenta: Unknown

4) Clinical Management

a)] Due to the lack of adequate, well-controlled studies in pregnant women, it is recommended that [venlafaxine](#) be used during pregnancy only if clearly needed [61][413][415]. Because adverse serotonergic-like effects have been reported in SSRI- and SNRI-exposed neonates late in the third trimester, the potential risks and benefits of [venlafaxine](#) therapy during this time should be taken into account. Tapering [venlafaxine](#) may be considered in pregnant women during the third trimester [61][413].

5) Literature Reports

a)] Serotonin and [norepinephrine](#) reuptake inhibitor (SNRI) withdrawal, complicated with recurrent seizures, was reported in the neonate of a 31-year-old woman administered [venlafaxine](#) 150 mg and 75 mg on alternate days for the treatment of anxiety and depression. Initially, the neonate was born at term via vaginal delivery following an uneventful pregnancy and there were no signs of withdrawal or toxicity other than mild [respiratory depression](#). The mother continued on [venlafaxine](#) therapy and chose to breastfeed the infant. After the third day of life, short episodes of jerks were observed in the upper extremities followed by myoclonic fits on the fourth day of life. Despite an initial improvement following treatment with phenobarbitone, he continued to have seizures. Treatment with supplemental [fosphenytoin](#) was implemented which resulted in normalization of the EEG. However, the infant became hypotonic and his reflexes diminished. Treatment with phenobarbitone and [fosphenytoin](#) were discontinued. Breastfeeding was discontinued due to the mother's continued [venlafaxine](#) use. Following further supportive care, including treatment with phenobarbitone, his condition gradually improved and he was discharged after 21 days. Treatment with antiepileptic agents was discontinued after 7 weeks, at which time neurologic function was completely restored and EEG recordings were normalized [411].

b)] A nested case-controlled study showed an increased risk of [spontaneous abortion](#) with SSRI use, and notably, [venlafaxine](#) or [paroxetine](#) use alone, during pregnancy. Data collected from the Quebec Pregnancy Registry between January 1998 and December 2003 on women who filled at least 1 antidepressant prescription during pregnancy and had a clinically detected [spontaneous abortion](#) by the twentieth week of gestation (n=284) showed an increased risk of [spontaneous abortion](#) (adjusted odds ratio (OR), 1.68; 95% confidence interval (CI), 1.38 to 2.06) when compared with randomly selected registry controls (4 matched controls per case) without antidepressant use. Tracked antidepressant categories included SSRIs, tricyclic antidepressants, serotonin-norepinephrine reuptake inhibitors, combined use of 2 or more antidepressant classes, or others. [Venlafaxine](#) use (adjusted OR 2.11; 95% CI, 1.34 to 3.3) or [paroxetine](#) use (adjusted OR 1.75; 95% CI, 1.31 to 2.34) alone were independently associated with a higher risk of [spontaneous abortion](#). The highest daily doses of [venlafaxine](#) or [paroxetine](#) during pregnancy was associated with the greatest [spontaneous abortion](#) risk; of the women taking [venlafaxine](#) (n=33) or [paroxetine](#) (n=84) who spontaneously aborted, an adjusted analysis showed 50% averaged daily doses greater than 150 mg of [venlafaxine](#) and 25.5% averaged daily doses of more than 25 mg of [paroxetine](#). Use of [sertraline](#), [fluoxetine](#), [citalopram](#), [fluvoxamine](#), or combined use of 2 or more SSRIs during pregnancy did not correspond with a significant increase in risk of [spontaneous abortion](#) [412].

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

the drug or a drug discontinuation syndrome. In some cases, clinical findings have been consistent with [serotonin syndrome](#) [61][413].

d) A multicenter, prospective, controlled study comparing the results of pregnant women who called into the Motherisk Program or other participating pregnancy counseling centers during their first trimester and who were being treated with [venlafaxine](#) (n=150), an SSRI (n=150), or a nonteratogenic drug (n=150) found that there was not a significant increase in major malformations in those patients taking [venlafaxine](#). Of the 150 patients in the [venlafaxine](#) group, all were treated with [venlafaxine](#) in the first trimester and 34 of the patients were treated with [venlafaxine](#) throughout their pregnancy. Of the patients treated with [venlafaxine](#), 105 patients took 75 mg/day of the immediate-release formulation and 45 patients took 37.5 to 300 mg/day. There were 2 major malformations ([hypospadias](#) and [neural tube defect](#) with club foot) reported in the [venlafaxine](#) group (1.6%), compared with the SSRI group (2.4%; p=0.99) and the nonteratogenic group (0.7%; p=0.93). There was not a significant difference in pregnancy outcomes among the three groups. An increase in [spontaneous abortions](#) was found in the [venlafaxine](#) group (12%), compared with the SSRI group (10.7%) and the nonteratogenic drugs group (7.3%), but it did not reach statistical significance [414].

e) Seventy-nine neonates of mothers treated with SSRIs or [venlafaxine](#) (n=76) during the third trimester exhibited a higher rate of behavioral changes compared with 91 neonates of untreated mothers (n=90). Treatment included [paroxetine](#) 5 to 40 mg (n=46), [fluoxetine](#) 10 to 40 mg (n=10), [venlafaxine](#) 75 to 150 mg (n=9), [citalopram](#) 10 to 30 mg (n=6), [sertraline](#) 125 to 150 mg (n=3), and [fluvoxamine](#) 50 to 150 mg (n=2) with a mean duration of 32 months for SSRI use. In the treated group, 1 patient and 2 patients were taking [olanzapine](#) and [lithium](#), respectively. A lower median gestational age was reported in exposed infants (38.3 weeks) compared with 39.7 weeks; p less than 0.001). CNS effects were reported in 63.2% of exposed infants and included tremors, agitation, spasms, hypotonia, irritability, sleep disturbances, [apnea](#)/bradycardia and tachypnea. Respiratory effects, including indrawing, [apnea](#)/bradycardia, and tachypnea, were noted in 43.2% of exposed neonates. Exposed neonates also had a longer median length of hospitalization compared with unexposed infants (3.9 days vs 2.4 days; p less than 0.001). For premature neonates, exposed infants were hospitalized nearly 4 times longer than unexposed infants (14.5 days vs 3.7 days; p less than 0.001). Effects were transient, resolving within 3 to 5 days. Authors recommend assessing the potential risks and benefits in continuing SSRI or [venlafaxine](#) treatment during pregnancy on an individual basis [415].

f) In a prospective, single-blind, cohort study, full-term infants who developed [neonatal abstinence syndrome](#) (NAS) at birth had similar cognitive abilities compared with full term infants without NAS at birth when reevaluated at 2 to 6 years of age. However, infants with NAS at birth were at an increased risk for social-behavioral abnormalities at 2 to 6 years of age. The study was designed to assess the long-term neurodevelopment of children exposed in utero to [fluoxetine](#), [paroxetine](#), [citalopram](#), [sertraline](#), [fluvoxamine](#), or [venlafaxine](#). Children with NAS at birth (n=30; Finnegan score of 4 or greater) were compared to children without NAS (n=52; Finnegan score 0 to 3); both groups were similar in mean cognitive ability (106.9 +/- 14 versus 100.5 +/- 14.6, respectively; p=0.12) and developmental scores (98.9 +/- 11.4 versus 95.7 +/- 9.9, respectively; p=0.21). Cognitive ability was based on scores from the Wechsler Preschool and Primary Scale of Intelligence II, the Stanford-Binet Intelligence Scales, or the Bayley Scale of Infant Development II. The NAS infants had an increased risk of social-behavior abnormalities (odds ratio (OR) 3.03, 95% CI, 1.07 to 8.6, p=0.04) based on the [Denver Developmental Screening Test II](#) (DDST-II) and NAS after birth was associated with advanced maternal age (OR 1.12, 95% CI, 1 to 1.25, p=0.04). In addition, there

was a trend towards small head circumference in the NAS group when compared with the children without NAS (n=6 (20%) versus n=3 (6%), respectively; p=0.068) [416].

g) A study of prospectively collected data suggests antenatal use of SSRI antidepressants is associated with QTc interval prolongation in exposed neonates. Between January 2000 and December 2005, researchers compared 52 neonates exposed to SSRI antidepressants ([paroxetine](#) (n=25), [citalopram](#) (n=13), [fluoxetine](#) (n=12), [fluvoxamine](#) (n=1), and [venlafaxine](#) (n=1)) in the immediate antenatal period to 52 matched neonates with no exposure. Prolonged QTc is defined as an interval of greater than 460 milliseconds (msec) (the widely used upper limit cited by authorities in both pediatric cardiology and neonatology). A pediatric cardiologist, blinded to drug exposure, interpreted all [electrocardiograms](#) (ECGs) using standard statistical analyses. ECG recordings revealed markedly prolonged mean QTc intervals in exposed neonates compared to unexposed neonates (mean; 409 +/- 42 msec vs 392 +/- 29 msec, p=0.02). The mean uncorrected QT interval was 7.5% longer among exposed neonates (mean; 280 +/- 31 msec vs 261 +/- 25 msec, p less than 0.001). Ten percent (n=5) of exposed neonates had a notable increase in QTc interval prolongation (greater than 460 msec) compared to none of the unexposed neonates. The longest QTc interval observed was 543 msec [417].

h) Two cases of seizures were reported in neonates born to mothers using [venlafaxine](#) during pregnancy. Seizures occurred within 24 hours of birth and were self-limited. No other etiology could be found in either case. Both children had subsequently normal growth and development at one year follow-up [418].

i) A case report described development of [necrotizing enterocolitis](#) in dichorial, diamniotic, twin infants on the sixth day of life following maternal [venlafaxine](#) use of 75 mg/day for depression throughout pregnancy until delivery. The mother, who experienced uneventful first and second trimesters, was hospitalized during week 31 due to vaginal bleeding. A [Chlamydia trachomatis infection](#) was diagnosed for which she received [azithromycin](#) for 4 days. She received [betamethasone](#) 12 g twice in 24 hours to augment fetal lung development. The twin infants were delivered via [cesarean section](#) at 33+2 weeks. Twin A and B weighed 1700 g and 1980 g, respectively, with Apgar scores of 6, 7, and 8 for twin A and 4, 5, and 8 for twin B at 1, 5, and 8 minutes, respectively. Both were intubated on day 1 of life. Twin A was successfully extubated on day 2. On day 6, signs of [necrotizing enterocolitis](#), abdominal distension, bloody stool, signs of [peritonitis](#), and gastric residuals were observed in the infants. Subsequently, oral feeding was withheld and IV [amikacin](#) and [amoxicillin](#) were given to both. Following antibiotics, feeding was well-tolerated in twin A. However, twin B continued to deteriorate and underwent surgery on day 10. Bowel necrosis was observed. Therefore, terminal ileum, right colon, and the proximal transverse colon were resected, and enterostomy was performed. He underwent a second surgery for stomal stenosis on day 22 of life. At 5 months of age, the stoma was closed. Histological examination confirmed a complete [luminal](#) obliteration of the remaining transverse colon and the proximal section of the descending colon for which an [intestinal anastomosis](#) was created. He was discharged 10 days after the stoma closure [419].

B) Breastfeeding

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

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

2) Clinical Management

a) **Venlafaxine** is excreted in human breast milk. Because of the potential for serious adverse effects in nursing infants, a decision should be made whether to discontinue the drug or discontinue nursing, taking into consideration the importance of the drug to the mother [61][413]. If **venlafaxine** is administered to a nursing woman, the nursing infant should be monitored closely for adverse effects [422].

3) Literature Reports

a) A study of 78 breast-feeding mothers treated with antidepressants (3 took **venlafaxine** at a dose of 162.5 mg/day) found normal weight gain patterns in six-month old infants exposed to **venlafaxine**. The mean weights of all infants exposed to antidepressants in the study were 7.26 +/- 0.71 kg for girls and 7.93 +/- 0.75 kg for boys. The reported weights did not differ significantly from normative growth data and remained similar in separate analyses of each antidepressant. However, infants of mothers who relapsed to a **major depressive episode** (defined as an episode lasting two months or more) despite antidepressant treatment weighed significantly less at 6 months ($p=0.002$) when compared with infants born to mothers who relapsed to a brief **depressive episode** and infants born to mothers who did not **relapse** to depression. The small **venlafaxine** sample size, maternal use of other medications (56 women used antidepressants during pregnancy and 6 women took psychotropics such as benzodiazepines or tricyclic antidepressants during the study), and absence of a control group limit the application of this study [420].

b) A study describing 3 lactating women treated with **venlafaxine** and their nursing infants found infant mean serum drug concentration to be 10.2% (range 5.3 to 19%) of maternal serum drug concentrations for the sum of **venlafaxine** plus O-desmethylvenlafaxine (ODV). The maternal drug dose was 75 to 225 mg/day. There was no evidence of adverse effects in the infants as reported by the mothers. The authors suggest that breast-feeding should generally not be discouraged in mothers treated with SSRI antidepressants [421].

c) **Venlafaxine** and its metabolite, O-desmethylvenlafaxine (ODV) were detected in six infant blood samples collected over a 12-hour dose interval at steady-state following a median maternal **venlafaxine** dose of 255 mg/day in a study of 6 women taking **venlafaxine** and their 7 nursing infants (mean age of 7 months). **Venlafaxine** was detected in the blood of one infant at a low concentration of 5 mcg/L, while ODV was present in four infants in concentrations ranging from 3 to 38 mcg/mL. Mean milk-to-plasma ratios for **venlafaxine** and ODV were 2.5 (range 2 to 3.2) and 2.74 (range 2.3 to 3.2), respectively. Although no adverse effects were noted in the infants, the authors recommend monitoring nursing infants whose mothers are receiving **venlafaxine** and assessing the potential risks and benefits of breast-feeding during **venlafaxine** therapy [422].

d) Detectable levels of the metabolite O-desmethylvenlafaxine (ODV) were reported in three infants exposed to **venlafaxine** through breast milk. Both **venlafaxine** and ODV were concentrated in the milk (milk-to-plasma concentration ratio of 4:1 and 3:1, respectively). Total infant exposure was 7.6% of the weight-adjusted maternal dose. No adverse effects were observed in the nursing infants [423].

4) Drug Levels in Breastmilk

a) **Venlafaxine** Hydrochloride

1) Parent Drug**a) Percent Adult Dose in Breastmilk****1) 7.6% [423]****2) Active Metabolites****a) O-desmethylvenlafaxine [4][5]****1) Milk to Maternal Plasma Ratio****a) 3.06 +/- 0.08 [423]****3.5] Drug Interactions****3.5.1] Drug-Drug Combinations****3.5.1.A] Abiraterone****1) Interaction Effect:** increased plasma concentrations of CYP2D6 substrate**2) Summary:** Coadministration of abiraterone (a CYP2D6 inhibitor) with a CYP2D6 substrate may result in increased plasma concentrations of the CYP2D6 substrate. When abiraterone (1000 mg/day) and [prednisone](#) (5 mg twice daily) were coadministered with the CYP2D6 substrate [dextromethorphan](#) (30 mg), the [dextromethorphan](#) C_{max} and AUC were increased 2.8-fold and 2.9-fold, respectively. If an alternative to the CYP2D6 substrate cannot be used, use caution and consider reducing the dose of the CYP2D6 substrate as necessary during coadministration[213].**3) Severity:** moderate**4) Onset:** unspecified**5) Substantiation:** theoretical**6) Clinical Management:** The concomitant use of abiraterone, a CYP2D6 inhibitor, with a CYP2D6 substrate may increase the exposure of the CYP2D6 substrate. If an alternative to the CYP2D6 substrate cannot be used, use caution and consider a dose reduction of the CYP2D6 substrate as indicated during coadministration[213].**7) Probable Mechanism:** inhibition of CYP2D6-mediated metabolism by abiraterone**3.5.1.B] Aceclofenac****1) Interaction Effect:** an increased risk of bleeding**2) Summary:** Use caution when coadministering NSAIDs and serotonin [norepinephrine](#) reuptake inhibitors (SNRI) as this may cause an increased risk of bleeding[318]. During clinical trials, concomitant use of NSAIDs and antidepressants, including tricyclic antidepressants, SSRIs, selective serotonin-norepinephrine reuptake inhibitors, and MOAIs, resulted in an increased risk of [intracranial hemorrhage](#) within 30 days of concomitant use compared with antidepressant use alone [319]. When NSAIDs and SNRIs are given concurrently, monitor the patient for signs of increased bleeding.**3) Severity:** major**4) Onset:** unspecified

5) Substantiation: established

6) Clinical Management: Serotonin [norepinephrine](#) reuptake inhibitors (SNRI) increase bleeding risk, especially with concomitant use of NSAIDs[318]. When NSAIDs and SNRIs are given concurrently, monitor the patient for signs of increased bleeding.

7) Probable Mechanism: unknown

8) Literature Reports

a) Concomitant use of NSAIDs and antidepressants, including tricyclic antidepressants, SSRIs, serotonin-norepinephrine reuptake inhibitors, and MAOIs, resulted in an increased risk of [intracranial hemorrhage](#) within 30 days of concomitant use compared with antidepressant use alone. There was no significant difference between the antidepressant drug classes and the increased risk; however, there was an increased risk associated with male patients compared with female patients [319].

3.5.1.C] Acemetacin

1) Interaction Effect: an increased risk of bleeding

2) Summary: Use caution when coadministering NSAIDs and serotonin [norepinephrine](#) reuptake inhibitors (SNRI) as this may cause an increased risk of bleeding[318]. During clinical trials, concomitant use of NSAIDs and antidepressants, including tricyclic antidepressants, SSRIs, selective serotonin-norepinephrine reuptake inhibitors, and MOAIs, resulted in an increased risk of [intracranial hemorrhage](#) within 30 days of concomitant use compared with antidepressant use alone [319]. When NSAIDs and SNRIs are given concurrently, monitor the patient for signs of increased bleeding.

3) Severity: major

4) Onset: unspecified

5) Substantiation: established

6) Clinical Management: Serotonin [norepinephrine](#) reuptake inhibitors (SNRI) increase bleeding risk, especially with concomitant use of NSAIDs[318]. When NSAIDs and SNRIs are given concurrently, monitor the patient for signs of increased bleeding.

7) Probable Mechanism: unknown

8) Literature Reports

a) Concomitant use of NSAIDs and antidepressants, including tricyclic antidepressants, SSRIs, serotonin-norepinephrine reuptake inhibitors, and MAOIs, resulted in an increased risk of [intracranial hemorrhage](#) within 30 days of concomitant use compared with antidepressant use alone. There was no significant difference between the antidepressant drug classes and the increased risk; however, there was an increased risk associated with male patients compared with female patients [319].

3.5.1.D] Acenocoumarol

1) Interaction Effect: an increased risk of bleeding

2) Summary: Case reports and epidemiological studies have shown that use of selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs), including [venlafaxine](#), is associated with [gastrointestinal bleeding](#). Bleeding events with SSRIs and SNRIs included cases of ecchymoses, [hematomas](#), [epistaxis](#), and [petechiae](#); life-threatening hemorrhages have also occurred. Coadministration with [warfarin](#) or other anticoagulants may potentiate the risk of bleeding. A population-based, case-controlled study of new coumarin users (acenocoumarol and phenprocoumon) with concomitant selective serotonin reuptake inhibitors (SSRIs) resulted in an increased risk of hospitalization due to nongastrointestinal bleeding[354]. Increases in prothrombin time, partial thromboplastin time, or INR have been reported when [venlafaxine](#) was administered to patients receiving [warfarin](#). Therefore,

concomitant use of [venlafaxine](#) with [warfarin](#) or other drugs affecting coagulation should be undertaken with caution. Whenever [venlafaxine](#) is initiated or discontinued in patients receiving an anticoagulant, close monitoring of coagulation parameters is recommended [321].

3) Severity: major

4) Onset: unspecified

5) Substantiation: probable

6) Clinical Management: Use caution when [venlafaxine](#) is used concomitantly with [warfarin](#) or other drugs affecting coagulation. Closely monitor coagulation parameters when [venlafaxine](#) is initiated or discontinued in patients receiving anticoagulants, such as [warfarin](#)[321].

7) Probable Mechanism: additive adverse events

8) Literature Reports

a) A population-based, case-controlled study of new coumarin users (acenocoumarol and phenprocoumon) with concomitant selective serotonin reuptake inhibitors (SSRIs) resulted in an increased risk of hospitalization due to nongastrointestinal bleeding. Using national pharmacy and hospitalization records, Netherlands researchers identified 1848 cases that were admitted for abnormal bleeding and compared them with 5818 control subjects also taking coumarins. Median duration of treatment in patients was 220 days (range, 1 to 4690 days). Patients on SSRIs showed greater risk for hospitalization for nongastrointestinal bleeding (adjusted odds ratio (OR) 1.7, 95% confidence interval (CI), 1.1 to 2.5), however, the rate of [gastrointestinal bleeding](#) (adjusted OR 0.8, 95% CI, 0.4 to 1.5) was not significantly different [354].

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[279]. 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](#) [258].

3) Severity: major

4) Onset: delayed

5) Substantiation: theoretical

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

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

8) Literature Reports

a) Concomitant administration of [fluoxetine](#) and [almotriptan](#) is well tolerated and [fluoxetine](#) has only a modest effect on [almotriptan](#) maximum plasma concentration (Cmax). Other [almotriptan](#) pharmacokinetics are not significantly affected. A randomized, open-label, two-way crossover study involving 14 healthy volunteers has been conducted. Subjects received each of the following treatments with a minimum 3-week washout between periods: (1) three 20 mg [fluoxetine](#) capsules on day 1 to 8 and one dose [almotriptan](#) 12.5 mg on day 8, (2) one dose of [almotriptan](#) 12.5 mg on day 8 with no treatment on days 1 through 7. Peak [almotriptan](#) concentrations were 18%

higher following concomitant administration of [fluoxetine](#) than after [almotriptan](#) administration alone. This difference was statistically significant (p equal 0.023). Mean [almotriptan](#) area under the concentration-time curve (AUC) and oral clearance were borderline statistically different between treatment groups. Mean half-life was not statistically different between the treatment groups. During [fluoxetine](#) coadministration, T_{max} was shorter, suggesting that the absorption rate of [almotriptan](#) may have been increased by [fluoxetine](#). The author concludes that based on the results of this study and the lack of effect of [fluoxetine](#) on [almotriptan](#) pharmacokinetics, [almotriptan](#) and [fluoxetine](#) can be safely used concomitantly in migraine management [278].

3.5.1.F] Amifampridine

- 1) Interaction Effect: increased risk of QT-interval prolongation
- 2) Summary: The concomitant use of amifampridine with drugs that cause QT-interval prolongation is contraindicated, as coadministration may increase the risk of [ventricular arrhythmias](#)[345].
- 3) Severity: contraindicated
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: The concomitant use of amifampridine with drugs that cause QT-interval prolongation is contraindicated, as coadministration may increase the risk of [ventricular arrhythmias](#)[345].
- 7) Probable Mechanism: additive QT-interval prolongation

3.5.1.G] Amiodarone

- 1) Interaction Effect: increased risk of QT prolongation and [torsades de pointes](#)
- 2) Summary: Avoid the concomitant administration of [amiodarone](#) and a QT prolonging agent since it may result in additive effects on the QT interval and increase the risk of [torsades de pointes](#). Due to the long half-life of [amiodarone](#), this interaction is possible even after the discontinuation of [amiodarone](#)[254].
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Avoid the concomitant administration of [amiodarone](#) and a QT prolonging agent since it may result in additive effects on the QT interval and increase the risk of [torsades de pointes](#). Due to the long half-life of [amiodarone](#), this interaction is possible even after the discontinuation of [amiodarone](#)[254].
- 7) Probable Mechanism: additive effects on QT interval

3.5.1.H] Amisulpride

- 1) Interaction Effect: increased risk of [torsades de pointes](#)
- 2) Summary: The concomitant use of amisulpride with other agents that may induce [torsade de pointes](#) is contraindicated. Because amisulpride by itself prolongs the QT interval in a dose-dependent manner, coadministration with another medication that prolongs the QT interval increases the risk of [torsade de pointes](#)[252].
- 3) Severity: contraindicated
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: The concomitant use of amisulpride with other agents that may induce [torsade de pointes](#) is contraindicated. Because amisulpride by itself prolongs the QT interval in a dose-dependent manner, coadministration with another medication that prolongs the QT interval increases the risk of [torsade de pointes](#)[252].
- 7) Probable Mechanism: additive QT prolongation

3.5.1.I] Amitriptyline

1) Interaction Effect: an increased risk of **cardiotoxicity** (QT prolongation, **torsades de pointes**, **cardiac arrest**) and adverse effects of both drugs

2) Summary: Tricyclic antidepressants (TCAs) and **venlafaxine** have been shown to prolong the QTc interval at the recommended therapeutic dose[297][298]. Even though no formal drug interaction studies have been done, the coadministration of tricyclic antidepressants and other drugs known to prolong the QTc interval, such as **venlafaxine**, is not recommended [299]. In addition, **venlafaxine** and tricyclic antidepressants (TCAs) may competitively inhibit each other's metabolism which may increase side effects of both drugs [300][297][301]. **Venlafaxine** increased the AUC, Cmax, and Cmin of **desipramine** by approximately 35%. The AUCs of 2-OH-desipramine increased by 2.5 and 4.5 fold when administered with **venlafaxine** 37.5 mg and 75 mg every 12 hours, respectively. The pharmacokinetics of **imipramine** and the 2-hydroxy metabolite were not affected [6].

3) Severity: major

4) Onset: rapid

5) Substantiation: theoretical

6) Clinical Management: Due to the potential for additive effects on the QT interval, the concurrent administration of **venlafaxine** and tricyclic antidepressants is not recommended.

7) Probable Mechanism: decreased TCA and **venlafaxine** metabolism; additive effects on QT prolongation

8) Literature Reports

a) When administered with **imipramine**, the pharmacokinetics of **imipramine** and the 2-hydroxy metabolite were not affected. **Venlafaxine** increased the area under the concentration-time curve (AUC), maximum concentration (Cmax), and minimum concentration (Cmin) of **desipramine** by approximately 35%. The 2-OH-desipramine AUCs increased by 2.5-fold (**venlafaxine** 37.5 mg every 12 hours) and by 4.5-fold (**venlafaxine** 75 mg every 12 hours). The clinical significance of this finding is unknown [6].

3.5.1.J] Amoxapine

1) Interaction Effect: an increased risk of **cardiotoxicity** (QT prolongation, **torsades de pointes**, **cardiac arrest**) and adverse effects of both drugs

2) Summary: Tricyclic antidepressants (TCAs) and **venlafaxine** have been shown to prolong the QTc interval at the recommended therapeutic dose[297][298]. Even though no formal drug interaction studies have been done, the coadministration of tricyclic antidepressants and other drugs known to prolong the QTc interval, such as **venlafaxine**, is not recommended [299]. In addition, **venlafaxine** and tricyclic antidepressants (TCAs) may competitively inhibit each other's metabolism which may increase side effects of both drugs [300][297][301]. **Venlafaxine** increased the AUC, Cmax, and Cmin of **desipramine** by approximately 35%. The AUCs of 2-OH-desipramine increased by 2.5 and 4.5 fold when administered with **venlafaxine** 37.5 mg and 75 mg every 12 hours, respectively. The pharmacokinetics of **imipramine** and the 2-hydroxy metabolite were not affected [6].

3) Severity: major

4) Onset: rapid

5) Substantiation: theoretical

6) Clinical Management: Due to the potential for additive effects on the QT interval, the concurrent administration of **venlafaxine** and tricyclic antidepressants is not recommended.

7) Probable Mechanism: decreased TCA and **venlafaxine** metabolism; additive effects on QT prolongation

8) Literature Reports

a) When administered with [imipramine](#), the pharmacokinetics of [imipramine](#) and the 2-hydroxy metabolite were not affected. [Venlafaxine](#) increased the area under the concentration-time curve (AUC), maximum concentration (C_{max}), and minimum concentration (C_{min}) of [desipramine](#) by approximately 35%. The 2-OH-desipramine AUCs increased by 2.5-fold ([venlafaxine](#) 37.5 mg every 12 hours) and by 4.5-fold ([venlafaxine](#) 75 mg every 12 hours). The clinical significance of this finding is unknown [6].

3.5.1.K] [Amoxicillin](#)

- 1) Interaction Effect: an increased risk of [serotonin syndrome](#)
- 2) Summary: A 56-year-old male on [venlafaxine](#) experienced [serotonin syndrome](#) within 3 hours of taking [amoxicillin/clavulanate](#) and had a positive-rechallenge 2 months later[256]. If [amoxicillin/clavulanate](#) and [venlafaxine](#) are used concomitantly, monitor closely for symptoms of [serotonin syndrome](#). If [serotonin syndrome](#) develops, discontinue the offending agents and provide supportive care and other therapy as necessary [119].
- 3) Severity: major
- 4) Onset: rapid
- 5) Substantiation: probable
- 6) Clinical Management: A case of [serotonin syndrome](#) was reported with coadministration of [amoxicillin/clavulanate](#) and [venlafaxine](#) and therefore, concomitant use is discouraged[256]. If [amoxicillin/clavulanate](#) and [venlafaxine](#) are used concomitantly, monitor closely for symptoms of [serotonin syndrome](#) such as neuromuscular abnormalities (including hyper-reflexia, tremor, muscle rigidity, clonus, peripheral hypertonicity, and shivering), autonomic hyperactivity (including [tachycardia](#), mydriasis, diaphoresis, the presence of bowel sounds, and diarrhea), and mental status changes (including agitation and [delirium](#)). [Serotonin syndrome](#) can be life-threatening. If [serotonin syndrome](#) develops, discontinue the offending agents and provide supportive care and other therapy as necessary [119].
- 7) Probable Mechanism: unknown
- 8) Literature Reports

a) A 56-year-old male on [venlafaxine](#) experienced [serotonin syndrome](#) within 3 hours of taking [amoxicillin/clavulanate](#) and had a positive-rechallenge 2 months later. He was on [venlafaxine](#) 37.5 mg twice daily for 10 months for depression. He experienced tingling in the tip of his tongue, intense paraesthesia in the fingers, severe abdominal cramps, profuse diarrhea, cold sweats, uncontrollable shivering and tremor, agitation, and he was frightened but not confused 2 hours after taking the first dose of [amoxicillin/clavulanate](#) 375 mg for [gingivitis](#) and [dental abscess](#). The symptoms resolved after 6 hours and then he slept a further 8 hours. No further [amoxicillin/clavulanate](#) doses were administered. Two months later he was re-challenged and he developed the same symptoms after the first dose. The patient continued on [venlafaxine](#) without further episodes. His medical history includes taking [amoxicillin/clavulanate](#), while at the time not on [venlafaxine](#), without any events [256].

3.5.1.L] [Amphetamine](#)

- 1) Interaction Effect: increased risk of [serotonin syndrome](#)
- 2) Summary: Coadministration of an [amphetamine](#) and another serotonergic agent may result in [serotonin syndrome](#), because both drugs affect the serotonergic neurotransmitter system. 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[235].
- 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. 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[235].
- 7) Probable Mechanism: additive serotonergic effect

3.5.1.M] Amtolmetin Guacil

- 1) Interaction Effect: an increased risk of bleeding
- 2) Summary: Use caution when coadministering NSAIDs and serotonin [norepinephrine](#) reuptake inhibitors (SNRI) as this may cause an increased risk of bleeding[318]. During clinical trials, concomitant use of NSAIDs and antidepressants, including tricyclic antidepressants, SSRIs, selective serotonin-norepinephrine reuptake inhibitors, and MOAIs, resulted in an increased risk of [intracranial hemorrhage](#) within 30 days of concomitant use compared with antidepressant use alone [319]. When NSAIDs and SNRIs are given concurrently, monitor the patient for signs of increased bleeding.
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: established
- 6) Clinical Management: Serotonin [norepinephrine](#) reuptake inhibitors (SNRI) increase bleeding risk, especially with concomitant use of NSAIDs[318]. When NSAIDs and SNRIs are given concurrently, monitor the patient for signs of increased bleeding.
- 7) Probable Mechanism: unknown
- 8) Literature Reports

a) Concomitant use of NSAIDs and antidepressants, including tricyclic antidepressants, SSRIs, serotonin-norepinephrine reuptake inhibitors, and MAOIs, resulted in an increased risk of [intracranial hemorrhage](#) within 30 days of concomitant use compared with antidepressant use alone. There was no significant difference between the antidepressant drug classes and the increased risk; however, there was an increased risk associated with male patients compared with female patients [319].

3.5.1.N] Anagrelide

- 1) Interaction Effect: an increased risk of bleeding
- 2) Summary: The release of serotonin by [platelets](#) is important for maintaining hemostasis. Case reports and epidemiological studies have shown that use of selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs), including [venlafaxine](#), is associated with [gastrointestinal bleeding](#). Bleeding events with SSRIs and SNRIs included cases of ecchymoses, [hematomas](#), [epistaxis](#), and [petechiae](#); life-threatening hemorrhages have also occurred. Coadministration with drugs that affect coagulation, such as antiplatelet agents, may potentiated the risk of bleeding[321].
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: probable
- 6) Clinical Management: Use caution when [venlafaxine](#) is used concomitantly with antiplatelet agents. Closely monitor patient for signs of bleeding when [venlafaxine](#) is initiated or discontinued in patients receiving antiplatelet agents concomitantly[321].
- 7) Probable Mechanism: unknown

3.5.1.O] Ancrod

1) Interaction Effect: an increased risk of bleeding

2) Summary: Case reports and epidemiological studies have shown that use of selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs), including [venlafaxine](#), is associated with [gastrointestinal bleeding](#). Bleeding events with SSRIs and SNRIs included cases of ecchymoses, [hematomas](#), [epistaxis](#), and [petechiae](#); life-threatening hemorrhages have also occurred. Coadministration with [warfarin](#) or other anticoagulants may potentiate the risk of bleeding. A population-based, case-controlled study of new coumarin users (acenocoumarol and phenprocoumon) with concomitant selective serotonin reuptake inhibitors (SSRIs) resulted in an increased risk of hospitalization due to nongastrointestinal bleeding[354]. Increases in prothrombin time, partial thromboplastin time, or INR have been reported when [venlafaxine](#) was administered to patients receiving [warfarin](#). Therefore, concomitant use of [venlafaxine](#) with [warfarin](#) or other drugs affecting coagulation should be undertaken with caution. Whenever [venlafaxine](#) is initiated or discontinued in patients receiving an anticoagulant, close monitoring of coagulation parameters is recommended [321].

3) Severity: major

4) Onset: unspecified

5) Substantiation: probable

6) Clinical Management: Use caution when [venlafaxine](#) is used concomitantly with [warfarin](#) or other drugs affecting coagulation. Closely monitor coagulation parameters when [venlafaxine](#) is initiated or discontinued in patients receiving anticoagulants, such as [warfarin](#)[321].

7) Probable Mechanism: additive adverse events

8) Literature Reports

a) A population-based, case-controlled study of new coumarin users (acenocoumarol and phenprocoumon) with concomitant selective serotonin reuptake inhibitors (SSRIs) resulted in an increased risk of hospitalization due to nongastrointestinal bleeding. Using national pharmacy and hospitalization records, Netherlands researchers identified 1848 cases that were admitted for abnormal bleeding and compared them with 5818 control subjects also taking coumarins. Median duration of treatment in patients was 220 days (range, 1 to 4690 days). Patients on SSRIs showed greater risk for hospitalization for nongastrointestinal bleeding (adjusted odds ratio (OR) 1.7, 95% confidence interval (CI), 1.1 to 2.5), however, the rate of [gastrointestinal bleeding](#) (adjusted OR 0.8, 95% CI, 0.4 to 1.5) was not significantly different [354].

3.5.1.P] Anisindione

1) Interaction Effect: an increased risk of bleeding

2) Summary: Case reports and epidemiological studies have shown that use of selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs), including [venlafaxine](#), is associated with [gastrointestinal bleeding](#). Bleeding events with SSRIs and SNRIs included cases of ecchymoses, [hematomas](#), [epistaxis](#), and [petechiae](#); life-threatening hemorrhages have also occurred. Coadministration with [warfarin](#) or other anticoagulants may potentiate the risk of bleeding. A population-based, case-controlled study of new coumarin users (acenocoumarol and phenprocoumon) with concomitant selective serotonin reuptake inhibitors (SSRIs) resulted in an increased risk of hospitalization due to nongastrointestinal bleeding[354]. Increases in prothrombin time, partial thromboplastin time, or INR have been reported when [venlafaxine](#) was administered to patients receiving [warfarin](#). Therefore, concomitant use of [venlafaxine](#) with [warfarin](#) or other drugs affecting coagulation should be undertaken with caution. Whenever [venlafaxine](#) is initiated or discontinued in patients receiving an anticoagulant, close monitoring of coagulation parameters is recommended [321].

3) Severity: major

- 4) Onset: unspecified
- 5) Substantiation: probable
- 6) Clinical Management: Use caution when [venlafaxine](#) is used concomitantly with [warfarin](#) or other drugs affecting coagulation. Closely monitor coagulation parameters when [venlafaxine](#) is initiated or discontinued in patients receiving anticoagulants, such as [warfarin](#)[321].
- 7) Probable Mechanism: additive adverse events
- 8) Literature Reports

a) A population-based, case-controlled study of new coumarin users (acenocoumarol and phenprocoumon) with concomitant selective serotonin reuptake inhibitors (SSRIs) resulted in an increased risk of hospitalization due to nongastrointestinal bleeding. Using national pharmacy and hospitalization records, Netherlands researchers identified 1848 cases that were admitted for abnormal bleeding and compared them with 5818 control subjects also taking coumarins. Median duration of treatment in patients was 220 days (range, 1 to 4690 days). Patients on SSRIs showed greater risk for hospitalization for nongastrointestinal bleeding (adjusted odds ratio (OR) 1.7, 95% confidence interval (CI), 1.1 to 2.5), however, the rate of [gastrointestinal bleeding](#) (adjusted OR 0.8, 95% CI, 0.4 to 1.5) was not significantly different [354].

3.5.1.Q] Antithrombin III Human

- 1) Interaction Effect: an increased risk of bleeding
- 2) Summary: Case reports and epidemiological studies have shown that use of selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs), including [venlafaxine](#), is associated with [gastrointestinal bleeding](#). Bleeding events with SSRIs and SNRIs included cases of ecchymoses, [hematomas](#), [epistaxis](#), and [petechiae](#); life-threatening hemorrhages have also occurred. Coadministration with [warfarin](#) or other anticoagulants may potentiate the risk of bleeding. A population-based, case-controlled study of new coumarin users (acenocoumarol and phenprocoumon) with concomitant selective serotonin reuptake inhibitors (SSRIs) resulted in an increased risk of hospitalization due to nongastrointestinal bleeding[354]. Increases in prothrombin time, partial thromboplastin time, or INR have been reported when [venlafaxine](#) was administered to patients receiving [warfarin](#). Therefore, concomitant use of [venlafaxine](#) with [warfarin](#) or other drugs affecting coagulation should be undertaken with caution. Whenever [venlafaxine](#) is initiated or discontinued in patients receiving an anticoagulant, close monitoring of coagulation parameters is recommended [321].
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: probable
- 6) Clinical Management: Use caution when [venlafaxine](#) is used concomitantly with [warfarin](#) or other drugs affecting coagulation. Closely monitor coagulation parameters when [venlafaxine](#) is initiated or discontinued in patients receiving anticoagulants, such as [warfarin](#)[321].
- 7) Probable Mechanism: additive adverse events
- 8) Literature Reports

a) A population-based, case-controlled study of new coumarin users (acenocoumarol and phenprocoumon) with concomitant selective serotonin reuptake inhibitors (SSRIs) resulted in an increased risk of hospitalization due to nongastrointestinal bleeding. Using national pharmacy and hospitalization records, Netherlands researchers identified 1848 cases that were admitted for abnormal bleeding and compared them with 5818 control subjects also taking coumarins. Median duration of treatment in patients was 220 days (range, 1 to 4690 days). Patients on SSRIs showed greater risk for hospitalization for nongastrointestinal bleeding (adjusted odds ratio (OR) 1.7, 95%

confidence interval (CI), 1.1 to 2.5), however, the rate of [gastrointestinal bleeding](#) (adjusted OR 0.8, 95% CI, 0.4 to 1.5) was not significantly different [354].

3.5.1.R] Apixaban

1) Interaction Effect: an increased risk of bleeding

2) Summary: Coadministration of apixaban, a factor Xa inhibitor, and drugs that also affect hemostasis, such as a serotonin [norepinephrine](#) reuptake inhibitor (SNRI), increases the risk of bleeding. There is no established reversal therapy or antidote for apixaban-induced bleeding, and its [anticoagulation](#) effects usually persist until 24 hours after the last dose. Discontinue apixaban if active pathological bleeding occurs[351]. If concomitant apixaban and SNRI therapy is necessary, monitor the patient closely and use with caution.

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Concomitant apixaban therapy with drugs that also affect hemostasis, such as a serotonin [norepinephrine](#) reuptake inhibitor (SNRI), increases the risk of bleeding. Discontinue apixaban if active pathological bleeding occurs. There is no established reversal therapy or antidote for apixaban-induced bleeding, and its [anticoagulation](#) effects usually persist until 24 hours after the last dose[351]. If concomitant apixaban and SNRI therapy is necessary, monitor the patient closely and use with caution.

7) Probable Mechanism: additive effects on hemostasis

3.5.1.S] Argatroban

1) Interaction Effect: an increased risk of bleeding

2) Summary: Case reports and epidemiological studies have shown that use of selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs), including [venlafaxine](#), is associated with [gastrointestinal bleeding](#). Bleeding events with SSRIs and SNRIs included cases of ecchymoses, [hematomas](#), [epistaxis](#), and [petechiae](#); life-threatening hemorrhages have also occurred. Coadministration with [warfarin](#) or other anticoagulants may potentiate the risk of bleeding. A population-based, case-controlled study of new coumarin users (acenocoumarol and phenprocoumon) with concomitant selective serotonin reuptake inhibitors (SSRIs) resulted in an increased risk of hospitalization due to nongastrointestinal bleeding[354]. Increases in prothrombin time, partial thromboplastin time, or INR have been reported when [venlafaxine](#) was administered to patients receiving [warfarin](#). Therefore, concomitant use of [venlafaxine](#) with [warfarin](#) or other drugs affecting coagulation should be undertaken with caution. Whenever [venlafaxine](#) is initiated or discontinued in patients receiving an anticoagulant, close monitoring of coagulation parameters is recommended [321].

3) Severity: major

4) Onset: unspecified

5) Substantiation: probable

6) Clinical Management: Use caution when [venlafaxine](#) is used concomitantly with [warfarin](#) or other drugs affecting coagulation. Closely monitor coagulation parameters when [venlafaxine](#) is initiated or discontinued in patients receiving anticoagulants, such as [warfarin](#)[321].

7) Probable Mechanism: additive adverse events

8) Literature Reports

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

duration of treatment in patients was 220 days (range, 1 to 4690 days). Patients on SSRIs showed greater risk for hospitalization for nongastrointestinal bleeding (adjusted odds ratio (OR) 1.7, 95% confidence interval (CI), 1.1 to 2.5), however, the rate of [gastrointestinal bleeding](#) (adjusted OR 0.8, 95% CI, 0.4 to 1.5) was not significantly different [354].

3.5.1.T] [Aripiprazole](#)

- 1) Interaction Effect: increased risk of QT interval prolongation
- 2) Summary: [Aripiprazole](#) has been associated with QTc interval prolongation[398], and coadministration with another drug known to prolong the QT interval should be undertaken with caution because of risk for additive effects on the QT interval that can lead to serious cardiac adverse effects, including [torsade de pointes](#).
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: [Aripiprazole](#) has been associated with QTc interval prolongation[398], and coadministration with another drug known to prolong the QT interval should be undertaken with caution because of risk for additive effects on the QT interval that can lead to serious cardiac adverse effects, including [torsade de pointes](#).
- 7) Probable Mechanism: additive effects on the QT interval

3.5.1.U] [Arsenic Trioxide](#)

- 1) Interaction Effect: increased risk of QT-interval prolongation and [torsade de pointes](#)
- 2) Summary: Avoid concurrent use of [arsenic trioxide](#), a drug known to prolong the QT interval, with other QT-prolonging drugs, as additive effects on the QT interval can progress to life-threatening [torsade de pointes](#). Whenever possible, discontinue or replace with an alternate drug that does not prolong the QT interval during [arsenic trioxide](#) treatment. Monitor ECGs more frequently if concomitant use is clinically required[238].
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Avoid concurrent use of [arsenic trioxide](#), a drug known to prolong the QT interval, with other QT-prolonging drugs, as additive effects on the QT interval can progress to life-threatening [torsade de pointes](#). Whenever possible, discontinue or replace with an alternate drug that does not prolong the QT interval during [arsenic trioxide](#) treatment. Monitor ECGs more frequently if concomitant use is clinically required[238].
- 7) Probable Mechanism: additive effects on the QT interval

3.5.1.V] [Aspirin](#)

- 1) Interaction Effect: an increased risk of bleeding
- 2) Summary: The release of serotonin by [platelets](#) is important for maintaining hemostasis. Case reports and epidemiological studies have shown that use of selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs), including [venlafaxine](#), is associated with [gastrointestinal bleeding](#). Bleeding events with SSRIs and SNRIs included cases of ecchymoses, [hematomas](#), [epistaxis](#), and [petechiae](#); life-threatening hemorrhages have also occurred. Coadministration with drugs that affect coagulation, such as antiplatelet agents, may potentiated the risk of bleeding[321].
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: probable

6) Clinical Management: Use caution when [venlafaxine](#) is used concomitantly with antiplatelet agents. Closely monitor patient for signs of bleeding when [venlafaxine](#) is initiated or discontinued in patients receiving antiplatelet agents concomitantly[321].

7) Probable Mechanism: unknown

3.5.1.W] [Atazanavir](#)

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

2) Summary: Caution is advised if a CYP3A4 inhibitor is administered with [venlafaxine](#) due to the possible increase in plasma concentration levels of both [venlafaxine](#) and O-desvenlafaxine (ODV)[6]. Patients should be monitored for [venlafaxine](#) toxicity.

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Patients should be monitored for signs of [venlafaxine](#) toxicity such as nausea, drowsiness, and dizziness; a decrease in dosage may be required with concomitant therapy.

7) Probable Mechanism: decreased [venlafaxine](#) clearance

8) Literature Reports

a) Caution is warranted with the concurrent use of CYP3A4 inhibitors, such as [atazanavir](#), and [venlafaxine](#) due to possible increases in plasma concentration levels of both [venlafaxine](#) and O-desvenlafaxine (ODV) [6].

3.5.1.X] [Bemiparin](#)

1) Interaction Effect: an increased risk of bleeding

2) Summary: Case reports and epidemiological studies have shown that use of selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs), including [venlafaxine](#), is associated with [gastrointestinal bleeding](#). Bleeding events with SSRIs and SNRIs included cases of ecchymoses, [hematomas](#), [epistaxis](#), and [petechiae](#); life-threatening hemorrhages have also occurred. Coadministration with [warfarin](#) or other anticoagulants may potentiate the risk of bleeding. A population-based, case-controlled study of new coumarin users (acenocoumarol and phenprocoumon) with concomitant selective serotonin reuptake inhibitors (SSRIs) resulted in an increased risk of hospitalization due to nongastrointestinal bleeding[354]. Increases in prothrombin time, partial thromboplastin time, or INR have been reported when [venlafaxine](#) was administered to patients receiving [warfarin](#). Therefore, concomitant use of [venlafaxine](#) with [warfarin](#) or other drugs affecting coagulation should be undertaken with caution. Whenever [venlafaxine](#) is initiated or discontinued in patients receiving an anticoagulant, close monitoring of coagulation parameters is recommended [321].

3) Severity: major

4) Onset: unspecified

5) Substantiation: probable

6) Clinical Management: Use caution when [venlafaxine](#) is used concomitantly with [warfarin](#) or other drugs affecting coagulation. Closely monitor coagulation parameters when [venlafaxine](#) is initiated or discontinued in patients receiving anticoagulants, such as [warfarin](#)[321].

7) Probable Mechanism: additive adverse events

8) Literature Reports

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

abnormal bleeding and compared them with 5818 control subjects also taking coumarins. Median duration of treatment in patients was 220 days (range, 1 to 4690 days). Patients on SSRIs showed greater risk for hospitalization for nongastrointestinal bleeding (adjusted odds ratio (OR) 1.7, 95% confidence interval (CI), 1.1 to 2.5), however, the rate of [gastrointestinal bleeding](#) (adjusted OR 0.8, 95% CI, 0.4 to 1.5) was not significantly different [354].

3.5.1.Y] [Benzphetamine](#)

- 1) Interaction Effect: increased risk of [serotonin syndrome](#)
- 2) Summary: Coadministration of an [amphetamine](#) and another serotonergic agent may result in [serotonin syndrome](#), because both drugs affect the serotonergic neurotransmitter system. 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[235].
- 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. 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[235].
- 7) Probable Mechanism: additive serotonergic effect

3.5.1.Z] [Bepridil](#)

- 1) Interaction Effect: increased risk of QT-interval prolongation
- 2) Summary: The concomitant use of [bepridil](#) with drugs that cause QT-interval prolongation is contraindicated[405], as coadministration may increase the risk of [ventricular arrhythmias](#).
- 3) Severity: contraindicated
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: The concomitant use of [bepridil](#) with drugs that cause QT-interval prolongation is contraindicated[405], as coadministration may increase the risk of [ventricular arrhythmias](#).
- 7) Probable Mechanism: additive QT-interval prolongation

3.5.1.AA] [Bivalirudin](#)

- 1) Interaction Effect: an increased risk of bleeding
- 2) Summary: Case reports and epidemiological studies have shown that use of selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs), including [venlafaxine](#), is associated with [gastrointestinal bleeding](#). Bleeding events with SSRIs and SNRIs included cases of ecchymoses, [hematomas](#), [epistaxis](#), and [petechiae](#); life-threatening hemorrhages have also occurred. Coadministration with [warfarin](#) or other anticoagulants may potentiate the risk of bleeding. A population-based, case-controlled study of new coumarin users (acenocoumarol and phenprocoumon) with concomitant selective serotonin reuptake inhibitors (SSRIs) resulted in an increased risk of hospitalization due to nongastrointestinal bleeding[354]. Increases in prothrombin time, partial thromboplastin time, or INR have been reported when [venlafaxine](#) was administered to patients receiving [warfarin](#). Therefore, concomitant use of [venlafaxine](#) with [warfarin](#) or other drugs affecting coagulation should be undertaken with caution. Whenever [venlafaxine](#) is initiated or discontinued in patients receiving an anticoagulant, close monitoring of coagulation parameters is recommended [321].

- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: probable
- 6) Clinical Management: Use caution when [venlafaxine](#) is used concomitantly with [warfarin](#) or other drugs affecting coagulation. Closely monitor coagulation parameters when [venlafaxine](#) is initiated or discontinued in patients receiving anticoagulants, such as [warfarin](#)[321].
- 7) Probable Mechanism: additive adverse events
- 8) Literature Reports

a) A population-based, case-controlled study of new coumarin users (acenocoumarol and phenprocoumon) with concomitant selective serotonin reuptake inhibitors (SSRIs) resulted in an increased risk of hospitalization due to nongastrointestinal bleeding. Using national pharmacy and hospitalization records, Netherlands researchers identified 1848 cases that were admitted for abnormal bleeding and compared them with 5818 control subjects also taking coumarins. Median duration of treatment in patients was 220 days (range, 1 to 4690 days). Patients on SSRIs showed greater risk for hospitalization for nongastrointestinal bleeding (adjusted odds ratio (OR) 1.7, 95% confidence interval (CI), 1.1 to 2.5), however, the rate of [gastrointestinal bleeding](#) (adjusted OR 0.8, 95% CI, 0.4 to 1.5) was not significantly different [354].

3.5.1.AB] [Bromfenac](#)

- 1) Interaction Effect: an increased risk of bleeding
- 2) Summary: Use caution when coadministering NSAIDs and serotonin [norepinephrine](#) reuptake inhibitors (SNRI) as this may cause an increased risk of bleeding[318]. During clinical trials, concomitant use of NSAIDs and antidepressants, including tricyclic antidepressants, SSRIs, selective serotonin-norepinephrine reuptake inhibitors, and MAOIs, resulted in an increased risk of [intracranial hemorrhage](#) within 30 days of concomitant use compared with antidepressant use alone [319]. When NSAIDs and SNRIs are given concurrently, monitor the patient for signs of increased bleeding.
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: established
- 6) Clinical Management: Serotonin [norepinephrine](#) reuptake inhibitors (SNRI) increase bleeding risk, especially with concomitant use of NSAIDs[318]. When NSAIDs and SNRIs are given concurrently, monitor the patient for signs of increased bleeding.
- 7) Probable Mechanism: unknown
- 8) Literature Reports

a) Concomitant use of NSAIDs and antidepressants, including tricyclic antidepressants, SSRIs, serotonin-norepinephrine reuptake inhibitors, and MAOIs, resulted in an increased risk of [intracranial hemorrhage](#) within 30 days of concomitant use compared with antidepressant use alone. There was no significant difference between the antidepressant drug classes and the increased risk; however, there was an increased risk associated with male patients compared with female patients [319].

3.5.1.AC] [Bromopride](#)

- 1) Interaction Effect: increased risk of extrapyramidal reactions
- 2) Summary: Concomitant use of bromopride and other drugs that may cause extrapyramidal reactions is contraindicated[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.AD] Bufexamac

- 1) Interaction Effect: an increased risk of bleeding
- 2) Summary: Use caution when coadministering NSAIDs and serotonin [norepinephrine](#) reuptake inhibitors (SNRI) as this may cause an increased risk of bleeding[318]. During clinical trials, concomitant use of NSAIDs and antidepressants, including tricyclic antidepressants, SSRIs, selective serotonin-norepinephrine reuptake inhibitors, and MOAIs, resulted in an increased risk of [intracranial hemorrhage](#) within 30 days of concomitant use compared with antidepressant use alone [319]. When NSAIDs and SNRIs are given concurrently, monitor the patient for signs of increased bleeding.
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: established
- 6) Clinical Management: Serotonin [norepinephrine](#) reuptake inhibitors (SNRI) increase bleeding risk, especially with concomitant use of NSAIDs[318]. When NSAIDs and SNRIs are given concurrently, monitor the patient for signs of increased bleeding.
- 7) Probable Mechanism: unknown
- 8) Literature Reports
 - a) Concomitant use of NSAIDs and antidepressants, including tricyclic antidepressants, SSRIs, serotonin-norepinephrine reuptake inhibitors, and MAOIs, resulted in an increased risk of [intracranial hemorrhage](#) within 30 days of concomitant use compared with antidepressant use alone. There was no significant difference between the antidepressant drug classes and the increased risk; however, there was an increased risk associated with male patients compared with female patients [319].

3.5.1.AE] Buprenorphine

- 1) Interaction Effect: increased risk of [serotonin syndrome](#)
- 2) Summary: Exercise caution with the concomitant use of [buprenorphine](#) and other agents that affect the serotonergic neurotransmitter system due to the potential of [serotonin syndrome](#). If concurrent use is required, monitor for [serotonin syndrome](#), particularly during treatment initiation and with dosage adjustments[255]
- 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[255]
- 7) Probable Mechanism: additive serotonergic effects

3.5.1.AF] Bupropion

- 1) Interaction Effect: increased exposure of CYP2D6 substrates; increased risk of seizure
- 2) Summary: Extreme caution is advised with concomitant use of [buPROPion](#) and other drugs that may lower the seizure threshold as this may increase the risk for seizures. Additionally, concurrent

administration of **buPROPion** (a CYP2D6 inhibitor) and a CYP2D6 substrate may increase the exposure of the CYP2D6 substrate. The CYP2D6 substrate should be initiated at the lower end of the dose range and titrated gradually. If **buPROPion** is added to an existing regimen with a CYP2D6 substrate, consider decreasing the substrate dose, especially if it has a narrow therapeutic index. Use a low initial dose of **buPROPion** and titrate slowly to reduce the risk of seizures[208].

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Extreme caution is advised with concomitant use of **buPROPion** and other drugs that may lower the seizure threshold as this may increase the risk for seizures. Additionally, concurrent administration of **buPROPion** (a CYP2D6 inhibitor) and a CYP2D6 substrate may increase the exposure of the CYP2D6 substrate. The CYP2D6 substrate should be initiated at the lower end of the CYP2D6 substrate dose range and titrated gradually. If **buPROPion** is added to an existing regimen with a CYP2D6 substrate, consider decreasing the CYP2D6 substrate dose, especially if it has a narrow therapeutic index. Use a low initial dose of **buPROPion** and titrate slowly to reduce the risk of seizures[208].

7) Probable Mechanism: inhibition of CYP2D6-mediated metabolism of CYP2D6 substrates by **buPROPion**; lowered seizure threshold

8) Literature Reports

a) The concomitant administration of **fluoxetine** and **buPROPion** was associated with a hyperactive libido in a patient receiving treatment for **major depression**. The patient, a 35-year-old woman, initially received treatment with **fluoxetine** 40 mg daily after converting from **clomipramine** therapy due to suboptimal therapeutic effect. She experienced a diminished libido from the onset of **clomipramine** therapy which did not resolve after conversion to **fluoxetine**. Three months after the conversion to **fluoxetine**, **buPROPion** 100 mg/day was added to her treatment regimen as a potential antidote for the sexual dysfunction. Sexual function appeared to normalize 1 month after the start of **buPROPion** therapy. Approximately 5 months after beginning **buPROPion**, the patient complained of having an exaggerated increase in libido, causing her to discontinue all medications. Her libido returned to normal within 2 months of stopping all medication, accompanied by a recurrence of depressive symptoms. **Fluoxetine** was reintroduced within the same time period, producing another reduction in libido yet accompanied by a full remission from depressive symptoms [209].

b) Coadministration of **buPROPion** 150 mg twice daily and a single dose of **desipramine** 50 mg (a CYP2D6 substrate) in healthy volunteers who were extensive CYP2D6 metabolizers (n=15) resulted in a 2-fold and 5-fold increase in **desipramine** C_{max} and AUC respectively. The effect persisted for 7 days following the last dose of **buPROPion** [210].

3.5.1.AG| Buserelin

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

2) Summary: Use caution with coadministration of gonadotropin-releasing hormone (GnRH) agonists with QT-interval prolonging drugs. Androgen deprivation caused by GnRH agonists may prolong the QT interval and cause additive effects when administered with QT-interval prolonging drugs[377][378][379]. If concurrent therapy is necessary, monitor patients closely for signs and symptoms of **cardiac toxicity**, including changes in the ECG.

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Use caution with coadministration of gonadotropin-releasing hormone (GnRH) agonists with QT-interval prolonging drugs, as additive effects on the QT interval may occur[377][378][379].

7) Probable Mechanism: additive effects on the QT interval

3.5.1.AH] Cannabis

1) Interaction Effect: manic symptoms

2) Summary: One case of mania following use of marijuana with fluoxetine therapy has been reported[143]. 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 [142].

3.5.1.AI] Celecoxib

1) Interaction Effect: an increased risk of bleeding

2) Summary: Use caution when coadministering NSAIDs and serotonin norepinephrine reuptake inhibitors (SNRI) as this may cause an increased risk of bleeding[318]. During clinical trials, concomitant use of NSAIDs and antidepressants, including tricyclic antidepressants, SSRIs, selective serotonin-norepinephrine reuptake inhibitors, and MOAIs, resulted in an increased risk of intracranial hemorrhage within 30 days of concomitant use compared with antidepressant use alone [319]. When NSAIDs and SNRIs are given concurrently, monitor the patient for signs of increased bleeding.

3) Severity: major

4) Onset: unspecified

5) Substantiation: established

6) Clinical Management: Serotonin norepinephrine reuptake inhibitors (SNRI) increase bleeding risk, especially with concomitant use of NSAIDs[318]. When NSAIDs and SNRIs are given concurrently, monitor the patient for signs of increased bleeding.

7) Probable Mechanism: unknown

8) Literature Reports

a) Concomitant use of NSAIDs and antidepressants, including tricyclic antidepressants, SSRIs, serotonin-norepinephrine reuptake inhibitors, and MAOIs, resulted in an increased risk of [intracranial hemorrhage](#) within 30 days of concomitant use compared with antidepressant use alone. There was no significant difference between the antidepressant drug classes and the increased risk; however, there was an increased risk associated with male patients compared with female patients [319].

3.5.1.AJ] Choline Salicylate

1) Interaction Effect: an increased risk of bleeding

2) Summary: Use caution when coadministering NSAIDs and serotonin [norepinephrine](#) reuptake inhibitors (SNRI) as this may cause an increased risk of bleeding[318]. During clinical trials, concomitant use of NSAIDs and antidepressants, including tricyclic antidepressants, SSRIs, selective serotonin-norepinephrine reuptake inhibitors, and MOAIs, resulted in an increased risk of [intracranial hemorrhage](#) within 30 days of concomitant use compared with antidepressant use alone [319]. When NSAIDs and SNRIs are given concurrently, monitor the patient for signs of increased bleeding.

3) Severity: major

4) Onset: unspecified

5) Substantiation: established

6) Clinical Management: Serotonin [norepinephrine](#) reuptake inhibitors (SNRI) increase bleeding risk, especially with concomitant use of NSAIDs[318]. When NSAIDs and SNRIs are given concurrently, monitor the patient for signs of increased bleeding.

7) Probable Mechanism: unknown

8) Literature Reports

a) Concomitant use of NSAIDs and antidepressants, including tricyclic antidepressants, SSRIs, serotonin-norepinephrine reuptake inhibitors, and MAOIs, resulted in an increased risk of [intracranial hemorrhage](#) within 30 days of concomitant use compared with antidepressant use alone. There was no significant difference between the antidepressant drug classes and the increased risk; however, there was an increased risk associated with male patients compared with female patients [319].

3.5.1.AK] Cilostazol

1) Interaction Effect: an increased risk of bleeding

2) Summary: The release of serotonin by [platelets](#) is important for maintaining hemostasis. Case reports and epidemiological studies have shown that use of selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs), including [venlafaxine](#), is associated with [gastrointestinal bleeding](#). Bleeding events with SSRIs and SNRIs included cases of ecchymoses, [hematomas](#), [epistaxis](#), and [petechiae](#); life-threatening hemorrhages have also occurred. Coadministration with drugs that affect coagulation, such as antiplatelet agents, may potentiated the risk of bleeding[321].

3) Severity: major

4) Onset: unspecified

5) Substantiation: probable

6) Clinical Management: Use caution when [venlafaxine](#) is used concomitantly with antiplatelet agents. Closely monitor patient for signs of bleeding when [venlafaxine](#) is initiated or discontinued in patients receiving antiplatelet agents concomitantly[321].

7) Probable Mechanism: unknown

3.5.1.AL] Cimetidine

1) Interaction Effect: an increased risk of [venlafaxine](#) toxicity (nausea, drowsiness, dizziness, ejaculatory disturbances)

2) Summary: Concurrent administration of [cimetidine](#) and [venlafaxine](#) (both at steady state) resulted in a 43% reduction in the oral clearance of [venlafaxine](#) and a 60% increase in the AUC and peak concentration of [venlafaxine](#)[6]. The major metabolite, O-desmethylvenlafaxine, was unaffected by [cimetidine](#), and is present in much greater amounts in the circulation than the parent drug. Because of this, it is unlikely that a clinically significant interaction will occur with this combination. However, this interaction could be more pronounced in patients with preexisting hepatic or renal dysfunction [363]. Therefore, caution is advised when [cimetidine](#) and [venlafaxine](#) are coadministered, particularly in patients with preexisting hepatic or renal function [6].

3) Severity: minor

4) Onset: delayed

5) Substantiation: probable

6) Clinical Management: Concomitant use of [cimetidine](#) and [venlafaxine](#) may result in decreased [venlafaxine](#) clearance. Therefore, patients should be monitored for signs of [venlafaxine](#) toxicity such as nausea, drowsiness, and dizziness; a decrease in dosage may be required with concomitant therapy. An alternative H-2 blocker that has not been reported to impair the metabolism of [venlafaxine](#), such as [ranitidine](#) or [famotidine](#), may be an alternative.

7) Probable Mechanism: decreased [venlafaxine](#) clearance

8) Literature Reports

a) Eighteen healthy volunteers received [venlafaxine](#) 50 mg three times daily for five days alone and in combination with [cimetidine](#) 800 mg daily to determine the influence of [cimetidine](#) on the pharmacokinetics of [venlafaxine](#). [Venlafaxine](#) has pharmacologic activity, and the metabolite O-desmethylvenlafaxine possesses approximately equimolar activity as the parent compound. When [cimetidine](#) was coadministered, the average steady-state concentration of [venlafaxine](#) increased from a mean of 105 ng/mL to 169 ng/mL. However, the mean steady-state concentration of O-desmethylvenlafaxine did not change in the presence of [cimetidine](#) (388 ng/mL vs. 387 ng/mL). Therefore, the sum of the plasma concentrations of [venlafaxine](#) and O-desmethylvenlafaxine increased by an average of 13%. This increase is not expected to produce clinically significant alterations in the response to [venlafaxine](#) in depressed patients without hepatic or renal dysfunction [362].

3.5.1.AM] Cisapride

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

2) Summary: The concomitant use of [cisapride](#) with drugs that cause QT-interval prolongation is contraindicated, as coadministration may increase the risk of QT prolongation and serious [ventricular arrhythmias](#)[154].

3) Severity: contraindicated

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: The concomitant use of [cisapride](#) with drugs that cause QT-interval prolongation is contraindicated, as coadministration may increase the risk of QT prolongation and serious [ventricular arrhythmias](#)[154].

7) Probable Mechanism: additive QT-interval prolongation

3.5.1.AN] Clarithromycin

- 1) Interaction Effect: increased [venlafaxine](#) and active metabolite plasma concentrations and increased risk of QT-interval prolongation
- 2) Summary: Coadministration of CYP3A4 inhibitors, such as [clarithromycin](#), and CYP3A4 substrates, such as [venlafaxine](#), may increase [venlafaxine](#) and active metabolite exposure, which may increase and prolong [venlafaxine](#) therapeutic and adverse effects, including additive prolongation of the QT interval[59]. Consider dosage adjustments, and when possible, monitor serum concentrations of the CYP3A4 substrate (eg, [venlafaxine](#)) [384]
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Coadministration of CYP3A4 inhibitors, such as [clarithromycin](#), and CYP3A4 substrates, such as [venlafaxine](#), may increase [venlafaxine](#) and active metabolite exposure, which may increase and prolong [venlafaxine](#) therapeutic and adverse effects, including additive prolongation of the QT interval[59]. Consider dosage adjustments, and when possible, monitor serum concentrations of the CYP3A4 substrate (eg, [venlafaxine](#)) [384]
- 7) Probable Mechanism: inhibition of CYP3A4-mediated [venlafaxine](#) metabolism by [clarithromycin](#); additive prolongation effects on QT interval

3.5.1.AO] Clomipramine

- 1) Interaction Effect: an increased risk of [cardiotoxicity](#) (QT prolongation, [torsades de pointes](#), [cardiac arrest](#)) and adverse effects of both drugs
- 2) Summary: Tricyclic antidepressants (TCAs) and [venlafaxine](#) have been shown to prolong the QTc interval at the recommended therapeutic dose[297][298]. Even though no formal drug interaction studies have been done, the coadministration of tricyclic antidepressants and other drugs known to prolong the QTc interval, such as [venlafaxine](#), is not recommended [299]. In addition, [venlafaxine](#) and tricyclic antidepressants (TCAs) may competitively inhibit each other's metabolism which may increase side effects of both drugs [300][297][301]. [Venlafaxine](#) increased the AUC, Cmax, and Cmin of [desipramine](#) by approximately 35%. The AUCs of 2-OH-desipramine increased by 2.5 and 4.5 fold when administered with [venlafaxine](#) 37.5 mg and 75 mg every 12 hours, respectively. The pharmacokinetics of [imipramine](#) and the 2-hydroxy metabolite were not affected [6].
- 3) Severity: major
- 4) Onset: rapid
- 5) Substantiation: theoretical
- 6) Clinical Management: Due to the potential for additive effects on the QT interval, the concurrent administration of [venlafaxine](#) and tricyclic antidepressants is not recommended.
- 7) Probable Mechanism: decreased TCA and [venlafaxine](#) metabolism; additive effects on QT prolongation
- 8) Literature Reports

a) When administered with [imipramine](#), the pharmacokinetics of [imipramine](#) and the 2-hydroxy metabolite were not affected. [Venlafaxine](#) increased the area under the concentration-time curve (AUC), maximum concentration (Cmax), and minimum concentration (Cmin) of [desipramine](#) by approximately 35%. The 2-OH-desipramine AUCs increased by 2.5-fold ([venlafaxine](#) 37.5 mg every 12 hours) and by 4.5-fold ([venlafaxine](#) 75 mg every 12 hours). The clinical significance of this finding is unknown [6].

3.5.1.AP] Clonixin

- 1) Interaction Effect: an increased risk of bleeding
- 2) Summary: Use caution when coadministering NSAIDs and serotonin [norepinephrine](#) reuptake inhibitors (SNRI) as this may cause an increased risk of bleeding[318]. During clinical trials, concomitant use of NSAIDs and antidepressants, including tricyclic antidepressants, SSRIs, selective serotonin-norepinephrine reuptake inhibitors, and MAOIs, resulted in an increased risk of [intracranial hemorrhage](#) within 30 days of concomitant use compared with antidepressant use alone [319]. When NSAIDs and SNRIs are given concurrently, monitor the patient for signs of increased bleeding.
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: established
- 6) Clinical Management: Serotonin [norepinephrine](#) reuptake inhibitors (SNRI) increase bleeding risk, especially with concomitant use of NSAIDs[318]. When NSAIDs and SNRIs are given concurrently, monitor the patient for signs of increased bleeding.
- 7) Probable Mechanism: unknown
- 8) Literature Reports

a) Concomitant use of NSAIDs and antidepressants, including tricyclic antidepressants, SSRIs, serotonin-norepinephrine reuptake inhibitors, and MAOIs, resulted in an increased risk of [intracranial hemorrhage](#) within 30 days of concomitant use compared with antidepressant use alone. There was no significant difference between the antidepressant drug classes and the increased risk; however, there was an increased risk associated with male patients compared with female patients [319].

3.5.1.AQ| [Clopidogrel](#)

- 1) Interaction Effect: an increased risk of bleeding
- 2) Summary: The release of serotonin by [platelets](#) is important for maintaining hemostasis. Case reports and epidemiological studies have shown that use of selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs), including [venlafaxine](#), is associated with [gastrointestinal bleeding](#). Bleeding events with SSRIs and SNRIs included cases of ecchymoses, [hematomas](#), [epistaxis](#), and [petechiae](#); life-threatening hemorrhages have also occurred. Coadministration with drugs that affect coagulation, such as antiplatelet agents, may potentiated the risk of bleeding[321].
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: probable
- 6) Clinical Management: Use caution when [venlafaxine](#) is used concomitantly with antiplatelet agents. Closely monitor patient for signs of bleeding when [venlafaxine](#) is initiated or discontinued in patients receiving antiplatelet agents concomitantly[321].
- 7) Probable Mechanism: unknown

3.5.1.AR| [Clozapine](#)

- 1) Interaction Effect: increased plasma levels of [clozapine](#), other CYP2D6 substrates, or both
- 2) Summary: Concomitant use of [clozapine](#), a CYP2D6 substrate, with other drugs metabolized by CYP2D6 can increase plasma levels of one or both CYP2D6 substrates. Use caution with concomitant use of [clozapine](#) and other drugs metabolized by CYP2D6. Lower doses than usually prescribed for either [clozapine](#) or other CYP2D6 substrates may be required[157]. Monitor for increased CYP2D6-mediated adverse effects.
- 3) Severity: moderate
- 4) Onset: unspecified
- 5) Substantiation: theoretical

6j) Clinical Management: Use caution with concomitant use of [clozapine](#) and other drugs metabolized by CYP2D6. Lower doses than usually prescribed for either [clozapine](#) or other CYP2D6 substrates may be required[157]. Monitor for increased CYP2D6-mediated adverse effects.

7j) Probable Mechanism: competitive substrate inhibition

8j) Literature Reports

a) [Paroxetine](#) had no significant effect on serum levels of [clozapine](#) in 14 patients with [schizophrenia](#). [Clozapine](#) 2.5 to 3 mg/kg/day was given for 14 days, then [paroxetine](#) 20 mg daily was added for 14 days. Serum concentrations of [clozapine](#) and 2 metabolites were measured on days 1, 7, and 14. Over the course of this study there was no significant difference in serum concentrations of [clozapine](#) or its metabolites [158].

b) Serum concentrations of [clozapine](#) and nortriptyline, the major metabolite, were evaluated when given in combination with the SSRIs [fluoxetine](#), [paroxetine](#), and [sertraline](#). Eighty outpatients receiving [clozapine](#) all had been diagnosed with [schizophrenia](#) or major affective disorder, and 40 of these patients were receiving an SSRI in combination with [clozapine](#). Of these 40 patients, 14 were receiving [fluoxetine](#), 10 were receiving [sertraline](#), and 16 were receiving [paroxetine](#) therapy. Among the patients on SSRI therapy, serum concentrations of [clozapine](#) and nortriptyline were 41.1% and 44.8% higher, respectively, than in matched patients who were not receiving an SSRI. The ratio of [clozapine](#) plus nortriptyline concentration to dose was also 37.7% higher in patients receiving SSRIs, indicating [clozapine](#) impaired clearance. The differences between the 3 SSRIs were minor, and the study groups were too limited for an accurate statistical comparison between the individual SSRIs [159].

3.5.1.AS] Crizotinib

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

2j) Summary: QT-interval prolongation has occurred during crizotinib therapy. Risk of additive QT-interval prolongation increases during coadministration with other drugs associated with QT prolongation. If concomitant use is clinically indicated, use caution and consider periodic ECG and [electrolyte monitoring](#) during therapy[251]. Dose reduction of crizotinib may be warranted.

3j) Severity: major

4j) Onset: unspecified

5j) Substantiation: theoretical

6j) Clinical Management: Use caution in coadministering crizotinib with a drug known to prolong the QT interval, as concurrent use of such agents may lead to an increased risk of serious cardiac adverse events. If concomitant use is clinically indicated, consider periodic ECG and [electrolyte monitoring](#) during therapy[251]. Dose reduction of crizotinib may be warranted.

7j) Probable Mechanism: additive effects on QT interval

3.5.1.AT] Cyclobenzaprine

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

2j) Summary: [Serotonin syndrome](#), a life-threatening condition, has occurred with coadministration of [cyclobenzaprine](#) and other drugs, such as serotonin [norepinephrine](#) reuptake inhibitors (SNRIs). If concurrent use is necessary, monitor patients closely for [serotonin syndrome](#), especially during treatment initiation and dose increases. Symptoms of [serotonin syndrome](#) include neuromuscular abnormalities (eg, hyperreflexia, tremor, and ataxia), autonomic instability (eg, [tachycardia](#), diaphoresis, and [hyperthermia](#)), gastrointestinal symptoms (eg, nausea, vomiting, diarrhea), or mental status changes (eg, agitation and confusion). Discontinue both drugs immediately if these symptoms occur and initiate supportive therapy[282][283].

- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Coadministration of [cyclobenzaprine](#) with a serotonin [norepinephrine](#) reuptake inhibitor (SNRI) may result in a life-threatening condition called [serotonin syndrome](#). If concurrent use is necessary, monitor patients closely for [serotonin syndrome](#), especially during treatment initiation and dose increases. Symptoms of [serotonin syndrome](#) include neuromuscular abnormalities (eg, hyperreflexia, tremor, and ataxia), autonomic instability (eg, [tachycardia](#), diaphoresis, and [hyperthermia](#)), gastrointestinal symptoms (eg, nausea, vomiting, diarrhea), or mental status changes (eg, agitation and confusion). Discontinue both drugs immediately if these symptoms occur and initiate supportive therapy[282][283].
- 7) Probable Mechanism: additive serotonergic effects

3.5.1.AU] Dabigatran Etexilate

- 1) Interaction Effect: an increased risk of bleeding
- 2) Summary: Case reports and epidemiological studies have shown that use of selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs), including [venlafaxine](#), is associated with [gastrointestinal bleeding](#). Bleeding events with SSRIs and SNRIs included cases of ecchymoses, [hematomas](#), [epistaxis](#), and [petechiae](#); life-threatening hemorrhages have also occurred. Coadministration with [warfarin](#) or other anticoagulants may potentiate the risk of bleeding. A population-based, case-controlled study of new coumarin users (acenocoumarol and phenprocoumon) with concomitant selective serotonin reuptake inhibitors (SSRIs) resulted in an increased risk of hospitalization due to nongastrointestinal bleeding[354]. Increases in prothrombin time, partial thromboplastin time, or INR have been reported when [venlafaxine](#) was administered to patients receiving [warfarin](#). Therefore, concomitant use of [venlafaxine](#) with [warfarin](#) or other drugs affecting coagulation should be undertaken with caution. Whenever [venlafaxine](#) is initiated or discontinued in patients receiving an anticoagulant, close monitoring of coagulation parameters is recommended [321].
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: probable
- 6) Clinical Management: Use caution when [venlafaxine](#) is used concomitantly with [warfarin](#) or other drugs affecting coagulation. Closely monitor coagulation parameters when [venlafaxine](#) is initiated or discontinued in patients receiving anticoagulants, such as [warfarin](#)[321].
- 7) Probable Mechanism: additive adverse events
- 8) Literature Reports

a) A population-based, case-controlled study of new coumarin users (acenocoumarol and phenprocoumon) with concomitant selective serotonin reuptake inhibitors (SSRIs) resulted in an increased risk of hospitalization due to nongastrointestinal bleeding. Using national pharmacy and hospitalization records, Netherlands researchers identified 1848 cases that were admitted for abnormal bleeding and compared them with 5818 control subjects also taking coumarins. Median duration of treatment in patients was 220 days (range, 1 to 4690 days). Patients on SSRIs showed greater risk for hospitalization for nongastrointestinal bleeding (adjusted odds ratio (OR) 1.7, 95% confidence interval (CI), 1.1 to 2.5), however, the rate of [gastrointestinal bleeding](#) (adjusted OR 0.8, 95% CI, 0.4 to 1.5) was not significantly different [354].

3.5.1.AV] Dabrafenib

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

2) Summary: Dabrafenib, as a single agent, has potential to prolong the QT interval; therefore, concomitant use with other drugs that can prolong the QT interval may cause additive effects on the QT interval[275]. Therefore, caution should be exercised with concomitant use and consider assessment and periodic monitoring for [ventricular arrhythmia](#).

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Coadministration of dabrafenib with other drugs that cause QT-interval prolongation may result in additive effects on the QT interval[275]. Exercise caution with concomitant use and consider assessment and periodic monitoring for [ventricular arrhythmia](#).

7) Probable Mechanism: additive QT prolongation

3.5.1.AW] [Dalteparin](#)

1) Interaction Effect: an increased risk of bleeding

2) Summary: Case reports and epidemiological studies have shown that use of selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs), including [venlafaxine](#), is associated with [gastrointestinal bleeding](#). Bleeding events with SSRIs and SNRIs included cases of ecchymoses, [hematomas](#), [epistaxis](#), and [petechiae](#); life-threatening hemorrhages have also occurred. Coadministration with [warfarin](#) or other anticoagulants may potentiate the risk of bleeding. A population-based, case-controlled study of new coumarin users (acenocoumarol and phenprocoumon) with concomitant selective serotonin reuptake inhibitors (SSRIs) resulted in an increased risk of hospitalization due to nongastrointestinal bleeding[354]. Increases in prothrombin time, partial thromboplastin time, or INR have been reported when [venlafaxine](#) was administered to patients receiving [warfarin](#). Therefore, concomitant use of [venlafaxine](#) with [warfarin](#) or other drugs affecting coagulation should be undertaken with caution. Whenever [venlafaxine](#) is initiated or discontinued in patients receiving an anticoagulant, close monitoring of coagulation parameters is recommended [321].

3) Severity: major

4) Onset: unspecified

5) Substantiation: probable

6) Clinical Management: Use caution when [venlafaxine](#) is used concomitantly with [warfarin](#) or other drugs affecting coagulation. Closely monitor coagulation parameters when [venlafaxine](#) is initiated or discontinued in patients receiving anticoagulants, such as [warfarin](#)[321].

7) Probable Mechanism: additive adverse events

8) Literature Reports

a) A population-based, case-controlled study of new coumarin users (acenocoumarol and phenprocoumon) with concomitant selective serotonin reuptake inhibitors (SSRIs) resulted in an increased risk of hospitalization due to nongastrointestinal bleeding. Using national pharmacy and hospitalization records, Netherlands researchers identified 1848 cases that were admitted for abnormal bleeding and compared them with 5818 control subjects also taking coumarins. Median duration of treatment in patients was 220 days (range, 1 to 4690 days). Patients on SSRIs showed greater risk for hospitalization for nongastrointestinal bleeding (adjusted odds ratio (OR) 1.7, 95% confidence interval (CI), 1.1 to 2.5), however, the rate of [gastrointestinal bleeding](#) (adjusted OR 0.8, 95% CI, 0.4 to 1.5) was not significantly different [354].

3.5.1.AX] [Danaparoid](#)

1) Interaction Effect: an increased risk of bleeding

2) Summary: Case reports and epidemiological studies have shown that use of selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs), including [venlafaxine](#),

is associated with [gastrointestinal bleeding](#). Bleeding events with SSRIs and SNRIs included cases of ecchymoses, [hematomas](#), [epistaxis](#), and [petechiae](#); life-threatening hemorrhages have also occurred. Coadministration with [warfarin](#) or other anticoagulants may potentiate the risk of bleeding. A population-based, case-controlled study of new coumarin users (acenocoumarol and phenprocoumon) with concomitant selective serotonin reuptake inhibitors (SSRIs) resulted in an increased risk of hospitalization due to nongastrointestinal bleeding[354]. Increases in prothrombin time, partial thromboplastin time, or INR have been reported when [venlafaxine](#) was administered to patients receiving [warfarin](#). Therefore, concomitant use of [venlafaxine](#) with [warfarin](#) or other drugs affecting coagulation should be undertaken with caution. Whenever [venlafaxine](#) is initiated or discontinued in patients receiving an anticoagulant, close monitoring of coagulation parameters is recommended [321].

3) Severity: major

4) Onset: unspecified

5) Substantiation: probable

6) Clinical Management: Use caution when [venlafaxine](#) is used concomitantly with [warfarin](#) or other drugs affecting coagulation. Closely monitor coagulation parameters when [venlafaxine](#) is initiated or discontinued in patients receiving anticoagulants, such as [warfarin](#)[321].

7) Probable Mechanism: additive adverse events

8) Literature Reports

a) A population-based, case-controlled study of new coumarin users (acenocoumarol and phenprocoumon) with concomitant selective serotonin reuptake inhibitors (SSRIs) resulted in an increased risk of hospitalization due to nongastrointestinal bleeding. Using national pharmacy and hospitalization records, Netherlands researchers identified 1848 cases that were admitted for abnormal bleeding and compared them with 5818 control subjects also taking coumarins. Median duration of treatment in patients was 220 days (range, 1 to 4690 days). Patients on SSRIs showed greater risk for hospitalization for nongastrointestinal bleeding (adjusted odds ratio (OR) 1.7, 95% confidence interval (CI), 1.1 to 2.5), however, the rate of [gastrointestinal bleeding](#) (adjusted OR 0.8, 95% CI, 0.4 to 1.5) was not significantly different [354].

3.5.1.AY] [Darunavir](#)

1) Interaction Effect: increased exposure of the CYP3A and CYP2D6 substrate

2) Summary: Use caution with coadministration of [darunavir](#) (a CYP3A and CYP2D6 inhibitor) with a drug that is a substrate of both CYP3A and CYP2D6. Coadministration may increase the substrate's exposure and increase the risk of clinically significant reactions, including life-threatening or fatal effects. Monitor for adverse reactions associated with concomitant drugs if coadministered[381].

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Use caution with coadministration of [darunavir](#) (a CYP3A and CYP2D6 inhibitor) with a CYP3A and CYP2D6 substrate. Coadministration may increase the substrate exposure and increase the risk of clinically significant reactions, including life-threatening or fatal effects. Monitor for adverse reactions associated with concomitant drugs if coadministered[381].

7) Probable Mechanism: inhibition of CYP3A and CYP3D6 substrate metabolism by [darunavir](#)

3.5.1.AZ] [Defibrotide](#)

1) Interaction Effect: an increased risk of bleeding

2) Summary: Case reports and epidemiological studies have shown that use of selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs), including [venlafaxine](#), is associated with [gastrointestinal bleeding](#). Bleeding events with SSRIs and SNRIs included cases

of ecchymoses, [hematomas](#), [epistaxis](#), and [petechiae](#); life-threatening hemorrhages have also occurred. Coadministration with [warfarin](#) or other anticoagulants may potentiate the risk of bleeding. A population-based, case-controlled study of new coumarin users (acenocoumarol and phenprocoumon) with concomitant selective serotonin reuptake inhibitors (SSRIs) resulted in an increased risk of hospitalization due to nongastrointestinal bleeding[354]. Increases in prothrombin time, partial thromboplastin time, or INR have been reported when [venlafaxine](#) was administered to patients receiving [warfarin](#). Therefore, concomitant use of [venlafaxine](#) with [warfarin](#) or other drugs affecting coagulation should be undertaken with caution. Whenever [venlafaxine](#) is initiated or discontinued in patients receiving an anticoagulant, close monitoring of coagulation parameters is recommended [321].

3) Severity: major

4) Onset: unspecified

5) Substantiation: probable

6) Clinical Management: Use caution when [venlafaxine](#) is used concomitantly with [warfarin](#) or other drugs affecting coagulation. Closely monitor coagulation parameters when [venlafaxine](#) is initiated or discontinued in patients receiving anticoagulants, such as [warfarin](#)[321].

7) Probable Mechanism: additive adverse events

8) Literature Reports

a) A population-based, case-controlled study of new coumarin users (acenocoumarol and phenprocoumon) with concomitant selective serotonin reuptake inhibitors (SSRIs) resulted in an increased risk of hospitalization due to nongastrointestinal bleeding. Using national pharmacy and hospitalization records, Netherlands researchers identified 1848 cases that were admitted for abnormal bleeding and compared them with 5818 control subjects also taking coumarins. Median duration of treatment in patients was 220 days (range, 1 to 4690 days). Patients on SSRIs showed greater risk for hospitalization for nongastrointestinal bleeding (adjusted odds ratio (OR) 1.7, 95% confidence interval (CI), 1.1 to 2.5), however, the rate of [gastrointestinal bleeding](#) (adjusted OR 0.8, 95% CI, 0.4 to 1.5) was not significantly different [354].

3.5.1.BA] Degarelix

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

2) Summary: Use caution with coadministration of gonadotropin-releasing hormone (GnRH) agonists with QT-interval prolonging drugs. Androgen deprivation caused by GnRH agonists may prolong the QT interval and cause additive effects when administered with QT-interval prolonging drugs[377][378][379]. If concurrent therapy is necessary, monitor patients closely for signs and symptoms of [cardiac toxicity](#), including changes in the ECG.

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Use caution with coadministration of gonadotropin-releasing hormone (GnRH) agonists with QT-interval prolonging drugs, as additive effects on the QT interval may occur[377][378][379].

7) Probable Mechanism: additive effects on the QT interval

3.5.1.BB] Delamanid

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

2) Summary: Delamanid is a QT-interval-prolonging drug. Treatment initiation is not recommended in patients on other QT-interval-prolonging agents due to increased risk of the additive QT-interval prolongation effect. If the concurrent use cannot be avoided, an ECG should be obtained baseline and frequently (eg, more than once a month) during the full course of delamanid therapy[355].

- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Delamanid is a QT-interval-prolonging drug. Treatment initiation is not recommended in patients on other QT-interval-prolonging agents due to increased risk of the additive QT-interval prolongation effect. If the concurrent use cannot be avoided, an ECG should be obtained baseline and frequently (eg, more than once a month) during the full course of delamanid therapy[355].
- 7) Probable Mechanism: additive QT- interval prolongation

3.5.1.BC] Dermatatan Sulfate

- 1) Interaction Effect: an increased risk of bleeding
- 2) Summary: Case reports and epidemiological studies have shown that use of selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs), including [venlafaxine](#), is associated with [gastrointestinal bleeding](#). Bleeding events with SSRIs and SNRIs included cases of ecchymoses, [hematomas](#), [epistaxis](#), and [petechiae](#); life-threatening hemorrhages have also occurred. Coadministration with [warfarin](#) or other anticoagulants may potentiate the risk of bleeding. A population-based, case-controlled study of new coumarin users (acenocoumarol and phenprocoumon) with concomitant selective serotonin reuptake inhibitors (SSRIs) resulted in an increased risk of hospitalization due to nongastrointestinal bleeding[354]. Increases in prothrombin time, partial thromboplastin time, or INR have been reported when [venlafaxine](#) was administered to patients receiving [warfarin](#). Therefore, concomitant use of [venlafaxine](#) with [warfarin](#) or other drugs affecting coagulation should be undertaken with caution. Whenever [venlafaxine](#) is initiated or discontinued in patients receiving an anticoagulant, close monitoring of coagulation parameters is recommended [321].
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: probable
- 6) Clinical Management: Use caution when [venlafaxine](#) is used concomitantly with [warfarin](#) or other drugs affecting coagulation. Closely monitor coagulation parameters when [venlafaxine](#) is initiated or discontinued in patients receiving anticoagulants, such as [warfarin](#)[321].
- 7) Probable Mechanism: additive adverse events
- 8) Literature Reports

a) A population-based, case-controlled study of new coumarin users (acenocoumarol and phenprocoumon) with concomitant selective serotonin reuptake inhibitors (SSRIs) resulted in an increased risk of hospitalization due to nongastrointestinal bleeding. Using national pharmacy and hospitalization records, Netherlands researchers identified 1848 cases that were admitted for abnormal bleeding and compared them with 5818 control subjects also taking coumarins. Median duration of treatment in patients was 220 days (range, 1 to 4690 days). Patients on SSRIs showed greater risk for hospitalization for nongastrointestinal bleeding (adjusted odds ratio (OR) 1.7, 95% confidence interval (CI), 1.1 to 2.5), however, the rate of [gastrointestinal bleeding](#) (adjusted OR 0.8, 95% CI, 0.4 to 1.5) was not significantly different [354].

3.5.1.BD] Desipramine

- 1) Interaction Effect: an increased risk of [cardiotoxicity](#) (QT prolongation, [torsades de pointes](#), [cardiac arrest](#)) and adverse effects of both drugs
- 2) Summary: Tricyclic antidepressants (TCAs) and [venlafaxine](#) have been shown to prolong the QTc interval at the recommended therapeutic dose[297][298]. Even though no formal drug interaction studies have been done, the coadministration of tricyclic antidepressants and other drugs known to prolong the QTc interval, such as [venlafaxine](#), is not recommended [299]. In addition, [venlafaxine](#) and tricyclic

antidepressants (TCAs) may competitively inhibit each other's metabolism which may increase side effects of both drugs [300][297][301]. Venlafaxine increased the AUC, Cmax, and Cmin of desipramine by approximately 35%. The AUCs of 2-OH-desipramine increased by 2.5 and 4.5 fold when administered with venlafaxine 37.5 mg and 75 mg every 12 hours, respectively. The pharmacokinetics of imipramine and the 2-hydroxy metabolite were not affected [6].

3) Severity: major

4) Onset: rapid

5) Substantiation: theoretical

6) Clinical Management: Due to the potential for additive effects on the QT interval, the concurrent administration of venlafaxine and tricyclic antidepressants is not recommended.

7) Probable Mechanism: decreased TCA and venlafaxine metabolism; additive effects on QT prolongation

8) Literature Reports

a) When administered with imipramine, the pharmacokinetics of imipramine and the 2-hydroxy metabolite were not affected. Venlafaxine increased the area under the concentration-time curve (AUC), maximum concentration (Cmax), and minimum concentration (Cmin) of desipramine by approximately 35%. The 2-OH-desipramine AUCs increased by 2.5-fold (venlafaxine 37.5 mg every 12 hours) and by 4.5-fold (venlafaxine 75 mg every 12 hours). The clinical significance of this finding is unknown [6].

3.5.1.BE] Desirudin

1) Interaction Effect: an increased risk of bleeding

2) Summary: Case reports and epidemiological studies have shown that use of selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs), including venlafaxine, is associated with gastrointestinal bleeding. Bleeding events with SSRIs and SNRIs included cases of ecchymoses, hematomas, epistaxis, and petechiae; life-threatening hemorrhages have also occurred. Coadministration with warfarin or other anticoagulants may potentiate the risk of bleeding. A population-based, case-controlled study of new coumarin users (acenocoumarol and phenprocoumon) with concomitant selective serotonin reuptake inhibitors (SSRIs) resulted in an increased risk of hospitalization due to nongastrointestinal bleeding[354]. Increases in prothrombin time, partial thromboplastin time, or INR have been reported when venlafaxine was administered to patients receiving warfarin. Therefore, concomitant use of venlafaxine with warfarin or other drugs affecting coagulation should be undertaken with caution. Whenever venlafaxine is initiated or discontinued in patients receiving an anticoagulant, close monitoring of coagulation parameters is recommended [321].

3) Severity: major

4) Onset: unspecified

5) Substantiation: probable

6) Clinical Management: Use caution when venlafaxine is used concomitantly with warfarin or other drugs affecting coagulation. Closely monitor coagulation parameters when venlafaxine is initiated or discontinued in patients receiving anticoagulants, such as warfarin[321].

7) Probable Mechanism: additive adverse events

8) Literature Reports

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

greater risk for hospitalization for nongastrointestinal bleeding (adjusted odds ratio (OR) 1.7, 95% confidence interval (CI), 1.1 to 2.5), however, the rate of [gastrointestinal bleeding](#) (adjusted OR 0.8, 95% CI, 0.4 to 1.5) was not significantly different [354].

3.5.1.BF] Deslorelin

- 1) Interaction Effect: increased risk of QT-interval prolongation
- 2) Summary: Use caution with coadministration of gonadotropin-releasing hormone (GnRH) agonists with QT-interval prolonging drugs. Androgen deprivation caused by GnRH agonists may prolong the QT interval and cause additive effects when administered with QT-interval prolonging drugs[377][378][379]. If concurrent therapy is necessary, monitor patients closely for signs and symptoms of [cardiac toxicity](#), including changes in the ECG.
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Use caution with coadministration of gonadotropin-releasing hormone (GnRH) agonists with QT-interval prolonging drugs, as additive effects on the QT interval may occur[377][378][379].
- 7) Probable Mechanism: additive effects on the QT interval

3.5.1.BG] Desvenlafaxine

- 1) Interaction Effect: increased CYP2D6 substrate exposure; increased risk of [serotonin syndrome](#) ([hypertension](#), [tachycardia](#), [hyperthermia](#), myoclonus, mental status changes)
- 2) Summary: Coadministration of desvenlafaxine, a weak CYP2D6 inhibitor and serotonergic drug, with another serotonergic agent that is also a CYP2D6 substrate may result in increased drug exposure and increased risk of [serotonin syndrome](#). [Serotonin syndrome](#) may be life-threatening. Symptoms may include mental status changes (eg, agitation, hallucinations, coma), autonomic instability (eg, [tachycardia](#), labile blood pressure, [hyperthermia](#)), neuromuscular aberrations (eg, hyperreflexia, incoordination), and gastrointestinal symptoms (eg, nausea, vomiting, diarrhea). If [serotonin syndrome](#) develops, discontinue both agents and initiate supportive symptomatic therapy. If concomitant use is required, no dose adjustment of the CYP2D6 substrate is needed with concurrent desvenlafaxine 100 mg/day or less. Reduce the CYP2D6 substrate dose by 50% if using concurrently with desvenlafaxine 400 mg/day (unapproved dosing) and increase the CYP2D6 substrate to the original dose if concurrent desvenlafaxine 400 mg/day is discontinued. Monitor all patients closely for signs and symptoms of [serotonin syndrome](#), especially during treatment initiation and dose increases of either drug[261].
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Use extreme caution with coadministration of desvenlafaxine (a weak CYP2D6 inhibitor and serotonergic agent) with serotonergic drugs that are also CYP2D6 substrates. Coadministration may result in additive serotonergic effects and may increase CYP2D6 substrate exposure. If concurrent use is required, CYP2D6 substrates may be given at the recommended dose when coadministered with desvenlafaxine 100 mg/day or less. Reduce the CYP2D6 substrate dose by 50% if using concurrently with desvenlafaxine 400 mg/day (unapproved dosing); increase the CYP2D6 substrate to the original dose if concurrent desvenlafaxine 400 mg/day is discontinued. Careful monitoring for signs and symptoms of [serotonin syndrome](#) is recommended, especially during treatment initiation and dose increases. Drug discontinuation and supportive symptomatic treatment is recommended if [serotonin syndrome](#) develops[261].

- 7J) Probable Mechanism: inhibition of CYP2D6-mediated metabolism by desvenlafaxine; additive serotonergic effect
- 8J) Literature Reports

aJ) Coadministration of [desipramine](#) (a CYP2D6 substrate) 50 mg with desvenlafaxine 400 mg/day (unapproved dosing) in a clinical study resulted in an increase of approximately 50% for the C_{max} and 90% for the AUC of [desipramine](#). The differences in [desipramine](#) metabolism were not considered clinically relevant when the dose of desvenlafaxine was 100 mg/day (25% increase in C_{max} and 17% in AUC) [261].

3.5.1.BHJ Dexfenfluramine

- 1J) Interaction Effect: [serotonin syndrome](#) ([hypertension](#), [hyperthermia](#), myoclonus, mental status changes)
- 2J) Summary: Dexfenfluramine is a nonspecific serotonin agonist that both enhances the release of serotonin and inhibits serotonin reuptake. Combination therapy with dexfenfluramine and another selective serotonin reuptake inhibitor, such as [venlafaxine](#), has the potential to cause [serotonin syndrome](#)[359]. [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 [360]. Dexfenfluramine should not be used in combination with [venlafaxine](#) [361].
- 3J) Severity: major
- 4J) Onset: rapid
- 5J) Substantiation: theoretical
- 6J) Clinical Management: Concurrent use of dexfenfluramine and [venlafaxine](#) 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 [venlafaxine](#) or other serotonin specific reuptake inhibitors.
- 7J) Probable Mechanism: additive serotonergic effects

3.5.1.BIJ Dexibuprofen

- 1J) Interaction Effect: an increased risk of bleeding
- 2J) Summary: Use caution when coadministering NSAIDs and serotonin [norepinephrine](#) reuptake inhibitors (SNRI) as this may cause an increased risk of bleeding[318]. During clinical trials, concomitant use of NSAIDs and antidepressants, including tricyclic antidepressants, SSRIs, selective serotonin-norepinephrine reuptake inhibitors, and MOAIs, resulted in an increased risk of [intracranial hemorrhage](#) within 30 days of concomitant use compared with antidepressant use alone [319]. When NSAIDs and SNRIs are given concurrently, monitor the patient for signs of increased bleeding.
- 3J) Severity: major
- 4J) Onset: unspecified
- 5J) Substantiation: established
- 6J) Clinical Management: Serotonin [norepinephrine](#) reuptake inhibitors (SNRI) increase bleeding risk, especially with concomitant use of NSAIDs[318]. When NSAIDs and SNRIs are given concurrently, monitor the patient for signs of increased bleeding.
- 7J) Probable Mechanism: unknown
- 8J) Literature Reports

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

alone. There was no significant difference between the antidepressant drug classes and the increased risk; however, there was an increased risk associated with male patients compared with female patients [319].

3.5.1.BJ] Dexketoprofen

- 1) Interaction Effect: an increased risk of bleeding
- 2) Summary: Use caution when coadministering NSAIDs and serotonin [norepinephrine](#) reuptake inhibitors (SNRI) as this may cause an increased risk of bleeding[318]. During clinical trials, concomitant use of NSAIDs and antidepressants, including tricyclic antidepressants, SSRIs, selective serotonin-norepinephrine reuptake inhibitors, and MOAIs, resulted in an increased risk of [intracranial hemorrhage](#) within 30 days of concomitant use compared with antidepressant use alone [319]. When NSAIDs and SNRIs are given concurrently, monitor the patient for signs of increased bleeding.
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: established
- 6) Clinical Management: Serotonin [norepinephrine](#) reuptake inhibitors (SNRI) increase bleeding risk, especially with concomitant use of NSAIDs[318]. When NSAIDs and SNRIs are given concurrently, monitor the patient for signs of increased bleeding.
- 7) Probable Mechanism: unknown
- 8) Literature Reports

a) Concomitant use of NSAIDs and antidepressants, including tricyclic antidepressants, SSRIs, serotonin-norepinephrine reuptake inhibitors, and MAOIs, resulted in an increased risk of [intracranial hemorrhage](#) within 30 days of concomitant use compared with antidepressant use alone. There was no significant difference between the antidepressant drug classes and the increased risk; however, there was an increased risk associated with male patients compared with female patients [319].

3.5.1.BK] Dextroamphetamine

- 1) Interaction Effect: increased risk of [serotonin syndrome](#)
- 2) Summary: Coadministration of an [amphetamine](#) and another serotonergic agent may result in [serotonin syndrome](#), because both drugs affect the serotonergic neurotransmitter system. 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[235].
- 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. 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[235].
- 7) Probable Mechanism: additive serotonergic effect

3.5.1.BL] Dextromethorphan

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

2) Summary: Venlafaxine is a relatively weak CYP2D6 inhibitor[60] and dextromethorphan is a CYP2D6 substrate. While not specifically studied with venlafaxine, 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 venlafaxine may increase the risk of serotonin syndrome, initial dose reductions of dextromethorphan may be warranted [399] along with monitoring for signs/symptoms of serotonin syndrome (eg, altered mental status, hypertension, restlessness, myoclonus, hyperthermia, hyperreflexia, diaphoresis, shivering, and tremor).

3) Severity: major

4) Onset: delayed

5) Substantiation: theoretical

6) Clinical Management: Use caution when prescribing dextromethorphan to patients who are taking an SSRI (such as venlafaxine), 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 venlafaxine[399].

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

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 dextrophan 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 dextrophan 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) [399].

3.5.1.BM] Dibenzepin

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest) and adverse effects of both drugs

2) Summary: Tricyclic antidepressants (TCAs) and venlafaxine have been shown to prolong the QTc interval at the recommended therapeutic dose[297][298]. Even though no formal drug interaction studies have been done, the coadministration of tricyclic antidepressants and other drugs known to prolong the QTc interval, such as venlafaxine, is not recommended [299]. In addition, venlafaxine and tricyclic antidepressants (TCAs) may competitively inhibit each other's metabolism which may increase side effects of both drugs [300][297][301]. Venlafaxine increased the AUC, Cmax, and Cmin of desipramine by approximately 35%. The AUCs of 2-OH-desipramine increased by 2.5 and 4.5 fold when administered with venlafaxine 37.5 mg and 75 mg every 12 hours, respectively. The pharmacokinetics of imipramine and the 2-hydroxy metabolite were not affected [6].

3) Severity: major

4) Onset: rapid

5) Substantiation: theoretical

6) Clinical Management: Due to the potential for additive effects on the QT interval, the concurrent administration of venlafaxine and tricyclic antidepressants is not recommended.

7) Probable Mechanism: decreased TCA and venlafaxine metabolism; additive effects on QT prolongation

8) Literature Reports

a) When administered with [imipramine](#), the pharmacokinetics of [imipramine](#) and the 2-hydroxy metabolite were not affected. [Venlafaxine](#) increased the area under the concentration-time curve (AUC), maximum concentration (C_{max}), and minimum concentration (C_{min}) of [desipramine](#) by approximately 35%. The 2-OH-desipramine AUCs increased by 2.5-fold ([venlafaxine](#) 37.5 mg every 12 hours) and by 4.5-fold ([venlafaxine](#) 75 mg every 12 hours). The clinical significance of this finding is unknown [6].

3.5.1.BN] [Diclofenac](#)

1) Interaction Effect: an increased risk of bleeding

2) Summary: Use caution when coadministering NSAIDs and serotonin [norepinephrine](#) reuptake inhibitors (SNRI) as this may cause an increased risk of bleeding[318]. During clinical trials, concomitant use of NSAIDs and antidepressants, including tricyclic antidepressants, SSRIs, selective serotonin-norepinephrine reuptake inhibitors, and MOAIs, resulted in an increased risk of [intracranial hemorrhage](#) within 30 days of concomitant use compared with antidepressant use alone [319]. When NSAIDs and SNRIs are given concurrently, monitor the patient for signs of increased bleeding.

3) Severity: major

4) Onset: unspecified

5) Substantiation: established

6) Clinical Management: Serotonin [norepinephrine](#) reuptake inhibitors (SNRI) increase bleeding risk, especially with concomitant use of NSAIDs[318]. When NSAIDs and SNRIs are given concurrently, monitor the patient for signs of increased bleeding.

7) Probable Mechanism: unknown

8) Literature Reports

a) Concomitant use of NSAIDs and antidepressants, including tricyclic antidepressants, SSRIs, serotonin-norepinephrine reuptake inhibitors, and MAOIs, resulted in an increased risk of [intracranial hemorrhage](#) within 30 days of concomitant use compared with antidepressant use alone. There was no significant difference between the antidepressant drug classes and the increased risk; however, there was an increased risk associated with male patients compared with female patients [319].

3.5.1.BO] [Dicumarol](#)

1) Interaction Effect: an increased risk of bleeding

2) Summary: Case reports and epidemiological studies have shown that use of selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs), including [venlafaxine](#), is associated with [gastrointestinal bleeding](#). Bleeding events with SSRIs and SNRIs included cases of ecchymoses, [hematomas](#), [epistaxis](#), and [petechiae](#); life-threatening hemorrhages have also occurred. Coadministration with [warfarin](#) or other anticoagulants may potentiate the risk of bleeding. A population-based, case-controlled study of new coumarin users (acenocoumarol and phenprocoumon) with concomitant selective serotonin reuptake inhibitors (SSRIs) resulted in an increased risk of hospitalization due to nongastrointestinal bleeding[354]. Increases in prothrombin time, partial thromboplastin time, or INR have been reported when [venlafaxine](#) was administered to patients receiving [warfarin](#). Therefore, concomitant use of [venlafaxine](#) with [warfarin](#) or other drugs affecting coagulation should be undertaken with caution. Whenever [venlafaxine](#) is initiated or discontinued in patients receiving an anticoagulant, close monitoring of coagulation parameters is recommended [321].

3) Severity: major

4) Onset: unspecified

5) Substantiation: probable

6) Clinical Management: Use caution when [venlafaxine](#) is used concomitantly with [warfarin](#) or other drugs affecting coagulation. Closely monitor coagulation parameters when [venlafaxine](#) is initiated or discontinued in patients receiving anticoagulants, such as [warfarin](#)[321].

7) Probable Mechanism: additive adverse events

8) Literature Reports

a) A population-based, case-controlled study of new coumarin users (acenocoumarol and phenprocoumon) with concomitant selective serotonin reuptake inhibitors (SSRIs) resulted in an increased risk of hospitalization due to nongastrointestinal bleeding. Using national pharmacy and hospitalization records, Netherlands researchers identified 1848 cases that were admitted for abnormal bleeding and compared them with 5818 control subjects also taking coumarins. Median duration of treatment in patients was 220 days (range, 1 to 4690 days). Patients on SSRIs showed greater risk for hospitalization for nongastrointestinal bleeding (adjusted odds ratio (OR) 1.7, 95% confidence interval (CI), 1.1 to 2.5), however, the rate of [gastrointestinal bleeding](#) (adjusted OR 0.8, 95% CI, 0.4 to 1.5) was not significantly different [354].

3.5.1.BP] [Diflunisal](#)

1) Interaction Effect: an increased risk of bleeding

2) Summary: Use caution when coadministering NSAIDs and serotonin [norepinephrine](#) reuptake inhibitors (SNRI) as this may cause an increased risk of bleeding[318]. During clinical trials, concomitant use of NSAIDs and antidepressants, including tricyclic antidepressants, SSRIs, selective serotonin-norepinephrine reuptake inhibitors, and MOAIs, resulted in an increased risk of [intracranial hemorrhage](#) within 30 days of concomitant use compared with antidepressant use alone [319]. When NSAIDs and SNRIs are given concurrently, monitor the patient for signs of increased bleeding.

3) Severity: major

4) Onset: unspecified

5) Substantiation: established

6) Clinical Management: Serotonin [norepinephrine](#) reuptake inhibitors (SNRI) increase bleeding risk, especially with concomitant use of NSAIDs[318]. When NSAIDs and SNRIs are given concurrently, monitor the patient for signs of increased bleeding.

7) Probable Mechanism: unknown

8) Literature Reports

a) Concomitant use of NSAIDs and antidepressants, including tricyclic antidepressants, SSRIs, serotonin-norepinephrine reuptake inhibitors, and MAOIs, resulted in an increased risk of [intracranial hemorrhage](#) within 30 days of concomitant use compared with antidepressant use alone. There was no significant difference between the antidepressant drug classes and the increased risk; however, there was an increased risk associated with male patients compared with female patients [319].

3.5.1.BQ] [Dipyridamole](#)

1) Interaction Effect: an increased risk of bleeding

2) Summary: The release of serotonin by [platelets](#) is important for maintaining hemostasis. Case reports and epidemiological studies have shown that use of selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs), including [venlafaxine](#), is associated with [gastrointestinal bleeding](#). Bleeding events with SSRIs and SNRIs included cases of ecchymoses, [hematomas](#), [epistaxis](#), and [petechiae](#); life-threatening hemorrhages have also occurred. Coadministration with drugs that affect coagulation, such as antiplatelet agents, may potentiated the risk of bleeding[321].

3) Severity: major

- 4) Onset: unspecified
- 5) Substantiation: probable
- 6) Clinical Management: Use caution when [venlafaxine](#) is used concomitantly with antiplatelet agents. Closely monitor patient for signs of bleeding when [venlafaxine](#) is initiated or discontinued in patients receiving antiplatelet agents concomitantly[321].
- 7) Probable Mechanism: unknown

3.5.1.BR] Dipyrrone

- 1) Interaction Effect: an increased risk of bleeding
- 2) Summary: Use caution when coadministering NSAIDs and serotonin [norepinephrine](#) reuptake inhibitors (SNRI) as this may cause an increased risk of bleeding[318]. During clinical trials, concomitant use of NSAIDs and antidepressants, including tricyclic antidepressants, SSRIs, selective serotonin-norepinephrine reuptake inhibitors, and MOAIs, resulted in an increased risk of [intracranial hemorrhage](#) within 30 days of concomitant use compared with antidepressant use alone [319]. When NSAIDs and SNRIs are given concurrently, monitor the patient for signs of increased bleeding.
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: established
- 6) Clinical Management: Serotonin [norepinephrine](#) reuptake inhibitors (SNRI) increase bleeding risk, especially with concomitant use of NSAIDs[318]. When NSAIDs and SNRIs are given concurrently, monitor the patient for signs of increased bleeding.
- 7) Probable Mechanism: unknown
- 8) Literature Reports

a) Concomitant use of NSAIDs and antidepressants, including tricyclic antidepressants, SSRIs, serotonin-norepinephrine reuptake inhibitors, and MAOIs, resulted in an increased risk of [intracranial hemorrhage](#) within 30 days of concomitant use compared with antidepressant use alone. There was no significant difference between the antidepressant drug classes and the increased risk; however, there was an increased risk associated with male patients compared with female patients [319].

3.5.1.BS] [Dolasetron](#)

- 1) Interaction Effect: increased risk of [serotonin syndrome](#)
- 2) Summary: Concomitant use of [dolasetron](#) with a serotonergic agent may increase the risk of [serotonin syndrome](#). Monitor for the emergence of [serotonin syndrome](#). Discontinue treatment with [dolasetron](#) and institute supportive therapy if symptoms of [serotonin syndrome](#) occur[201][202].
- 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[201][202].
- 7) Probable Mechanism: unknown

3.5.1.BT] Domperidone

- 1) Interaction Effect: increased risk of QT interval prolongation
- 2) Summary: Use caution with coadministration of [venlafaxine](#), a potential QT interval prolonging drug, and domperidone, a drug that has been associated with an increased risk of sudden cardiac death. In case

control studies, an increased risk of sudden cardiac death was observed with the use of oral domperidone, particularly at doses greater than 30 mg/day and in patients older than 60 years. If coadministration is necessary, initiate domperidone at the lowest possible dose and titrate with caution. Discontinue domperidone if the patient experiences dizziness, palpitations, syncope, or seizure[337].

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Use caution when coadministering domperidone and [venlafaxine](#) as it may increase the risk of serious cardiac effects, including [ventricular arrhythmias](#) and sudden cardiac death, particularly at domperidone doses greater than 30 mg/day and in patients older than 60 years. If coadministration is necessary, initiate domperidone at the lowest possible dose and titrate with caution. Discontinue domperidone if the patient experiences dizziness, palpitations, syncope, or seizure[337].

7) Probable Mechanism: additive effects on the QT interval

3.5.1.BU] [Donepezil](#)

1) Interaction Effect: increased risk of QT-interval prolongation and [torsade de pointes](#)

2) Summary: [Donepezil](#) has been associated with QT-interval prolongation[249][250]. Use caution when administering [donepezil](#) concomitantly with other drugs that cause QT-interval prolongation.

3) Severity: major

4) Onset: delayed

5) Substantiation: probable

6) Clinical Management: [Donepezil](#) has been associated with QT-interval prolongation[249][250]. Use caution when administering [donepezil](#) concomitantly with other drugs that cause QT-interval prolongation

7) Probable Mechanism: additive QT-interval prolongation

3.5.1.BV] [Dothiepin](#)

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

2) Summary: Tricyclic antidepressants (TCAs) and [venlafaxine](#) have been shown to prolong the QTc interval at the recommended therapeutic dose[297][298]. Even though no formal drug interaction studies have been done, the coadministration of tricyclic antidepressants and other drugs known to prolong the QTc interval, such as [venlafaxine](#), is not recommended [299]. In addition, [venlafaxine](#) and tricyclic antidepressants (TCAs) may competitively inhibit each other's metabolism which may increase side effects of both drugs [300][297][301]. [Venlafaxine](#) increased the AUC, Cmax, and Cmin of [desipramine](#) by approximately 35%. The AUCs of 2-OH-desipramine increased by 2.5 and 4.5 fold when administered with [venlafaxine](#) 37.5 mg and 75 mg every 12 hours, respectively. The pharmacokinetics of [imipramine](#) and the 2-hydroxy metabolite were not affected [6].

3) Severity: major

4) Onset: rapid

5) Substantiation: theoretical

6) Clinical Management: Due to the potential for additive effects on the QT interval, the concurrent administration of [venlafaxine](#) and tricyclic antidepressants is not recommended.

7) Probable Mechanism: decreased TCA and [venlafaxine](#) metabolism; additive effects on QT prolongation

8) Literature Reports

a) When administered with [imipramine](#), the pharmacokinetics of [imipramine](#) and the 2-hydroxy metabolite were not affected. [Venlafaxine](#) increased the area under the concentration-time curve (AUC), maximum concentration (Cmax), and minimum concentration (Cmin) of [desipramine](#)

by approximately 35%. The 2-OH-desipramine AUCs increased by 2.5-fold (venlafaxine 37.5 mg every 12 hours) and by 4.5-fold (venlafaxine 75 mg every 12 hours). The clinical significance of this finding is unknown [6].

3.5.1.BW] Doxepin

1) Interaction Effect: an increased risk of **cardiotoxicity** (QT prolongation, **torsades de pointes**, **cardiac arrest**) and adverse effects of both drugs

2) Summary: Tricyclic antidepressants (TCAs) and venlafaxine have been shown to prolong the QTc interval at the recommended therapeutic dose[297][298]. Even though no formal drug interaction studies have been done, the coadministration of tricyclic antidepressants and other drugs known to prolong the QTc interval, such as venlafaxine, is not recommended [299]. In addition, venlafaxine and tricyclic antidepressants (TCAs) may competitively inhibit each other's metabolism which may increase side effects of both drugs [300][297][301]. Venlafaxine increased the AUC, Cmax, and Cmin of desipramine by approximately 35%. The AUCs of 2-OH-desipramine increased by 2.5 and 4.5 fold when administered with venlafaxine 37.5 mg and 75 mg every 12 hours, respectively. The pharmacokinetics of imipramine and the 2-hydroxy metabolite were not affected [6].

3) Severity: major

4) Onset: rapid

5) Substantiation: theoretical

6) Clinical Management: Due to the potential for additive effects on the QT interval, the concurrent administration of venlafaxine and tricyclic antidepressants is not recommended.

7) Probable Mechanism: decreased TCA and venlafaxine metabolism; additive effects on QT prolongation

8) Literature Reports

a) When administered with imipramine, the pharmacokinetics of imipramine and the 2-hydroxy metabolite were not affected. Venlafaxine increased the area under the concentration-time curve (AUC), maximum concentration (Cmax), and minimum concentration (Cmin) of desipramine by approximately 35%. The 2-OH-desipramine AUCs increased by 2.5-fold (venlafaxine 37.5 mg every 12 hours) and by 4.5-fold (venlafaxine 75 mg every 12 hours). The clinical significance of this finding is unknown [6].

3.5.1.BX] Dronedaron

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

2) Summary: The concomitant use of dronedarone with drugs that cause QT-interval prolongation is contraindicated, as coadministration may increase the risk of QT prolongation and serious **ventricular arrhythmias**[353].

3) Severity: contraindicated

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: The concomitant use of dronedarone with drugs that cause QT-interval prolongation is contraindicated, as coadministration may increase the risk of QT prolongation and serious **ventricular arrhythmias**[353].

7) Probable Mechanism: additive QT-interval prolongation

3.5.1.BY] Droxicam

1) Interaction Effect: an increased risk of bleeding

2) Summary: Use caution when coadministering NSAIDs and serotonin **norepinephrine** reuptake inhibitors (SNRI) as this may cause an increased risk of bleeding[318]. During clinical trials, concomitant

use of NSAIDs and antidepressants, including tricyclic antidepressants, SSRIs, selective serotonin-norepinephrine reuptake inhibitors, and MAOIs, resulted in an increased risk of [intracranial hemorrhage](#) within 30 days of concomitant use compared with antidepressant use alone [319]. When NSAIDs and SNRIs are given concurrently, monitor the patient for signs of increased bleeding.

3) Severity: major

4) Onset: unspecified

5) Substantiation: established

6) Clinical Management: Serotonin [norepinephrine](#) reuptake inhibitors (SNRI) increase bleeding risk, especially with concomitant use of NSAIDs[318]. When NSAIDs and SNRIs are given concurrently, monitor the patient for signs of increased bleeding.

7) Probable Mechanism: unknown

8) Literature Reports

a) Concomitant use of NSAIDs and antidepressants, including tricyclic antidepressants, SSRIs, serotonin-norepinephrine reuptake inhibitors, and MAOIs, resulted in an increased risk of [intracranial hemorrhage](#) within 30 days of concomitant use compared with antidepressant use alone. There was no significant difference between the antidepressant drug classes and the increased risk; however, there was an increased risk associated with male patients compared with female patients [319].

3.5.1.BZ] [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 [venlafaxine](#), also a selective serotonin and [norepinephrine](#) reuptake inhibitor, is not recommended due to the potential for [serotonin syndrome](#)[343].

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: The concomitant use of [duloxetine](#) and [venlafaxine](#) is not recommended due to the potential for development of [serotonin syndrome](#)[343].

7) Probable Mechanism: additive serotonergic effects

3.5.1.CA] [Edoxaban](#)

1) Interaction Effect: an increased risk of bleeding

2) Summary: Case reports and epidemiological studies have shown that use of selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs), including [venlafaxine](#), is associated with [gastrointestinal bleeding](#). Bleeding events with SSRIs and SNRIs included cases of ecchymoses, [hematomas](#), [epistaxis](#), and [petechiae](#); life-threatening hemorrhages have also occurred. Coadministration with [warfarin](#) or other anticoagulants may potentiate the risk of bleeding. A population-based, case-controlled study of new coumarin users (acenocoumarol and phenprocoumon) with concomitant selective serotonin reuptake inhibitors (SSRIs) resulted in an increased risk of hospitalization due to nongastrointestinal bleeding[354]. Increases in prothrombin time, partial thromboplastin time, or INR have been reported when [venlafaxine](#) was administered to patients receiving [warfarin](#). Therefore, concomitant use of [venlafaxine](#) with [warfarin](#) or other drugs affecting coagulation should be undertaken with caution. Whenever [venlafaxine](#) is initiated or discontinued in patients receiving an anticoagulant, close monitoring of coagulation parameters is recommended [321].

3) Severity: major

4) Onset: unspecified

5) Substantiation: probable

6) Clinical Management: Use caution when [venlafaxine](#) is used concomitantly with [warfarin](#) or other drugs affecting coagulation. Closely monitor coagulation parameters when [venlafaxine](#) is initiated or discontinued in patients receiving anticoagulants, such as [warfarin](#)[321].

7) Probable Mechanism: additive adverse events

8) Literature Reports

a) A population-based, case-controlled study of new coumarin users (acenocoumarol and phenprocoumon) with concomitant selective serotonin reuptake inhibitors (SSRIs) resulted in an increased risk of hospitalization due to nongastrointestinal bleeding. Using national pharmacy and hospitalization records, Netherlands researchers identified 1848 cases that were admitted for abnormal bleeding and compared them with 5818 control subjects also taking coumarins. Median duration of treatment in patients was 220 days (range, 1 to 4690 days). Patients on SSRIs showed greater risk for hospitalization for nongastrointestinal bleeding (adjusted odds ratio (OR) 1.7, 95% confidence interval (CI), 1.1 to 2.5), however, the rate of [gastrointestinal bleeding](#) (adjusted OR 0.8, 95% CI, 0.4 to 1.5) was not significantly different [354].

3.5.1.CB] [Efavirenz](#)

1) Interaction Effect: increased risk of QT interval prolongation

2) Summary: Consider alternatives to [efavirenz](#) when used concomitantly with another drug that prolongs the QT interval or has a known risk of [torsade de pointes](#), because additive effects on the QT interval may occur. In a QT study of 58 healthy subjects, the mean C_{max} in patients with the CYP2B6 *6/*6 genotype was 2.25-fold higher than the mean C_{max} in those with the CYP2B6 *1/*1 genotype and the mean QTc interval prolongation was 8.7 milliseconds in subjects with the CYP2B6 *6/*6 genotype[253].

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Consider alternatives to [efavirenz](#) when used concomitantly with another drug that prolongs the QT interval or has a known risk of [torsade de pointes](#), because additive effects on the QT interval may occur[253].

7) Probable Mechanism: additive effects on the QT interval

8) Literature Reports

a) In a QT study of healthy subjects (N=58) enriched for CYP2B6 polymorphisms, a positive association between [efavirenz](#) concentration and QTc prolongation was observed. Following administration of [efavirenz](#) 600 mg/day for 14 days, the mean C_{max} in subjects with the CYP2B6 *6/*6 genotype was 2.25-fold higher than the mean C_{max} in subjects with the CYP2B6 *1/*1 genotype and the mean QTc interval prolongation was 8.7 milliseconds in subjects with the CYP2B6 *6/*6 genotype [253].

3.5.1.CC] [Eletriptan](#)

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

2) Summary: Concomitant use of [eletriptan](#) with a serotonin [norepinephrine](#) reuptake inhibitor (SNRI) may result in [serotonin syndrome](#) due to additive serotonergic effects. Cases of life-threatening [serotonin syndrome](#) have been reported following coadministration of triptans and SNRIs. If treatment with [eletriptan](#) and an SNRI is required, the patient should be monitored closely for signs and symptoms of [serotonin syndrome](#), particularly during treatment initiation and dose increases[130].

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Concomitant use of [eletriptan](#) and a serotonin [norepinephrine](#) reuptake inhibitor (SNRI) may result in [serotonin syndrome](#). Cases of life-threatening [serotonin syndrome](#) have been reported following coadministration of triptans and SNRIs. Symptoms may include agitation, hallucinations, coma, incoordination, [tachycardia](#), labile blood pressure, [hyperthermia](#), hyperreflexia, nausea, vomiting, and diarrhea. If concomitant use is warranted, closely observe the patient for signs and symptoms of [serotonin syndrome](#), especially during treatment initiation and dose increases[130].

7) Probable Mechanism: additive serotonergic effects

3.5.1.CD] Eliglustat

1) Interaction Effect: increased CYP2D6 substrate exposure

2) Summary: Use caution with coadministration of eliglustat, a CYP2D6 inhibitor, with CYP2D6 substrates, as concurrent use may increase serum concentrations of CYP2D6 substrates. Among patients with [Gaucher disease type 1](#), concurrent use of eliglustat increased mean Cmax and AUC of [metoprolol](#) (a CYP2D6 substrate) from 1.2- to 1.7-fold in intermediate CYP2D6 metabolizers and 1.6- to 2.3-fold higher than baseline in extensive CYP2D6 metabolizers, respectively. If concurrent use is necessary, monitor therapeutic drug concentrations as clinically indicated, or consider reducing the dose of the CYP2D6 substrate and titrating to clinical effect[284].

3) Severity: moderate

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Use caution with coadministration of eliglustat with CYP2D6 substrates, as concurrent use may increase serum concentrations of CYP2D6 substrates. If concurrent use is necessary, monitor therapeutic drug concentrations as clinically indicated, or consider reducing the dose of the CYP2D6 substrate and titrating to clinical effect[284].

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

8) Literature Reports

a) Among patients with [Gaucher disease type 1](#) who were extensive CYP2D6 metabolizers, mean Cmax and AUC of [metoprolol](#) (a CYP2D6 substrate) increased by 1.7- and 2.3-fold over baseline, respectively, when used concurrently with eliglustat 127 mg twice daily (unapproved dose) and by 1.2- and 1.6-fold, respectively, in intermediate CYP2D6 metabolizers [284].

3.5.1.CE] Enoxaparin

1) Interaction Effect: an increased risk of bleeding

2) Summary: Case reports and epidemiological studies have shown that use of selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs), including [venlafaxine](#), is associated with [gastrointestinal bleeding](#). Bleeding events with SSRIs and SNRIs included cases of ecchymoses, [hematomas](#), [epistaxis](#), and [petechiae](#); life-threatening hemorrhages have also occurred. Coadministration with [warfarin](#) or other anticoagulants may potentiate the risk of bleeding. A population-based, case-controlled study of new coumarin users (acenocoumarol and phenprocoumon) with concomitant selective serotonin reuptake inhibitors (SSRIs) resulted in an increased risk of hospitalization due to nongastrointestinal bleeding[354]. Increases in prothrombin time, partial thromboplastin time, or INR have been reported when [venlafaxine](#) was administered to patients receiving [warfarin](#). Therefore, concomitant use of [venlafaxine](#) with [warfarin](#) or other drugs affecting coagulation should be undertaken with caution. Whenever [venlafaxine](#) is initiated or discontinued in patients receiving an anticoagulant, close monitoring of coagulation parameters is recommended [321].

3) Severity: major

4) Onset: unspecified

5) Substantiation: probable

6) Clinical Management: Use caution when [venlafaxine](#) is used concomitantly with [warfarin](#) or other drugs affecting coagulation. Closely monitor coagulation parameters when [venlafaxine](#) is initiated or discontinued in patients receiving anticoagulants, such as [warfarin](#)[321].

7) Probable Mechanism: additive adverse events

8) Literature Reports

a) A population-based, case-controlled study of new coumarin users (acenocoumarol and phenprocoumon) with concomitant selective serotonin reuptake inhibitors (SSRIs) resulted in an increased risk of hospitalization due to nongastrointestinal bleeding. Using national pharmacy and hospitalization records, Netherlands researchers identified 1848 cases that were admitted for abnormal bleeding and compared them with 5818 control subjects also taking coumarins. Median duration of treatment in patients was 220 days (range, 1 to 4690 days). Patients on SSRIs showed greater risk for hospitalization for nongastrointestinal bleeding (adjusted odds ratio (OR) 1.7, 95% confidence interval (CI), 1.1 to 2.5), however, the rate of [gastrointestinal bleeding](#) (adjusted OR 0.8, 95% CI, 0.4 to 1.5) was not significantly different [354].

3.5.1.CF| [Entacapone](#)

1) Interaction Effect: an increased risk of [tachycardia](#), [hypertension](#), and [arrhythmias](#)

2) Summary: [Entacapone](#) is an inhibitor of catechol-o-methyltransferase (COMT), and inhibits the metabolism of [norepinephrine](#) and related catecholamines. [Venlafaxine](#) is a [norepinephrine](#) reuptake inhibitor; the concurrent administration of [entacapone](#) and [venlafaxine](#) may theoretically provoke a supratherapeutic increase in [norepinephrine](#) serum concentrations, increasing the risk of cardiovascular adverse events[280][281].

3) Severity: major

4) Onset: rapid

5) Substantiation: theoretical

6) Clinical Management: Coadministration of [entacapone](#) with [venlafaxine](#) is not recommended. Caution should be exercised if coadministration of these two drugs are unavoidable. Patients should be monitored for excessively increased heart rate, [increased blood pressure](#), and [cardiac arrhythmias](#).

7) Probable Mechanism: augmented inhibition of [norepinephrine](#) metabolism and clearance

3.5.1.CG| [Epoprostenol](#)

1) Interaction Effect: an increased risk of bleeding

2) Summary: The release of serotonin by [platelets](#) is important for maintaining hemostasis. Case reports and epidemiological studies have shown that use of selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs), including [venlafaxine](#), is associated with [gastrointestinal bleeding](#). Bleeding events with SSRIs and SNRIs included cases of ecchymoses, [hematomas](#), [epistaxis](#), and [petechiae](#); life-threatening hemorrhages have also occurred. Coadministration with drugs that affect coagulation, such as antiplatelet agents, may potentiated the risk of bleeding[321].

3) Severity: major

4) Onset: unspecified

5) Substantiation: probable

6) Clinical Management: Use caution when [venlafaxine](#) is used concomitantly with antiplatelet agents. Closely monitor patient for signs of bleeding when [venlafaxine](#) is initiated or discontinued in patients receiving antiplatelet agents concomitantly[321].

7) Probable Mechanism: unknown

3.5.1.CH| [Eptifibatide](#)

- 1) Interaction Effect: an increased risk of bleeding
- 2) Summary: The release of serotonin by [platelets](#) is important for maintaining hemostasis. Case reports and epidemiological studies have shown that use of selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs), including [venlafaxine](#), is associated with [gastrointestinal bleeding](#). Bleeding events with SSRIs and SNRIs included cases of ecchymoses, [hematomas](#), [epistaxis](#), and [petechiae](#); life-threatening hemorrhages have also occurred. Coadministration with drugs that affect coagulation, such as antiplatelet agents, may potentiated the risk of bleeding[321].
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: probable
- 6) Clinical Management: Use caution when [venlafaxine](#) is used concomitantly with antiplatelet agents. Closely monitor patient for signs of bleeding when [venlafaxine](#) is initiated or discontinued in patients receiving antiplatelet agents concomitantly[321].
- 7) Probable Mechanism: unknown

3.5.1.CI] Escitalopram

- 1) Interaction Effect: increased risk of QT-interval prolongation
- 2) Summary: Escitalopram is a QT-interval-prolonging drug[277]. Use caution with concurrent use of other QT-interval-prolonging agents, due to increased risk of additive QT-interval prolongation.
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Escitalopram is a QT-interval-prolonging drug[277]. Use caution with concurrent use of other QT-interval-prolonging agents, due to increased risk of additive QT-interval prolongation.
- 7) Probable Mechanism: additive QT-interval prolongation

3.5.1.CJ] Etodolac

- 1) Interaction Effect: an increased risk of bleeding
- 2) Summary: Use caution when coadministering NSAIDs and serotonin [norepinephrine](#) reuptake inhibitors (SNRI) as this may cause an increased risk of bleeding[318]. During clinical trials, concomitant use of NSAIDs and antidepressants, including tricyclic antidepressants, SSRIs, selective serotonin-norepinephrine reuptake inhibitors, and MAOIs, resulted in an increased risk of [intracranial hemorrhage](#) within 30 days of concomitant use compared with antidepressant use alone [319]. When NSAIDs and SNRIs are given concurrently, monitor the patient for signs of increased bleeding.
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: established
- 6) Clinical Management: Serotonin [norepinephrine](#) reuptake inhibitors (SNRI) increase bleeding risk, especially with concomitant use of NSAIDs[318]. When NSAIDs and SNRIs are given concurrently, monitor the patient for signs of increased bleeding.
- 7) Probable Mechanism: unknown
- 8) Literature Reports

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

increased risk; however, there was an increased risk associated with male patients compared with female patients [319].

3.5.1.CK] Etofenamate

1) Interaction Effect: an increased risk of bleeding

2) Summary: Use caution when coadministering NSAIDs and serotonin [norepinephrine](#) reuptake inhibitors (SNRI) as this may cause an increased risk of bleeding[318]. During clinical trials, concomitant use of NSAIDs and antidepressants, including tricyclic antidepressants, SSRIs, selective serotonin-norepinephrine reuptake inhibitors, and MAOIs, resulted in an increased risk of [intracranial hemorrhage](#) within 30 days of concomitant use compared with antidepressant use alone [319]. When NSAIDs and SNRIs are given concurrently, monitor the patient for signs of increased bleeding.

3) Severity: major

4) Onset: unspecified

5) Substantiation: established

6) Clinical Management: Serotonin [norepinephrine](#) reuptake inhibitors (SNRI) increase bleeding risk, especially with concomitant use of NSAIDs[318]. When NSAIDs and SNRIs are given concurrently, monitor the patient for signs of increased bleeding.

7) Probable Mechanism: unknown

8) Literature Reports

a) Concomitant use of NSAIDs and antidepressants, including tricyclic antidepressants, SSRIs, serotonin-norepinephrine reuptake inhibitors, and MAOIs, resulted in an increased risk of [intracranial hemorrhage](#) within 30 days of concomitant use compared with antidepressant use alone. There was no significant difference between the antidepressant drug classes and the increased risk; however, there was an increased risk associated with male patients compared with female patients [319].

3.5.1.CL] Etoricoxib

1) Interaction Effect: an increased risk of bleeding

2) Summary: Use caution when coadministering NSAIDs and serotonin [norepinephrine](#) reuptake inhibitors (SNRI) as this may cause an increased risk of bleeding[318]. During clinical trials, concomitant use of NSAIDs and antidepressants, including tricyclic antidepressants, SSRIs, selective serotonin-norepinephrine reuptake inhibitors, and MAOIs, resulted in an increased risk of [intracranial hemorrhage](#) within 30 days of concomitant use compared with antidepressant use alone [319]. When NSAIDs and SNRIs are given concurrently, monitor the patient for signs of increased bleeding.

3) Severity: major

4) Onset: unspecified

5) Substantiation: established

6) Clinical Management: Serotonin [norepinephrine](#) reuptake inhibitors (SNRI) increase bleeding risk, especially with concomitant use of NSAIDs[318]. When NSAIDs and SNRIs are given concurrently, monitor the patient for signs of increased bleeding.

7) Probable Mechanism: unknown

8) Literature Reports

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

increased risk; however, there was an increased risk associated with male patients compared with female patients [319].

3.5.1.CM] Felbinac

- 1) Interaction Effect: an increased risk of bleeding
- 2) Summary: Use caution when coadministering NSAIDs and serotonin [norepinephrine](#) reuptake inhibitors (SNRI) as this may cause an increased risk of bleeding[318]. During clinical trials, concomitant use of NSAIDs and antidepressants, including tricyclic antidepressants, SSRIs, selective serotonin-norepinephrine reuptake inhibitors, and MAOIs, resulted in an increased risk of [intracranial hemorrhage](#) within 30 days of concomitant use compared with antidepressant use alone [319]. When NSAIDs and SNRIs are given concurrently, monitor the patient for signs of increased bleeding.
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: established
- 6) Clinical Management: Serotonin [norepinephrine](#) reuptake inhibitors (SNRI) increase bleeding risk, especially with concomitant use of NSAIDs[318]. When NSAIDs and SNRIs are given concurrently, monitor the patient for signs of increased bleeding.
- 7) Probable Mechanism: unknown
- 8) Literature Reports

a) Concomitant use of NSAIDs and antidepressants, including tricyclic antidepressants, SSRIs, serotonin-norepinephrine reuptake inhibitors, and MAOIs, resulted in an increased risk of [intracranial hemorrhage](#) within 30 days of concomitant use compared with antidepressant use alone. There was no significant difference between the antidepressant drug classes and the increased risk; however, there was an increased risk associated with male patients compared with female patients [319].

3.5.1.CN] 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 [venlafaxine](#), has the potential to cause [serotonin syndrome](#)[333]. [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 [334]. Until more data are available, [fenfluramine](#) should not be used in combination with [venlafaxine](#).
- 3) Severity: major
- 4) Onset: rapid
- 5) Substantiation: theoretical
- 6) Clinical Management: Concurrent use of [fenfluramine](#) and [venlafaxine](#) 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 [venlafaxine](#) or other serotonin specific reuptake inhibitors.
- 7) Probable Mechanism: additive serotonergic effects

3.5.1.CO] Fenoprofen

- 1) Interaction Effect: an increased risk of bleeding

2j) Summary: Use caution when coadministering NSAIDs and serotonin [norepinephrine](#) reuptake inhibitors (SNRI) as this may cause an increased risk of bleeding[318]. During clinical trials, concomitant use of NSAIDs and antidepressants, including tricyclic antidepressants, SSRIs, selective serotonin-norepinephrine reuptake inhibitors, and MAOIs, resulted in an increased risk of [intracranial hemorrhage](#) within 30 days of concomitant use compared with antidepressant use alone [319]. When NSAIDs and SNRIs are given concurrently, monitor the patient for signs of increased bleeding.

3j) Severity: major

4j) Onset: unspecified

5j) Substantiation: established

6j) Clinical Management: Serotonin [norepinephrine](#) reuptake inhibitors (SNRI) increase bleeding risk, especially with concomitant use of NSAIDs[318]. When NSAIDs and SNRIs are given concurrently, monitor the patient for signs of increased bleeding.

7j) Probable Mechanism: unknown

8j) Literature Reports

a) Concomitant use of NSAIDs and antidepressants, including tricyclic antidepressants, SSRIs, serotonin-norepinephrine reuptake inhibitors, and MAOIs, resulted in an increased risk of [intracranial hemorrhage](#) within 30 days of concomitant use compared with antidepressant use alone. There was no significant difference between the antidepressant drug classes and the increased risk; however, there was an increased risk associated with male patients compared with female patients [319].

3.5.1.CP] [Fentanyl](#)

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

2j) Summary: [Fentanyl](#) is proserotonergic and has been associated with [serotonin syndrome](#) when coadministered with serotonergic drugs[203], including SSRIs [366][365][367]. [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 [203]. 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 [119].

3j) Severity: major

4j) Onset: delayed

5j) Substantiation: theoretical

6j) Clinical Management: [Fentanyl](#) is a proserotonergic, synthetic piperidine opioid and has been associated with [serotonin syndrome](#) when coadministered with other serotonergic drugs. Therefore, use caution with coadministration of [fentanyl](#) and a serotonergic drug, such as an SSRI, serotonin-norepinephrine reuptake inhibitor, tricyclic antidepressant, or another synthetic piperidine opioid, as this may result in additive serotonergic effects and may increase the risk of [serotonin syndrome](#). If possible, consider replacing serotonergic opioids (eg, [fentanyl](#)) with non-serotonergic opioids (eg, [morphine](#)) [203]. 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 [119].

7j) Probable Mechanism: additive serotonergic effect

8j) Literature Reports

a) **Serotonin syndrome** associated with **fentanyl** use during an **esophagogastroduodenoscopy** was reported in a 39-year-old woman also taking **sertraline** 100 mg daily as an outpatient. The patient initially presented with **hematemesis** and a history of **alcoholic cirrhosis**. Prior to the **esophagogastroduodenoscopy**, an **octreotide** and **pantoprazole** drip was started, 2 doses of **fentanyl** 50 micrograms, and 2 doses of **midazolam** 1 mg were administered. The patient became somnolent and extremely rigid in all four extremities following the procedure, and **vecuronium** and **etomidate** were given for immediate intubation. The rigidity progressed with diffuse diaphoresis, horizontal **roving eye movements**, and a fever of 105 degrees F. Due to the potential for seizure activity, **lorazepam** 2 mg IV was given with no improvement and a **propofol** drip was started for continued sedation during intubation. A CPK value of 2800 units/L and an ammonia level of 340 micromols/L indicated **rhabdomyolysis**. An acute intracranial process was ruled out on a **CT scan** of the brain and the neurology team made the diagnosis of **serotonin syndrome** secondary to an interaction between **fentanyl** and **sertraline**. **Propofol** was continued for sedation and the patient received supportive treatment with a cooling blanket and **cycloheptadine**. After 3 days, the patient's temperature and CPK level normalized and she later extubated with no further complications [365].

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 [366].

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 [367].

3.5.1.CQ] Fepradinol

- 1) Interaction Effect: an increased risk of bleeding
- 2) Summary: Use caution when coadministering NSAIDs and serotonin norepinephrine reuptake inhibitors (SNRI) as this may cause an increased risk of bleeding[318]. During clinical trials, concomitant use of NSAIDs and antidepressants, including tricyclic antidepressants, SSRIs, selective serotonin-norepinephrine reuptake inhibitors, and MOAIs, resulted in an increased risk of intracranial hemorrhage within 30 days of concomitant use compared with antidepressant use alone [319]. When NSAIDs and SNRIs are given concurrently, monitor the patient for signs of increased bleeding.
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: established
- 6) Clinical Management: Serotonin norepinephrine reuptake inhibitors (SNRI) increase bleeding risk, especially with concomitant use of NSAIDs[318]. When NSAIDs and SNRIs are given concurrently, monitor the patient for signs of increased bleeding.
- 7) Probable Mechanism: unknown
- 8) Literature Reports

a) Concomitant use of NSAIDs and antidepressants, including tricyclic antidepressants, SSRIs, serotonin-norepinephrine reuptake inhibitors, and MAOIs, resulted in an increased risk of intracranial hemorrhage within 30 days of concomitant use compared with antidepressant use alone. There was no significant difference between the antidepressant drug classes and the increased risk; however, there was an increased risk associated with male patients compared with female patients [319].

3.5.1.CR] Feprazone

- 1) Interaction Effect: an increased risk of bleeding
- 2) Summary: Use caution when coadministering NSAIDs and serotonin norepinephrine reuptake inhibitors (SNRI) as this may cause an increased risk of bleeding[318]. During clinical trials, concomitant use of NSAIDs and antidepressants, including tricyclic antidepressants, SSRIs, selective serotonin-norepinephrine reuptake inhibitors, and MOAIs, resulted in an increased risk of intracranial hemorrhage within 30 days of concomitant use compared with antidepressant use alone [319]. When NSAIDs and SNRIs are given concurrently, monitor the patient for signs of increased bleeding.
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: established
- 6) Clinical Management: Serotonin norepinephrine reuptake inhibitors (SNRI) increase bleeding risk, especially with concomitant use of NSAIDs[318]. When NSAIDs and SNRIs are given concurrently, monitor the patient for signs of increased bleeding.
- 7) Probable Mechanism: unknown
- 8) Literature Reports

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

[intracranial hemorrhage](#) within 30 days of concomitant use compared with antidepressant use alone. There was no significant difference between the antidepressant drug classes and the increased risk; however, there was an increased risk associated with male patients compared with female patients [319].

3.5.1.CS] Floctafenine

- 1) Interaction Effect: an increased risk of bleeding
- 2) Summary: Use caution when coadministering NSAIDs and serotonin [norepinephrine](#) reuptake inhibitors (SNRI) as this may cause an increased risk of bleeding[318]. During clinical trials, concomitant use of NSAIDs and antidepressants, including tricyclic antidepressants, SSRIs, selective serotonin-norepinephrine reuptake inhibitors, and MAOIs, resulted in an increased risk of [intracranial hemorrhage](#) within 30 days of concomitant use compared with antidepressant use alone [319]. When NSAIDs and SNRIs are given concurrently, monitor the patient for signs of increased bleeding.
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: established
- 6) Clinical Management: Serotonin [norepinephrine](#) reuptake inhibitors (SNRI) increase bleeding risk, especially with concomitant use of NSAIDs[318]. When NSAIDs and SNRIs are given concurrently, monitor the patient for signs of increased bleeding.
- 7) Probable Mechanism: unknown
- 8) Literature Reports

a) Concomitant use of NSAIDs and antidepressants, including tricyclic antidepressants, SSRIs, serotonin-norepinephrine reuptake inhibitors, and MAOIs, resulted in an increased risk of [intracranial hemorrhage](#) within 30 days of concomitant use compared with antidepressant use alone. There was no significant difference between the antidepressant drug classes and the increased risk; however, there was an increased risk associated with male patients compared with female patients [319].

3.5.1.CT] Flufenamic Acid

- 1) Interaction Effect: an increased risk of bleeding
- 2) Summary: Use caution when coadministering NSAIDs and serotonin [norepinephrine](#) reuptake inhibitors (SNRI) as this may cause an increased risk of bleeding[318]. During clinical trials, concomitant use of NSAIDs and antidepressants, including tricyclic antidepressants, SSRIs, selective serotonin-norepinephrine reuptake inhibitors, and MAOIs, resulted in an increased risk of [intracranial hemorrhage](#) within 30 days of concomitant use compared with antidepressant use alone [319]. When NSAIDs and SNRIs are given concurrently, monitor the patient for signs of increased bleeding.
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: established
- 6) Clinical Management: Serotonin [norepinephrine](#) reuptake inhibitors (SNRI) increase bleeding risk, especially with concomitant use of NSAIDs[318]. When NSAIDs and SNRIs are given concurrently, monitor the patient for signs of increased bleeding.
- 7) Probable Mechanism: unknown
- 8) Literature Reports

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

alone. There was no significant difference between the antidepressant drug classes and the increased risk; however, there was an increased risk associated with male patients compared with female patients [319].

3.5.1.CU] Fluoxetine

- 1) Interaction Effect: increased [venlafaxine](#) exposure; increased risk of [serotonin syndrome](#) (hypertension, hyperthermia, myoclonus, mental status changes); increased risk of QT-interval prolongation
- 2) Summary: The concomitant use of [fluoxetine](#), a CYP2D6 inhibitor, with [venlafaxine](#), a CYP2D6 substrate, may increase [venlafaxine](#) exposure and increase the risk of adverse effects. Coadministration of [fluoxetine](#) and [venlafaxine](#) may also result in additive serotonergic effects and increase the risk of [serotonin syndrome](#)[340][57]. Additionally, concomitant administration of [fluoxetine](#) and [ritonavir](#) may result in additive effects on the QT interval and should be avoided. If concomitant use is required, consider periodic [ECG monitoring](#) [340]. Discontinue [fluoxetine](#) and [venlafaxine](#) if [serotonin syndrome](#) occurs [340][57].
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Concurrent use of [fluoxetine](#), a CYP2D6 inhibitor, and [venlafaxine](#), a CYP2D6 substrate, may increase [venlafaxine](#) exposure and increase the risk of adverse effects. Coadministration of [fluoxetine](#) and [venlafaxine](#) may also result in additive serotonergic effects and increase the risk of [serotonin syndrome](#)[340][57]. Additionally, concomitant administration of [fluoxetine](#) and [ritonavir](#) may result in additive effects on the QT interval and should be avoided. If concomitant use is required, consider periodic [ECG monitoring](#) [340]. Discontinue [fluoxetine](#) and [venlafaxine](#) if [serotonin syndrome](#) occurs [340][57].
- 7) Probable Mechanism: inhibition of CYP2D6-mediated metabolism of [venlafaxine](#) by [fluoxetine](#); additive serotonergic effect; additive QT-interval prolongation effects

3.5.1.CV] Flurbiprofen

- 1) Interaction Effect: an increased risk of bleeding
- 2) Summary: Use caution when coadministering NSAIDs and serotonin [norepinephrine](#) reuptake inhibitors (SNRI) as this may cause an increased risk of bleeding[318]. During clinical trials, concomitant use of NSAIDs and antidepressants, including tricyclic antidepressants, SSRIs, selective serotonin-norepinephrine reuptake inhibitors, and MOAIs, resulted in an increased risk of [intracranial hemorrhage](#) within 30 days of concomitant use compared with antidepressant use alone [319]. When NSAIDs and SNRIs are given concurrently, monitor the patient for signs of increased bleeding.
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: established
- 6) Clinical Management: Serotonin [norepinephrine](#) reuptake inhibitors (SNRI) increase bleeding risk, especially with concomitant use of NSAIDs[318]. When NSAIDs and SNRIs are given concurrently, monitor the patient for signs of increased bleeding.
- 7) Probable Mechanism: unknown
- 8) Literature Reports

a) Concomitant use of NSAIDs and antidepressants, including tricyclic antidepressants, SSRIs, serotonin-norepinephrine reuptake inhibitors, and MAOIs, resulted in an increased risk of [intracranial hemorrhage](#) within 30 days of concomitant use compared with antidepressant use alone. There was no significant difference between the antidepressant drug classes and the increased risk; however, there was an increased risk associated with male patients compared with female patients [319].

3.5.1.CW] Fondaparinux

1) Interaction Effect: an increased risk of bleeding

2) Summary: Case reports and epidemiological studies have shown that use of selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs), including [venlafaxine](#), is associated with [gastrointestinal bleeding](#). Bleeding events with SSRIs and SNRIs included cases of ecchymoses, [hematomas](#), [epistaxis](#), and [petechiae](#); life-threatening hemorrhages have also occurred. Coadministration with [warfarin](#) or other anticoagulants may potentiate the risk of bleeding. A population-based, case-controlled study of new coumarin users (acenocoumarol and phenprocoumon) with concomitant selective serotonin reuptake inhibitors (SSRIs) resulted in an increased risk of hospitalization due to nongastrointestinal bleeding[354]. Increases in prothrombin time, partial thromboplastin time, or INR have been reported when [venlafaxine](#) was administered to patients receiving [warfarin](#). Therefore, concomitant use of [venlafaxine](#) with [warfarin](#) or other drugs affecting coagulation should be undertaken with caution. Whenever [venlafaxine](#) is initiated or discontinued in patients receiving an anticoagulant, close monitoring of coagulation parameters is recommended [321].

3) Severity: major

4) Onset: unspecified

5) Substantiation: probable

6) Clinical Management: Use caution when [venlafaxine](#) is used concomitantly with [warfarin](#) or other drugs affecting coagulation. Closely monitor coagulation parameters when [venlafaxine](#) is initiated or discontinued in patients receiving anticoagulants, such as [warfarin](#)[321].

7) Probable Mechanism: additive adverse events

8) Literature Reports

a) A population-based, case-controlled study of new coumarin users (acenocoumarol and phenprocoumon) with concomitant selective serotonin reuptake inhibitors (SSRIs) resulted in an increased risk of hospitalization due to nongastrointestinal bleeding. Using national pharmacy and hospitalization records, Netherlands researchers identified 1848 cases that were admitted for abnormal bleeding and compared them with 5818 control subjects also taking coumarins. Median duration of treatment in patients was 220 days (range, 1 to 4690 days). Patients on SSRIs showed greater risk for hospitalization for nongastrointestinal bleeding (adjusted odds ratio (OR) 1.7, 95% confidence interval (CI), 1.1 to 2.5), however, the rate of [gastrointestinal bleeding](#) (adjusted OR 0.8, 95% CI, 0.4 to 1.5) was not significantly different [354].

3.5.1.CX] Frovatriptan

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

2) Summary: A life-threatening condition known as [serotonin syndrome](#) may occur when triptans, such as [frovatriptan](#), are used in combination with a selective [norepinephrine](#) reuptake inhibitor (SNRI), such as [venlafaxine](#). Symptoms of [serotonin syndrome](#) may include restlessness, hallucinations, loss of coordination, fast heart beat, rapid changes in blood pressure, increased body temperature, overreactive reflexes, nausea, vomiting, and diarrhea. Clinicians should be aware that triptans may be commonly used intermittently and that either the triptan or the SNRI may be prescribed by a different physician. Discuss the risks of [serotonin syndrome](#) with patients who are prescribed this combination and monitor them closely for symptoms of [serotonin syndrome](#)[258].

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Coadministration of a triptan, such as [frovatriptan](#), and an SNRI, such as [venlafaxine](#), may result in a life-threatening condition called [serotonin syndrome](#). Be aware that triptans

may be commonly used intermittently and that either the triptan or the SNRI may be prescribed by a different physician. If these agents are used together, discuss the risks of [serotonin syndrome](#) with the patient and monitor closely for symptoms of [serotonin syndrome](#) (restlessness, [hyperthermia](#), hyperreflexia, incoordination).

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

3.5.1.CY| [Furazolidone](#)

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

2J) Summary: Concurrent use of [furazolidone](#), an MAOI, and [venlafaxine](#) is contraindicated. Wait at least 14 days after discontinuing [furazolidone](#) before initiating [venlafaxine](#). Wait at least 7 days after discontinuing [venlafaxine](#) before initiating therapy with [furazolidone](#)[123].

3J) Severity: contraindicated

4J) Onset: unspecified

5J) Substantiation: theoretical

6J) Clinical Management: Concurrent use of [furazolidone](#) (an MAOI) and [venlafaxine](#) is contraindicated. Wait at least 14 days after discontinuing [furazolidone](#) before initiating [venlafaxine](#). Wait at least 7 days after discontinuing [venlafaxine](#) before initiating therapy with [furazolidone](#)[123].

7J) Probable Mechanism: additive serotonergic effect

3.5.1.CZ| [Ginkgo](#)

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

2J) Summary: The addition of [Ginkgo biloba](#) and/or [St. John's Wort](#) to therapy with [buspirone](#) and [fluoxetine](#) may have precipitated a hypomanic episode in a case report[303]. 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 [304][305], and has demonstrated serotonergic activity in animals [306] 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 [307]. [Ginkgo biloba](#) extract inhibited MAO-A/MAO-B in the rat brain in vitro [304][305] and MAO-B in human [platelets](#) in vitro [305]. No significant MAO inhibition was found in mice following oral consumption [308].

3J) Severity: moderate

4J) Onset: delayed

5J) Substantiation: probable

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

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

8J) Literature Reports

aJ) A 42-year-old female experienced symptoms consistent with a mixed hypomanic episode following concomitant use of [fluoxetine](#), [buspirone](#), [Ginkgo biloba](#), and [St. John's Wort](#). The symptoms resolved following discontinuation of [Ginkgo](#) and [St. John's Wort](#). The patient was being treated for depression following a mild [traumatic brain injury](#) with [fluoxetine](#) 20 milligrams (mg) twice daily and [buspirone](#) 15 mg twice daily. Several weeks prior to presentation, [buspirone](#) was increased to 20 mg twice daily for persistent anxiety and the patient began taking [Ginkgo biloba](#), [melatonin](#), and [St. John's Wort](#) in unspecified doses. [Melatonin](#) was considered unlikely

to have contributed to her symptoms. Ginkgo and St. John's Wort were considered possible contributors since they may potentiate antidepressants, and considering the temporal relationship between the use of the herbs and onset of symptoms and discontinuation of the herbs and resolution of symptoms. However, the [brain injury](#) was considered a possible contributor [302].

3.5.1.DA| [Gonadorelin](#)

- 1) Interaction Effect: increased risk of QT-interval prolongation
- 2) Summary: Use caution with coadministration of gonadotropin-releasing hormone (GnRH) agonists with QT-interval prolonging drugs. Androgen deprivation caused by GnRH agonists may prolong the QT interval and cause additive effects when administered with QT-interval prolonging drugs[377][378][379]. If concurrent therapy is necessary, monitor patients closely for signs and symptoms of [cardiac toxicity](#), including changes in the ECG.
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Use caution with coadministration of gonadotropin-releasing hormone (GnRH) agonists with QT-interval prolonging drugs, as additive effects on the QT interval may occur[377][378][379].
- 7) Probable Mechanism: additive effects on the QT interval

3.5.1.DB| [Goserelin](#)

- 1) Interaction Effect: increased risk of QT-interval prolongation
- 2) Summary: Use caution with coadministration of gonadotropin-releasing hormone (GnRH) agonists with QT-interval prolonging drugs. Androgen deprivation caused by GnRH agonists may prolong the QT interval and cause additive effects when administered with QT-interval prolonging drugs[377][378][379]. If concurrent therapy is necessary, monitor patients closely for signs and symptoms of [cardiac toxicity](#), including changes in the ECG.
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Use caution with coadministration of gonadotropin-releasing hormone (GnRH) agonists with QT-interval prolonging drugs, as additive effects on the QT interval may occur[377][378][379].
- 7) Probable Mechanism: additive effects on the QT interval

3.5.1.DC| [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[198].
- 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[198].

7J) Probable Mechanism: unknown

3.5.1.DD] Haloperidol

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

2J) Summary: [Venlafaxine](#) may inhibit [haloperidol](#) metabolism[395]. [Haloperidol](#) is associated with QTc prolongation and [torsade de pointes](#) [396][397]. [Venlafaxine](#) has been shown to prolong the QTc interval at the recommended therapeutic dose [395]. Concomitant use is not recommended.

3J) Severity: major

4J) Onset: rapid

5J) Substantiation: probable

6J) Clinical Management: The concurrent administration of [haloperidol](#) and [venlafaxine](#) is not recommended.

7J) Probable Mechanism: decreased [haloperidol](#) metabolism; theoretical additive effect on QT prolongation

8J) Literature Reports

aJ) Under steady-state conditions, [venlafaxine](#) 150 mg daily decreased the total oral clearance of a single 2 mg dose of [haloperidol](#) by 42% in 24 healthy subjects. This resulted in a 70% increase in the [haloperidol](#) area under the concentration-time curve (AUC). The [haloperidol](#) maximum concentration (Cmax) was increased by 88% when [venlafaxine](#) was coadministered, but the elimination half-life of [haloperidol](#) was not affected. The mechanism behind this interaction is not known [393].

bJ) Numerous case reports have described significant QTc prolongation and [torsades de pointes](#) (TdP) associated with [haloperidol](#). Hemodynamically significant ventricular [tachyarrhythmias](#), [ventricular fibrillation](#), [asystole](#), and death have been reported. The risk of TdP appears to be greater with intravenous [haloperidol](#), but has occurred with oral and intramuscular use. The risk increases with doses greater than 35 milligrams (mg) over 24 hours, although TdP has been associated with a dose as low as 10 mg administered intravenously over 4 hours. To prevent haloperidol-induced TdP, screen patients for a history of [dilated cardiomyopathy](#) or alcohol abuse, testing for [hypothyroidism](#) before therapy, obtaining an [electrocardiogram](#) at baseline and throughout therapy, and monitoring potassium, magnesium, and [calcium](#). In patients with a baseline QTc greater than 450 milliseconds (msec), [haloperidol](#) should be used cautiously or an alternative agent should be used. Discontinue [haloperidol](#) if the QTc increases more than 25% from baseline or if flattening of T-waves or development of U-waves occurs [394].

3.5.1.DE] Heparin

1J) Interaction Effect: an increased risk of bleeding

2J) Summary: Case reports and epidemiological studies have shown that use of selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs), including [venlafaxine](#), is associated with [gastrointestinal bleeding](#). Bleeding events with SSRIs and SNRIs included cases of ecchymoses, [hematomas](#), [epistaxis](#), and [petechiae](#); life-threatening hemorrhages have also occurred. Coadministration with [warfarin](#) or other anticoagulants may potentiate the risk of bleeding. A population-based, case-controlled study of new coumarin users (acenocoumarol and phenprocoumon) with concomitant selective serotonin reuptake inhibitors (SSRIs) resulted in an increased risk of hospitalization due to nongastrointestinal bleeding[354]. Increases in prothrombin time, partial thromboplastin time, or INR have been reported when [venlafaxine](#) was administered to patients receiving [warfarin](#). Therefore, concomitant use of [venlafaxine](#) with [warfarin](#) or other drugs affecting coagulation should be undertaken

with caution. Whenever [venlafaxine](#) is initiated or discontinued in patients receiving an anticoagulant, close monitoring of coagulation parameters is recommended [321].

3) Severity: major

4) Onset: unspecified

5) Substantiation: probable

6) Clinical Management: Use caution when [venlafaxine](#) is used concomitantly with [warfarin](#) or other drugs affecting coagulation. Closely monitor coagulation parameters when [venlafaxine](#) is initiated or discontinued in patients receiving anticoagulants, such as [warfarin](#)[321].

7) Probable Mechanism: additive adverse events

8) Literature Reports

a) A population-based, case-controlled study of new coumarin users (acenocoumarol and phenprocoumon) with concomitant selective serotonin reuptake inhibitors (SSRIs) resulted in an increased risk of hospitalization due to nongastrointestinal bleeding. Using national pharmacy and hospitalization records, Netherlands researchers identified 1848 cases that were admitted for abnormal bleeding and compared them with 5818 control subjects also taking coumarins. Median duration of treatment in patients was 220 days (range, 1 to 4690 days). Patients on SSRIs showed greater risk for hospitalization for nongastrointestinal bleeding (adjusted odds ratio (OR) 1.7, 95% confidence interval (CI), 1.1 to 2.5), however, the rate of [gastrointestinal bleeding](#) (adjusted OR 0.8, 95% CI, 0.4 to 1.5) was not significantly different [354].

3.5.1.DF| [Histrelin](#)

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

2) Summary: Use caution with coadministration of gonadotropin-releasing hormone (GnRH) agonists with QT-interval prolonging drugs. Androgen deprivation caused by GnRH agonists may prolong the QT interval and cause additive effects when administered with QT-interval prolonging drugs[377][378][379]. If concurrent therapy is necessary, monitor patients closely for signs and symptoms of [cardiac toxicity](#), including changes in the ECG.

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Use caution with coadministration of gonadotropin-releasing hormone (GnRH) agonists with QT-interval prolonging drugs, as additive effects on the QT interval may occur[377][378][379].

7) Probable Mechanism: additive effects on the QT interval

3.5.1.DG| [Hydroxychloroquine](#)

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

2) Summary: [Hydroxychloroquine](#) has been associated with QT interval prolongation[322][323], [ventricular premature contractions](#), and [torsade de pointes](#) [323]. Therefore, use caution with coadministration of [hydroxychloroquine](#) and other QT interval-prolonging drugs, as life-threatening additive effects on the QT interval, including [torsades de pointes](#), may occur. Consider close [ECG monitoring](#) at baseline and during concurrent therapy with QT-interval prolonging drugs.

3) Severity: major

4) Onset: unspecified

5) Substantiation: probable

6) Clinical Management: [Hydroxychloroquine](#) has been associated with QT interval prolongation[322][323]. Therefore, use caution with coadministration of [hydroxychloroquine](#) and other QT interval-prolonging drugs, as life-threatening additive effects on the QT interval, including [torsades de pointes](#),

may occur. Consider close [ECG monitoring](#) at baseline and during concurrent therapy with QT-interval prolonging drugs.

7) Probable Mechanism: additive QT interval effects

8) Literature Reports

a) Hydroxychloroquine-associated QT interval prolongation was reported in a 41-year-old woman with [congestive heart failure](#) with [systolic left ventricular dysfunction](#). Her comorbidities included [hypertension](#), [systemic lupus erythematosus](#), and [stage 5 chronic kidney disease](#). One week after reinitiation of [hydroxychloroquine](#) therapy, a significant prolongation of the QT interval (QTc 614 msec) was observed during a routine ECG. Following treatment discontinuation of [hydroxychloroquine](#), serial ECGs demonstrated a shortening of the QTc interval. The patient's QTc was 473 msec at a follow up 1 year after discharge [322].

b) QT prolongation and refractory [ventricular arrhythmia](#) were reported with chronic [hydroxychloroquine](#) use in a 67-year-old woman with [systemic lupus erythematosus](#). The patient had been receiving [prednisolone](#), [theophylline](#), and [hydroxychloroquine](#) 200 mg/day for 1 year. The patient had a medical history of [cirrhosis](#), [hepatitis B](#) virus related [hepatoma](#) with portal vein [thrombosis](#), and [asthma](#). The patient experienced a sudden episode of unconsciousness and generalized rigidity while at home. Although the patient regained consciousness within minutes and had no complaints of chest pain, palpitation, limb weakness, incontinence, or confusion, the episode recurred several times. Upon admission the ECG showed multiple [ventricular premature contractions](#), [torsade de pointes](#), and prolongation of the QT interval. Treatment with [hydroxychloroquine](#) was discontinued. Following medical management, [ventricular arrhythmia](#) subsided after 4 days and the QT interval shortened [323].

3.5.1.DH] [Hydroxyzine](#)

1) Interaction Effect: increased risk of QT interval prolongation

2) Summary: [Hydroxyzine](#) has been associated with QT interval prolongation and development of [Torsade de Pointes](#). Caution is advised if [hydroxyzine](#) is used concomitantly with this drug as additive effects on QT prolongation may occur[370]. Consider close [ECG monitoring](#) at baseline and during concurrent therapy with QT-interval prolonging drugs.

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: [Hydroxyzine](#) has been associated with QT interval prolongation and development of [Torsade de Pointes](#). Caution is advised if [hydroxyzine](#) is used concomitantly with this drug as additive effects on QT prolongation may occur[370]. Consider close [ECG monitoring](#) at baseline and during concurrent therapy with QT-interval prolonging drugs.

7) Probable Mechanism: additive effects on the QT interval

3.5.1.DI] [Ibuprofen](#)

1) Interaction Effect: an increased risk of bleeding

2) Summary: Use caution when coadministering NSAIDs and serotonin [norepinephrine](#) reuptake inhibitors (SNRI) as this may cause an increased risk of bleeding[318]. During clinical trials, concomitant use of NSAIDs and antidepressants, including tricyclic antidepressants, SSRIs, selective serotonin-norepinephrine reuptake inhibitors, and MOAIs, resulted in an increased risk of [intracranial hemorrhage](#) within 30 days of concomitant use compared with antidepressant use alone [319]. When NSAIDs and SNRIs are given concurrently, monitor the patient for signs of increased bleeding.

3) Severity: major

- 4) Onset: unspecified
- 5) Substantiation: established
- 6) Clinical Management: Serotonin [norepinephrine](#) reuptake inhibitors (SNRI) increase bleeding risk, especially with concomitant use of NSAIDs[318]. When NSAIDs and SNRIs are given concurrently, monitor the patient for signs of increased bleeding.
- 7) Probable Mechanism: unknown
- 8) Literature Reports

a) Concomitant use of NSAIDs and antidepressants, including tricyclic antidepressants, SSRIs, serotonin-norepinephrine reuptake inhibitors, and MAOIs, resulted in an increased risk of [intracranial hemorrhage](#) within 30 days of concomitant use compared with antidepressant use alone. There was no significant difference between the antidepressant drug classes and the increased risk; however, there was an increased risk associated with male patients compared with female patients [319].

3.5.1.DJ] [Iloprost](#)

- 1) Interaction Effect: an increased risk of bleeding
- 2) Summary: The release of serotonin by [platelets](#) is important for maintaining hemostasis. Case reports and epidemiological studies have shown that use of selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs), including [venlafaxine](#), is associated with [gastrointestinal bleeding](#). Bleeding events with SSRIs and SNRIs included cases of ecchymoses, [hematomas](#), [epistaxis](#), and [petechiae](#); life-threatening hemorrhages have also occurred. Coadministration with drugs that affect coagulation, such as antiplatelet agents, may potentiated the risk of bleeding[321].
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: probable
- 6) Clinical Management: Use caution when [venlafaxine](#) is used concomitantly with antiplatelet agents. Closely monitor patient for signs of bleeding when [venlafaxine](#) is initiated or discontinued in patients receiving antiplatelet agents concomitantly[321].
- 7) Probable Mechanism: unknown

3.5.1.DK] [Imipramine](#)

- 1) Interaction Effect: an increased risk of [cardiotoxicity](#) (QT prolongation, [torsades de pointes](#), [cardiac arrest](#)) and adverse effects of both drugs
- 2) Summary: Tricyclic antidepressants (TCAs) and [venlafaxine](#) have been shown to prolong the QTc interval at the recommended therapeutic dose[297][298]. Even though no formal drug interaction studies have been done, the coadministration of tricyclic antidepressants and other drugs known to prolong the QTc interval, such as [venlafaxine](#), is not recommended [299]. In addition, [venlafaxine](#) and tricyclic antidepressants (TCAs) may competitively inhibit each other's metabolism which may increase side effects of both drugs [300][297][301]. [Venlafaxine](#) increased the AUC, Cmax, and Cmin of [desipramine](#) by approximately 35%. The AUCs of 2-OH-desipramine increased by 2.5 and 4.5 fold when administered with [venlafaxine](#) 37.5 mg and 75 mg every 12 hours, respectively. The pharmacokinetics of [imipramine](#) and the 2-hydroxy metabolite were not affected [6].
- 3) Severity: major
- 4) Onset: rapid
- 5) Substantiation: theoretical
- 6) Clinical Management: Due to the potential for additive effects on the QT interval, the concurrent administration of [venlafaxine](#) and tricyclic antidepressants is not recommended.
- 7) Probable Mechanism: decreased TCA and [venlafaxine](#) metabolism; additive effects on QT prolongation

8) Literature Reports

a) When administered with **imipramine**, the pharmacokinetics of **imipramine** and the 2-hydroxy metabolite were not affected. **Venlafaxine** increased the area under the concentration-time curve (AUC), maximum concentration (C_{max}), and minimum concentration (C_{min}) of **desipramine** by approximately 35%. The 2-OH-desipramine AUCs increased by 2.5-fold (**venlafaxine** 37.5 mg every 12 hours) and by 4.5-fold (**venlafaxine** 75 mg every 12 hours). The clinical significance of this finding is unknown [6].

3.5.1.DL| Indinavir

1) Interaction Effect: decreased **indinavir** serum concentrations

2) Summary: **Venlafaxine** 150 mg per day was administered under steady-state conditions to nine healthy volunteers. The area under the concentration-time curve (AUC) for **indinavir** decreased by 28% for a single 800 mg oral dose of **indinavir**, while the C_{max} decreased by 36%. The pharmacokinetics of **venlafaxine** or its metabolite, O-desmethylvenlafaxine, were not influenced by the administration of **indinavir**. The clinical significance of this has not been determined[6].

3) Severity: minor

4) Onset: rapid

5) Substantiation: probable

6) Clinical Management: Although the clinical significance of this interaction is unknown, monitor patient for an adequate response to **indinavir** therapy.

7) Probable Mechanism: increased **indinavir** metabolism

3.5.1.DM| Indomethacin

1) Interaction Effect: an increased risk of bleeding

2) Summary: Use caution when coadministering NSAIDs and serotonin **norepinephrine** reuptake inhibitors (SNRI) as this may cause an increased risk of bleeding[318]. During clinical trials, concomitant use of NSAIDs and antidepressants, including tricyclic antidepressants, SSRIs, selective serotonin-norepinephrine reuptake inhibitors, and MOAIs, resulted in an increased risk of **intracranial hemorrhage** within 30 days of concomitant use compared with antidepressant use alone [319]. When NSAIDs and SNRIs are given concurrently, monitor the patient for signs of increased bleeding.

3) Severity: major

4) Onset: unspecified

5) Substantiation: established

6) Clinical Management: Serotonin **norepinephrine** reuptake inhibitors (SNRI) increase bleeding risk, especially with concomitant use of NSAIDs[318]. When NSAIDs and SNRIs are given concurrently, monitor the patient for signs of increased bleeding.

7) Probable Mechanism: unknown

8) Literature Reports

a) Concomitant use of NSAIDs and antidepressants, including tricyclic antidepressants, SSRIs, serotonin-norepinephrine reuptake inhibitors, and MAOIs, resulted in an increased risk of **intracranial hemorrhage** within 30 days of concomitant use compared with antidepressant use alone. There was no significant difference between the antidepressant drug classes and the increased risk; however, there was an increased risk associated with male patients compared with female patients [319].

3.5.1.DN| Iobenguane I 123

- 1) Interaction Effect: potential for false negative imaging results
- 2) Summary: Iobenguane is similar in structure to the neurotransmitter [norepinephrine](#) and is taken up by the [norepinephrine](#) transporter in adrenergic nerve terminals. It is stored in the presynaptic storage vesicles. Iobenguane will accumulate in adrenergically innervated tissues and labeling iobenguane with the isotope [iodine 123](#) will provide images of specific organs and tissues. Antidepressants that inhibit [norepinephrine](#) transporter function, such as SSRIs, tricyclic antidepressants, and MAOIs, may interfere with the clinical efficacy of [iobenguane I 123](#). Increasing the dose of [iobenguane I 123](#) will not overcome any potential [norepinephrine](#) uptake inhibition by these drugs. If [iobenguane I 123](#) imaging is necessary, discontinue this drug for at least 5 biological half-lives when clinically feasible[276].
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Concomitant use of [iobenguane I 123](#) and this drug has the potential to inhibit [norepinephrine](#) transporter function and cause false negative imaging results. Increasing the dose of [iobenguane I 123](#) will not overcome any potential [norepinephrine](#) uptake inhibition by these drugs. If [iobenguane I 123](#) imaging is necessary, discontinue this drug for at least 5 biological half-lives when clinically feasible[276].
- 7) Probable Mechanism: inhibition of [norepinephrine](#) transporter function by antidepressants

3.5.1.DO| Iproniazid

- 1) Interaction Effect: CNS toxicity or [serotonin syndrome](#) ([hypertension](#), [hyperthermia](#), myoclonus, mental status changes)
- 2) Summary: Concurrent administration or overlapping therapy with [venlafaxine](#) 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[219][220][221][222]. A 60-year old woman developed a serious case of [serotonin syndrome](#) after the inadvertent ingestion of a single dose of [venlafaxine](#) while on chronic [tranylecypromine](#) therapy [223]. Concomitant use is contraindicated.
- 3) Severity: contraindicated
- 4) Onset: rapid
- 5) Substantiation: probable
- 6) Clinical Management: Concurrent use of [venlafaxine](#) and a MAO inhibitor is contraindicated. Wait at least 14 days after discontinuing a MAO inhibitor before initiating therapy with [venlafaxine](#). Wait at least seven days after discontinuing [venlafaxine](#) 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](#) [214]. [Serotonin syndrome](#) is a condition of serotonergic hyperstimulation and manifests as restlessness, myoclonus, changes in mental status, hyperreflexia, diaphoresis, shivering, and tremor. If the syndrome is not recognized and correctly treated, death can result.

b) A 26-year old woman who had been taking [isocarboxazid](#) for eight weeks stopped taking the drug for 11 days before beginning therapy with [sertraline](#). After a single 100 mg [sertraline](#) dose, the patient became restless and developed leg twitches. The patient was later admitted to the emergency room with diaphoresis, [tachycardia](#), hyperreflexia, and various neuromuscular disturbances. After treatment with [diazepam](#) and [propranolol](#) the patient did not improve. The

patient was then given two 4 mg doses of [cyproheptadine](#) an hour apart, with notable improvement in symptoms after the second dose [215].

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 [216].

d) Two cases reports suggested a possible interaction between [fluoxetine](#) and [selegiline](#) [217]. One case involved a first episode of mania being observed approximately one month after adding [selegiline](#) to [fluoxetine](#) therapy. The patient improved two months after both drugs were discontinued, and no further details were provided. The second case involved diaphoresis, vasoconstriction, and cyanosis of the hands which occurred in close temporal relationship to adding [fluoxetine](#) and [selegiline](#). Both drugs were discontinued, with relatively quick resolution of symptoms. Rechallenge with [fluoxetine](#) alone occurred without incident.

e) A case of a 60-year old female who developed [serotonin syndrome](#) after the inadvertent ingestion of a single dose of [venlafaxine](#) while on chronic [tranylcypromine](#) therapy was reported. Approximately four hours after taking the [venlafaxine](#), the patient became weak, confused, and collapsed. Upon examination, the patient exhibited [tachycardia](#), restlessness, tremor, fever, hyperreflexia, and diaphoresis. After treatment with [diazepam](#), [dantrolene](#), and other supportive therapy, the patient's condition returned to normal over the next four days [218].

3.5.1.DP] [Isocarboxazid](#)

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

2) Summary: Concurrent administration or overlapping therapy with [venlafaxine](#) 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[149][150][151][152]. Concomitant use is contraindicated [153].

3) Severity: contraindicated

4) Onset: rapid

5) Substantiation: probable

6) Clinical Management: Concurrent use of [venlafaxine](#) and a MAO inhibitor is contraindicated. Wait at least 14 days after discontinuing a MAO inhibitor before initiating therapy with [venlafaxine](#). Wait at least seven days after discontinuing [venlafaxine](#) 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](#) [144]. [Serotonin syndrome](#) is a condition of serotonergic hyperstimulation and manifests as restlessness, myoclonus, changes in

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

b)) A 26-year old woman who had been taking [isocarboxazid](#) for eight weeks stopped taking the drug for 11 days before beginning therapy with [sertraline](#). After a single 100 mg [sertraline](#) dose, the patient became restless and developed leg twitches. The patient was later admitted to the emergency room with diaphoresis, [tachycardia](#), hyperreflexia, and various neuromuscular disturbances. After treatment with [diazepam](#) and [propranolol](#) the patient did not improve. The patient was then given two 4 mg doses of [cyproheptadine](#) an hour apart, with notable improvement in symptoms after the second dose [145].

c)) A 43-year old man began taking [venlafaxine](#) 75 mg after showing only a partial response to [isocarboxazid](#) 30 mg daily for depression. After the second dose of [venlafaxine](#), the man developed agitation, [hypomania](#), diaphoresis, shivering, and dilated pupils. The symptoms resolved after discontinuation of [venlafaxine](#). Approximately three months later, the patient was again treated with [venlafaxine](#) and [isocarboxazid](#). After approximately six weeks of treatment, the patient was admitted to the emergency room with agitation, myoclonic jerks, and suspected visual hallucinations. The following day the patient continued to present with symptoms of [serotonin syndrome](#), such as increased muscle tone, myoclonic jerks, diaphoresis, and hyperreflexia. [Cyproheptadine](#) 4 mg was given every six hours and symptoms slowly resolved over the next six days [146].

d)) 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 5 half-lives of the parent drug and any active metabolites [147].

e)) Two cases reports suggested a possible interaction between [fluoxetine](#) and [selegiline](#) [148]. 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.DQI [Itraconazole](#)

- 1))** Interaction Effect: increased plasma concentrations of [venlafaxine](#)
- 2))** Summary: Caution is advised if a CYP3A4 inhibitor, such as [itraconazole](#), is administered with [venlafaxine](#), due to a possible increase in plasma concentration levels of both [venlafaxine](#) and O-desvenlafaxine (ODV)[6]. Patients should be monitored for [venlafaxine](#) toxicity.
- 3))** Severity: major
- 4))** Onset: unspecified
- 5))** Substantiation: theoretical

- 6) Clinical Management: Patients should be monitored for signs of [venlafaxine](#) toxicity such as nausea, drowsiness, and dizziness; a decrease in dosage may be required with concomitant therapy.
- 7) Probable Mechanism: decreased [venlafaxine](#) clearance
- 8) Literature Reports

a) Caution is warranted with the concurrent use of CYP3A4 inhibitors, such as [itraconazole](#), and [venlafaxine](#) due to possible increases in plasma concentration levels of both [venlafaxine](#) and O-desvenlafaxine (ODV) [6].

3.5.1.DR] Ivabradine

- 1) Interaction Effect: increased risk of QT prolongation
- 2) Summary: Use caution with the concomitant administration of ivabradine and other drugs that prolong the QT interval due to the potential for additive QT prolongation[331].
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Use caution with the concomitant administration of ivabradine and other drugs that prolong the QT interval due to the potential for additive QT prolongation[331].
- 7) Probable Mechanism: additive QT-interval prolongation

3.5.1.DS] Jujube

- 1) Interaction Effect: an increased risk of [serotonin syndrome](#)
- 2) Summary: [Serotonin syndrome](#) developed within one hour in a 40-year-old female, when [venlafaxine](#) was added to Ziziphus jujube therapy (also known as Suan Zao Ren, Chinese date, sour date nut)[125]. If Ziziphus jujube and [venlafaxine](#) are used concomitantly, monitor closely for symptoms of [serotonin syndrome](#). [Serotonin syndrome](#) can be life-threatening. If [serotonin syndrome](#) develops, discontinue the offending agents and provide supportive care and other therapy as necessary [119].
- 3) Severity: major
- 4) Onset: rapid
- 5) Substantiation: probable
- 6) Clinical Management: A case of [serotonin syndrome](#) was reported with coadministration of Ziziphus jujube (also known as Suan Zao Ren, Chinese date, sour date nut) and [venlafaxine](#) and therefore, concomitant use is discouraged[125]. If Ziziphus jujube and [venlafaxine](#) are used concomitantly, monitor closely for symptoms of [serotonin syndrome](#) such as neuromuscular abnormalities (including hyperreflexia, tremor, muscle rigidity, clonus, peripheral hypertonicity, and shivering), autonomic hyperactivity (including [tachycardia](#), mydriasis, diaphoresis, the presence of bowel sounds, and diarrhea), and mental status changes (including agitation and [delirium](#)). [Serotonin syndrome](#) can be life-threatening. If [serotonin syndrome](#) develops, discontinue the offending agents and provide supportive care and other therapy as necessary [119].
- 7) Probable Mechanism: additive pharmacologic effects
- 8) Literature Reports

a) [Serotonin syndrome](#) developed in a 40-year-old female, when [venlafaxine](#) was added to Ziziphus jujube (also known as Suan Zao Ren, Chinese date, sour date nut). She was on Ziziphus jujube 500 mg/day for insomnia, fatigue, nervousness, and poor appetite. After several weeks of treatment, [venlafaxine](#) 37.5 mg/day was added. Within 1 hour of taking the first dose of [venlafaxine](#) she experienced restlessness, nausea, dizziness, and ataxia. She then collapsed. She was observed to be pale, drooling, unable to sit, profusely diaphoretic, tachypneic, trembling, and shivering. Peripheral pulses were absent but she had a carotid pulse of 50 bpm. Vital signs were 60/40 mmHg,

40 breaths/minute, and dilated but reactive pupils. Within 30 minutes, her vital signs were 180/100 mmHg, 80 beats/minute, and 14 breaths/minute. Vital signs and mental status normalized 8 hours later. Over the following 24 hours, there was no recurrence. She restarted [venlafaxine](#) at 150 mg/day, but did not restart jujube, and 1 month later remained stable [125].

3.5.1.DT] [Ketoconazole](#)

- 1) Interaction Effect: increased [venlafaxine](#) exposure; increased risk for QT interval prolongation
- 2) Summary: Caution is advised when using [ketoconazole](#) together with [venlafaxine](#) as both agents are known to prolong the QT interval and concomitant use may result in additive effects on the QT interval, increasing the risk for serious [ventricular arrhythmias](#) including [torsades de pointes](#)[336]. In addition, concomitant use may result in elevated plasma concentrations of [venlafaxine](#). A [pharmacokinetic study](#) demonstrated an increase in Cmax and AUC of both [venlafaxine](#) and the O-desvenlafaxine active metabolite with concomitant use [57][5].
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: established
- 6) Clinical Management: Caution is advised when using [ketoconazole](#) together with [venlafaxine](#) as both agents are known to prolong the QT interval and concomitant use may result in additive effects on the QT interval, increasing the risk for serious [ventricular arrhythmias](#) including [torsades de pointes](#)[336]. In addition, concomitant use may result in elevated plasma concentrations of [venlafaxine](#) [57][5].
- 7) Probable Mechanism: decreased [venlafaxine](#) clearance; additive effects on the QT interval
- 8) Literature Reports

a) Higher plasma concentrations of both [venlafaxine](#) and the active metabolite O-desvenlafaxine (ODV) occurred during a [pharmacokinetic study](#) of [ketoconazole](#) 100 mg twice daily plus a single dose of [venlafaxine](#) (50 mg to 14 extensive metabolizers (EM) and 25 mg to 6 poor metabolizers (PM)). The Cmax of [venlafaxine](#) increased by 48% in PM and 26% in EM. Cmax of ODV increased by 29% in PM and 14% in EM subjects. [Venlafaxine](#) AUC increased by 70% (range, -2% to 206%) and 21% in PM and EM subjects, respectively. The ODV metabolite AUC increased by 33% (range, -38% to 105%) and 23% in PM and EM subjects, respectively, and the combined AUCs of [venlafaxine](#) plus ODV increased an average of 53% (range, 4% to 134%) and 23%, respectively [60].

3.5.1.DU] [Ketoprofen](#)

- 1) Interaction Effect: an increased risk of bleeding
- 2) Summary: Use caution when coadministering NSAIDs and serotonin [norepinephrine](#) reuptake inhibitors (SNRI) as this may cause an increased risk of bleeding[318]. During clinical trials, concomitant use of NSAIDs and antidepressants, including tricyclic antidepressants, SSRIs, selective serotonin-norepinephrine reuptake inhibitors, and MOAIs, resulted in an increased risk of [intracranial hemorrhage](#) within 30 days of concomitant use compared with antidepressant use alone [319]. When NSAIDs and SNRIs are given concurrently, monitor the patient for signs of increased bleeding.
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: established
- 6) Clinical Management: Serotonin [norepinephrine](#) reuptake inhibitors (SNRI) increase bleeding risk, especially with concomitant use of NSAIDs[318]. When NSAIDs and SNRIs are given concurrently, monitor the patient for signs of increased bleeding.
- 7) Probable Mechanism: unknown
- 8) Literature Reports

a) Concomitant use of NSAIDs and antidepressants, including tricyclic antidepressants, SSRIs, serotonin-norepinephrine reuptake inhibitors, and MAOIs, resulted in an increased risk of [intracranial hemorrhage](#) within 30 days of concomitant use compared with antidepressant use alone. There was no significant difference between the antidepressant drug classes and the increased risk; however, there was an increased risk associated with male patients compared with female patients [319].

3.5.1.DV] Ketorolac

1) Interaction Effect: an increased risk of bleeding

2) Summary: Use caution when coadministering NSAIDs and serotonin [norepinephrine](#) reuptake inhibitors (SNRI) as this may cause an increased risk of bleeding[318]. During clinical trials, concomitant use of NSAIDs and antidepressants, including tricyclic antidepressants, SSRIs, selective serotonin-norepinephrine reuptake inhibitors, and MOAIs, resulted in an increased risk of [intracranial hemorrhage](#) within 30 days of concomitant use compared with antidepressant use alone [319]. When NSAIDs and SNRIs are given concurrently, monitor the patient for signs of increased bleeding.

3) Severity: major

4) Onset: unspecified

5) Substantiation: established

6) Clinical Management: Serotonin [norepinephrine](#) reuptake inhibitors (SNRI) increase bleeding risk, especially with concomitant use of NSAIDs[318]. When NSAIDs and SNRIs are given concurrently, monitor the patient for signs of increased bleeding.

7) Probable Mechanism: unknown

8) Literature Reports

a) Concomitant use of NSAIDs and antidepressants, including tricyclic antidepressants, SSRIs, serotonin-norepinephrine reuptake inhibitors, and MAOIs, resulted in an increased risk of [intracranial hemorrhage](#) within 30 days of concomitant use compared with antidepressant use alone. There was no significant difference between the antidepressant drug classes and the increased risk; however, there was an increased risk associated with male patients compared with female patients [319].

3.5.1.DW] Lamifiban

1) Interaction Effect: an increased risk of bleeding

2) Summary: The release of serotonin by [platelets](#) is important for maintaining hemostasis. Case reports and epidemiological studies have shown that use of selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs), including [venlafaxine](#), is associated with [gastrointestinal bleeding](#). Bleeding events with SSRIs and SNRIs included cases of ecchymoses, [hematomas](#), [epistaxis](#), and [petechiae](#); life-threatening hemorrhages have also occurred. Coadministration with drugs that affect coagulation, such as antiplatelet agents, may potentiated the risk of bleeding[321].

3) Severity: major

4) Onset: unspecified

5) Substantiation: probable

6) Clinical Management: Use caution when [venlafaxine](#) is used concomitantly with antiplatelet agents. Closely monitor patient for signs of bleeding when [venlafaxine](#) is initiated or discontinued in patients receiving antiplatelet agents concomitantly[321].

7) Probable Mechanism: unknown

3.5.1.DX] Lepirudin

1) Interaction Effect: an increased risk of bleeding

2) Summary: Case reports and epidemiological studies have shown that use of selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs), including [venlafaxine](#), is associated with [gastrointestinal bleeding](#). Bleeding events with SSRIs and SNRIs included cases of ecchymoses, [hematomas](#), [epistaxis](#), and [petechiae](#); life-threatening hemorrhages have also occurred. Coadministration with [warfarin](#) or other anticoagulants may potentiate the risk of bleeding. A population-based, case-controlled study of new coumarin users (acenocoumarol and phenprocoumon) with concomitant selective serotonin reuptake inhibitors (SSRIs) resulted in an increased risk of hospitalization due to nongastrointestinal bleeding[354]. Increases in prothrombin time, partial thromboplastin time, or INR have been reported when [venlafaxine](#) was administered to patients receiving [warfarin](#). Therefore, concomitant use of [venlafaxine](#) with [warfarin](#) or other drugs affecting coagulation should be undertaken with caution. Whenever [venlafaxine](#) is initiated or discontinued in patients receiving an anticoagulant, close monitoring of coagulation parameters is recommended [321].

3) Severity: major

4) Onset: unspecified

5) Substantiation: probable

6) Clinical Management: Use caution when [venlafaxine](#) is used concomitantly with [warfarin](#) or other drugs affecting coagulation. Closely monitor coagulation parameters when [venlafaxine](#) is initiated or discontinued in patients receiving anticoagulants, such as [warfarin](#)[321].

7) Probable Mechanism: additive adverse events

8) Literature Reports

a) A population-based, case-controlled study of new coumarin users (acenocoumarol and phenprocoumon) with concomitant selective serotonin reuptake inhibitors (SSRIs) resulted in an increased risk of hospitalization due to nongastrointestinal bleeding. Using national pharmacy and hospitalization records, Netherlands researchers identified 1848 cases that were admitted for abnormal bleeding and compared them with 5818 control subjects also taking coumarins. Median duration of treatment in patients was 220 days (range, 1 to 4690 days). Patients on SSRIs showed greater risk for hospitalization for nongastrointestinal bleeding (adjusted odds ratio (OR) 1.7, 95% confidence interval (CI), 1.1 to 2.5), however, the rate of [gastrointestinal bleeding](#) (adjusted OR 0.8, 95% CI, 0.4 to 1.5) was not significantly different [354].

3.5.1.DY] Leuprolide

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

2) Summary: Use caution with coadministration of gonadotropin-releasing hormone (GnRH) agonists with QT-interval prolonging drugs. Androgen deprivation caused by GnRH agonists may prolong the QT interval and cause additive effects when administered with QT-interval prolonging drugs[377][378][379]. If concurrent therapy is necessary, monitor patients closely for signs and symptoms of [cardiac toxicity](#), including changes in the ECG.

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Use caution with coadministration of gonadotropin-releasing hormone (GnRH) agonists with QT-interval prolonging drugs, as additive effects on the QT interval may occur[377][378][379].

7) Probable Mechanism: additive effects on the QT interval

3.5.1.DZ| Levofloxacin

- 1) Interaction Effect: increased risk of QT interval prolongation
- 2) Summary: The concomitant use of [levofloxacin](#) together with another agent known to cause QT-interval prolongation should be avoided. Concomitant use may result in additive effects on the QT interval and increase the risk of cardiac adverse events, including [arrhythmia](#) and [torsade de pointes](#). The elderly and patients with risk factors for [torsade de pointes](#) (known QT prolongation, uncorrected hypokalemia) may be more susceptible to QT interval effects[403].
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: The concomitant use of [levofloxacin](#) together with another agent known to cause QT-interval prolongation should be avoided. Concomitant use may result in additive effects on the QT interval and increase the risk of cardiac adverse events, including [arrhythmia](#) and [torsade de pointes](#). The elderly and patients with risk factors for [torsade de pointes](#) (known QT prolongation, uncorrected hypokalemia) may be more susceptible to QT interval effects[403].
- 7) Probable Mechanism: additive effects on QT interval

3.5.1.EA| 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[404].
- 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[404].
- 7) Probable Mechanism: additive serotonergic effects

3.5.1.EB| Lexipafant

- 1) Interaction Effect: an increased risk of bleeding
- 2) Summary: The release of serotonin by [platelets](#) is important for maintaining hemostasis. Case reports and epidemiological studies have shown that use of selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs), including [venlafaxine](#), is associated with [gastrointestinal bleeding](#). Bleeding events with SSRIs and SNRIs included cases of ecchymoses, [hematomas](#), [epistaxis](#), and [petechiae](#); life-threatening hemorrhages have also occurred. Coadministration with drugs that affect coagulation, such as antiplatelet agents, may potentiated the risk of bleeding[321].
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: probable

6) Clinical Management: Use caution when [venlafaxine](#) is used concomitantly with antiplatelet agents. Closely monitor patient for signs of bleeding when [venlafaxine](#) is initiated or discontinued in patients receiving antiplatelet agents concomitantly[321].

7) Probable Mechanism: unknown

3.5.1.EC] [Linezolid](#)

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

2) Summary: Concurrent use of [linezolid](#), an MAOI, and [venlafaxine](#) is contraindicated[123]. Several case reports in patients who received concomitant [linezolid](#) and [venlafaxine](#) therapy have illustrated a delayed onset (greater than 24 hours) of clinical findings consistent with [serotonin syndrome](#), all of which resolved with dose reduction or drug withdrawal [325][326][327][328][329][330]. If urgent treatment with [linezolid](#) is necessary and alternatives are not available, promptly discontinue [venlafaxine](#) and then [linezolid](#) may be administered after the risk/benefit has been evaluated. Monitor for [serotonin syndrome](#) for 7 days or until 24 hours after the last dose of [linezolid](#), whichever comes first. [Venlafaxine](#) can be resumed 24 hours after the last dose of [linezolid](#) [123].

3) Severity: contraindicated

4) Onset: unspecified

5) Substantiation: probable

6) Clinical Management: Concurrent use of [venlafaxine](#) and [linezolid](#) (an MAOI) is contraindicated. If urgent treatment with [linezolid](#) is necessary and alternatives are not available, promptly discontinue [venlafaxine](#) and then [linezolid](#) may be administered after the risk/benefit has been evaluated. Monitor for [serotonin syndrome](#) for 7 days or until 24 hours after the last dose of [linezolid](#), whichever comes first. [Venlafaxine](#) can be resumed 24 hours after the last dose of [linezolid](#)[123].

7) Probable Mechanism: additive serotonergic effects

8) Literature Reports

a) A case report described serotonin toxicity in a 58-year-old woman following concomitant use of [linezolid](#) and [venlafaxine](#). The patient, who had a history of urological problems after bladder resection for [transitional cell carcinoma](#) 18 years earlier and had undergone a bilateral total hip [arthroplasty](#) (THA), was being treated with [venlafaxine](#) 75 mg for severe depression and prior episodes of self-harm. She presented with symptoms of systemic infection. Increased activity at the site of the bilateral THA was revealed and a diagnosis of [MRSA infection](#) was made. Subsequently, the patient was initiated on [vancomycin](#) and rifampicin intravenously. A 2-stage revision THA was performed due to the [MRSA infection](#). Because of problems with intravenous antibiotic administration, her regimen was changed to oral [linezolid](#) and oral rifampicin 2 weeks postoperatively. On day 4 following [linezolid](#) initiation, acute disorientation was observed. Physical examination and [CT scan of the head](#) did not reveal any abnormal findings or autonomic dysfunction. Over the next 24 hours, however, her condition deteriorated. Subsequently, [linezolid](#) and [venlafaxine](#) were stopped due to possible serotonin toxicity. The patient's condition normalized 48 hours after [linezolid](#) and [venlafaxine](#) were discontinued [325].

b) A case report described [serotonin syndrome](#) in a 36-year-old woman following the concomitant use of [linezolid](#) and [venlafaxine](#). The patient, who had no history of seizures and whose regimen included [lithium](#), [venlafaxine](#), and [imipramine](#) for [bipolar disorder](#), [depression](#), and headaches, respectively, presented to the emergency room (ER) with seizures. Ten days prior to presenting to the ER, the patient received [vancomycin](#) for treatment of MRSA empyema. However, therapy was switched to [linezolid](#) approximately 36 hours before her ER visit. At presentation, she had a blood pressure (BP) of 234/196 mmHg, a heart rate of 160 beats/min, respiratory rate of 24

breaths/min, and diaphoresis. Her pupils were dilated with slow reaction to light and she was unresponsive to verbal instructions. The patient was intubated and administered multiple doses of [lorazepam](#), which lessened her tremors and decreased BP to 150/85 mmHg. Her serum [lithium](#) level was 1.2 mEq/L and there were no electrolyte abnormalities. Within 3 hours of intubation, mental status and breathing pattern normalized and the patient was extubated. While both [imipramine](#) and [venlafaxine](#) were withheld, [lithium](#) was continued and [linezolid](#) was replaced with [trimethoprim](#) and [sulfamethoxazole](#). The patient remained alert and oriented over the following days and had reduced anxiety. Three weeks following discharge, the patient reported tremors and anxiety after reinstituting [venlafaxine](#) and [imipramine](#). It was postulated that her 3 chronic serotonergic medications led to a baseline hyperserotonergic state, which was acutely aggravated by the addition of [linezolid](#) [326].

c) In one case report, a 30-year-old woman experienced symptoms of [serotonin syndrome](#) after concomitant treatment with [linezolid](#) and [venlafaxine](#). After having received treatment since the age of 15 years for depression, social anxiety, [bulimia](#), and alcohol/benzodiazepine abuse, she had become drug- and alcohol-free and was receiving extended-release [venlafaxine](#) 225 mg daily. After two weeks of treatment with [linezolid](#), the patient complained of dizziness, syncope, and ataxia. At presentation, the patient appeared confused and disheveled. [Venlafaxine](#) was discontinued and intensive therapy was instituted. Although her neurological symptoms dissipated, she continued to experience rapid mood shifts, irritability, impulsivity, and insomnia for which [quetiapine](#) 25 mg 3 times daily was prescribed. Two weeks later, [venlafaxine](#) was gradually reinitiated [327].

d) 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 diagnosed with a high probability of having SS after receiving concomitant [linezolid](#) and [venlafaxine](#) followed by [citalopram](#). [Linezolid](#) was given for a vancomycin-resistant *Enterococcus* urinary tract infection. 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 mm Hg 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 [328].

e) A case report described serotonin toxicity in a 38-year-old woman following the concomitant administration of [linezolid](#) and [venlafaxine](#). The patient, who had [cystic fibrosis](#), [fibromyalgia](#), and a recent [rib fracture](#) was admitted after 3 weeks of coughing, progressive dyspnea, and green-colored sputum. She had been receiving extended-release [venlafaxine](#) 300 mg once daily and [gabapentin](#) 100 mg 3 times daily for one year, and [hydromorphone](#) 1 mg every 4 hours as needed for the preceding 3 weeks. Due to a history of [vancomycin](#) intolerance, she was prescribed [linezolid](#) 600 mg IV every 12 hours for confirmed methicillin-resistant *Staphylococcus aureus* infection. Four days later, the patient had a blood pressure (BP) of 150/90 mmHg and experienced hot flashes, dyspnea, and tiredness. Eight days following [linezolid](#) initiation, the [venlafaxine](#) dose

was reduced to 150 mg daily. The patient's hot flashes and headache persisted; additionally, she reported nervousness, muscle rigidity of the mouth, fine tremors (fingers), and involuntary arm, trunk, and leg movements. However, approximately 2 days after the [venlafaxine](#) dose reduction, her BP normalized to 142/84 mmHg; other symptoms dissipated the next day. Upon discharge on day 10, the patient was prescribed oral [linezolid](#) 600 mg twice daily for 4 days and [venlafaxine](#) 150 mg once daily. In the subsequent 2-year period, the patient received two 10-day courses of [linezolid](#) while receiving concomitant [venlafaxine](#) 187.5 mg and 225 mg daily with no symptoms of serotonin toxicity [329].

f) [Serotonin syndrome](#) was reported in the case of an 85-year-old man who was receiving [venlafaxine](#) 150 mg daily for depression and oral [linezolid](#) 600 mg twice daily with [ciprofloxacin](#) and rifampicin for a closed [wound](#) due to the removal of a chronically infected hip prosthesis. His medical history included [Parkinson's disease](#), [ischemic heart disease](#), [atrial fibrillation](#), [diabetes](#), and a permanent pacemaker. After 20 days of receiving oral antibiotic therapy, the patient was reportedly confused and disoriented with intermittent aggression and abnormal sleep patterns. A brain [CT scan](#) and serum chemistries were all normal with no evidence of sepsis; vital signs were also within normal limits. Four days later, the patient was transferred to an acute care rehabilitation hospital due to drowsiness. He had a fever of 37.6 degrees Celsius and a decreased level of consciousness, along with generalized myoclonic jerks and decreasing plantar reflexes. [Linezolid](#) and [venlafaxine](#) were discontinued due to a suspected drug interaction. Within 2 days, the patient's mental status had returned to normal [330].

3.5.1.ED] Lisdexamfetamine

- 1) Interaction Effect: increased risk of [serotonin syndrome](#)
- 2) Summary: Coadministration of an [amphetamine](#) and another serotonergic agent may result in [serotonin syndrome](#), because both drugs affect the serotonergic neurotransmitter system. 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[235].
- 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. 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[235].
- 7) Probable Mechanism: additive serotonergic effect

3.5.1.EE] Lorcaserin

- 1) Interaction Effect: increased [venlafaxine](#) plasma concentrations and increased risk of [serotonin syndrome](#)
- 2) Summary: In a clinical trial in 21 CYP2D6 extensive metabolizers, coadministration of lorcaserin, a CYP2D6 inhibitor, 10 mg twice a day for 4 days increased [dextromethorphan](#), a CYP2D6 substrate, peak concentrations (C_{max}) by approximately 76% and exposure (AUC) by approximately 2-fold[316]. Therefore the concomitant use of [venlafaxine](#), a CYP2D6 substrate [117], and lorcaserin may cause increased [venlafaxine](#) plasma concentrations resulting in increased [venlafaxine](#) adverse effects. Lorcaserin is a serotonergic drug and concomitant use with another agent that affects the serotonergic

neurotransmitter system, such as [venlafaxine](#), may result in an increased risk of [serotonin syndrome](#) and should be approached with extreme caution [316].

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Use extreme caution with the concomitant use of [venlafaxine](#) with lorcaserin as this may cause increased [venlafaxine](#) plasma concentrations and may also result in additive serotonergic effects, increasing the risk of [serotonin syndrome](#)[316].

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

3.5.1.EF] Lornoxicam

1) Interaction Effect: an increased risk of bleeding

2) Summary: Use caution when coadministering NSAIDs and serotonin [norepinephrine](#) reuptake inhibitors (SNRI) as this may cause an increased risk of bleeding[318]. During clinical trials, concomitant use of NSAIDs and antidepressants, including tricyclic antidepressants, SSRIs, selective serotonin-norepinephrine reuptake inhibitors, and MOAIs, resulted in an increased risk of [intracranial hemorrhage](#) within 30 days of concomitant use compared with antidepressant use alone [319]. When NSAIDs and SNRIs are given concurrently, monitor the patient for signs of increased bleeding.

3) Severity: major

4) Onset: unspecified

5) Substantiation: established

6) Clinical Management: Serotonin [norepinephrine](#) reuptake inhibitors (SNRI) increase bleeding risk, especially with concomitant use of NSAIDs[318]. When NSAIDs and SNRIs are given concurrently, monitor the patient for signs of increased bleeding.

7) Probable Mechanism: unknown

8) Literature Reports

a) Concomitant use of NSAIDs and antidepressants, including tricyclic antidepressants, SSRIs, serotonin-norepinephrine reuptake inhibitors, and MAOIs, resulted in an increased risk of [intracranial hemorrhage](#) within 30 days of concomitant use compared with antidepressant use alone. There was no significant difference between the antidepressant drug classes and the increased risk; however, there was an increased risk associated with male patients compared with female patients [319].

3.5.1.EG] Loxoprofen

1) Interaction Effect: an increased risk of bleeding

2) Summary: Use caution when coadministering NSAIDs and serotonin [norepinephrine](#) reuptake inhibitors (SNRI) as this may cause an increased risk of bleeding[318]. During clinical trials, concomitant use of NSAIDs and antidepressants, including tricyclic antidepressants, SSRIs, selective serotonin-norepinephrine reuptake inhibitors, and MOAIs, resulted in an increased risk of [intracranial hemorrhage](#) within 30 days of concomitant use compared with antidepressant use alone [319]. When NSAIDs and SNRIs are given concurrently, monitor the patient for signs of increased bleeding.

3) Severity: major

4) Onset: unspecified

5) Substantiation: established

6) Clinical Management: Serotonin [norepinephrine](#) reuptake inhibitors (SNRI) increase bleeding risk, especially with concomitant use of NSAIDs[318]. When NSAIDs and SNRIs are given concurrently, monitor the patient for signs of increased bleeding.

7) Probable Mechanism: unknown

8) Literature Reports

a) Concomitant use of NSAIDs and antidepressants, including tricyclic antidepressants, SSRIs, serotonin-norepinephrine reuptake inhibitors, and MAOIs, resulted in an increased risk of [intracranial hemorrhage](#) within 30 days of concomitant use compared with antidepressant use alone. There was no significant difference between the antidepressant drug classes and the increased risk; however, there was an increased risk associated with male patients compared with female patients [319].

3.5.1.EH] Lumiracoxib

1) Interaction Effect: an increased risk of bleeding

2) Summary: Use caution when coadministering NSAIDs and serotonin [norepinephrine](#) reuptake inhibitors (SNRI) as this may cause an increased risk of bleeding[318]. During clinical trials, concomitant use of NSAIDs and antidepressants, including tricyclic antidepressants, SSRIs, selective serotonin-norepinephrine reuptake inhibitors, and MOAIs, resulted in an increased risk of [intracranial hemorrhage](#) within 30 days of concomitant use compared with antidepressant use alone [319]. When NSAIDs and SNRIs are given concurrently, monitor the patient for signs of increased bleeding.

3) Severity: major

4) Onset: unspecified

5) Substantiation: established

6) Clinical Management: Serotonin [norepinephrine](#) reuptake inhibitors (SNRI) increase bleeding risk, especially with concomitant use of NSAIDs[318]. When NSAIDs and SNRIs are given concurrently, monitor the patient for signs of increased bleeding.

7) Probable Mechanism: unknown

8) Literature Reports

a) Concomitant use of NSAIDs and antidepressants, including tricyclic antidepressants, SSRIs, serotonin-norepinephrine reuptake inhibitors, and MAOIs, resulted in an increased risk of [intracranial hemorrhage](#) within 30 days of concomitant use compared with antidepressant use alone. There was no significant difference between the antidepressant drug classes and the increased risk; however, there was an increased risk associated with male patients compared with female patients [319].

3.5.1.EI] Meclofenamate

1) Interaction Effect: an increased risk of bleeding

2) Summary: Use caution when coadministering NSAIDs and serotonin [norepinephrine](#) reuptake inhibitors (SNRI) as this may cause an increased risk of bleeding[318]. During clinical trials, concomitant use of NSAIDs and antidepressants, including tricyclic antidepressants, SSRIs, selective serotonin-norepinephrine reuptake inhibitors, and MOAIs, resulted in an increased risk of [intracranial hemorrhage](#) within 30 days of concomitant use compared with antidepressant use alone [319]. When NSAIDs and SNRIs are given concurrently, monitor the patient for signs of increased bleeding.

3) Severity: major

4) Onset: unspecified

5) Substantiation: established

6) Clinical Management: Serotonin [norepinephrine](#) reuptake inhibitors (SNRI) increase bleeding risk, especially with concomitant use of NSAIDs[318]. When NSAIDs and SNRIs are given concurrently, monitor the patient for signs of increased bleeding.

7) Probable Mechanism: unknown

8) Literature Reports

a) Concomitant use of NSAIDs and antidepressants, including tricyclic antidepressants, SSRIs, serotonin-norepinephrine reuptake inhibitors, and MAOIs, resulted in an increased risk of [intracranial hemorrhage](#) within 30 days of concomitant use compared with antidepressant use alone. There was no significant difference between the antidepressant drug classes and the increased risk; however, there was an increased risk associated with male patients compared with female patients [319].

3.5.1.EJ] Mefenamic Acid

1) Interaction Effect: an increased risk of bleeding

2) Summary: Use caution when coadministering NSAIDs and serotonin [norepinephrine](#) reuptake inhibitors (SNRI) as this may cause an increased risk of bleeding[318]. During clinical trials, concomitant use of NSAIDs and antidepressants, including tricyclic antidepressants, SSRIs, selective serotonin-norepinephrine reuptake inhibitors, and MOAIs, resulted in an increased risk of [intracranial hemorrhage](#) within 30 days of concomitant use compared with antidepressant use alone [319]. When NSAIDs and SNRIs are given concurrently, monitor the patient for signs of increased bleeding.

3) Severity: major

4) Onset: unspecified

5) Substantiation: established

6) Clinical Management: Serotonin [norepinephrine](#) reuptake inhibitors (SNRI) increase bleeding risk, especially with concomitant use of NSAIDs[318]. When NSAIDs and SNRIs are given concurrently, monitor the patient for signs of increased bleeding.

7) Probable Mechanism: unknown

8) Literature Reports

a) Concomitant use of NSAIDs and antidepressants, including tricyclic antidepressants, SSRIs, serotonin-norepinephrine reuptake inhibitors, and MAOIs, resulted in an increased risk of [intracranial hemorrhage](#) within 30 days of concomitant use compared with antidepressant use alone. There was no significant difference between the antidepressant drug classes and the increased risk; however, there was an increased risk associated with male patients compared with female patients [319].

3.5.1.EK] Meloxicam

1) Interaction Effect: an increased risk of bleeding

2) Summary: Use caution when coadministering NSAIDs and serotonin [norepinephrine](#) reuptake inhibitors (SNRI) as this may cause an increased risk of bleeding[318]. During clinical trials, concomitant use of NSAIDs and antidepressants, including tricyclic antidepressants, SSRIs, selective serotonin-norepinephrine reuptake inhibitors, and MOAIs, resulted in an increased risk of [intracranial hemorrhage](#) within 30 days of concomitant use compared with antidepressant use alone [319]. When NSAIDs and SNRIs are given concurrently, monitor the patient for signs of increased bleeding.

3) Severity: major

4) Onset: unspecified

5) Substantiation: established

6) Clinical Management: Serotonin [norepinephrine](#) reuptake inhibitors (SNRI) increase bleeding risk, especially with concomitant use of NSAIDs[318]. When NSAIDs and SNRIs are given concurrently, monitor the patient for signs of increased bleeding.

7) Probable Mechanism: unknown

8) Literature Reports

a) Concomitant use of NSAIDs and antidepressants, including tricyclic antidepressants, SSRIs, serotonin-norepinephrine reuptake inhibitors, and MAOIs, resulted in an increased risk of [intracranial hemorrhage](#) within 30 days of concomitant use compared with antidepressant use alone. There was no significant difference between the antidepressant drug classes and the increased risk; however, there was an increased risk associated with male patients compared with female patients [319].

3.5.1.EL] [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[203]. 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 [119]. 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.EM] [Mesoridazine](#)

- 1) Interaction Effect: increased risk of QT-interval prolongation
- 2) Summary: The concomitant use of [mesoridazine](#) with drugs that cause QT-interval prolongation is contraindicated, as coadministration may increase the risk of QT prolongation and serious [ventricular arrhythmias](#)[352].
- 3) Severity: contraindicated
- 4) Onset: unspecified
- 5) Substantiation: established
- 6) Clinical Management: The concomitant use of [mesoridazine](#) with drugs that cause QT-interval prolongation is contraindicated, as coadministration may increase the risk of QT prolongation and serious [ventricular arrhythmias](#)[352].
- 7) Probable Mechanism: additive QT-interval prolongation

3.5.1.EN] [Methamphetamine](#)

- 1) Interaction Effect: increased risk of [serotonin syndrome](#)
- 2) Summary: Coadministration of an [amphetamine](#) and another serotonergic agent may result in [serotonin syndrome](#), because both drugs affect the serotonergic neurotransmitter system. 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[235].

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. 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[235].

7J) Probable Mechanism: additive serotonergic effect

3.5.1.EOJ Methylene Blue

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

2J) Summary: Concomitant use of IV methylene blue, an MAOI, and [venlafaxine](#) is contraindicated. Reports have involved IV methylene blue in doses of 1 mg/kg to 8 mg/kg. Reports have not included other routes of administration, such as oral or local tissue injection, or at lower doses; however, the possibility of emergent symptoms of [serotonin syndrome](#) cannot be ruled out. If urgent treatment with IV methylene blue is necessary and alternatives are not available, promptly discontinue [venlafaxine](#) and then IV methylene blue may be administered after the risk/benefit has been evaluated[123]. Use the lowest possible dose of methylene blue [124]. Monitor for [serotonin syndrome](#) for 7 days or until 24 hours after the last dose of IV methylene blue, whichever comes first. [Venlafaxine](#) can be resumed 24 hours after the last dose of IV methylene blue [123].

3J) Severity: contraindicated

4J) Onset: unspecified

5J) Substantiation: theoretical

6J) Clinical Management: Concurrent use of IV methylene blue (an MAOI) and [venlafaxine](#) is contraindicated. If urgent treatment with IV methylene blue is necessary and alternatives are not available, promptly discontinue [venlafaxine](#) and then IV methylene blue may be administered after the risk/benefit has been evaluated[123]. Use the lowest possible dose of methylene blue [124]. Monitor for [serotonin syndrome](#) for 7 days or until 24 hours after the last dose of IV methylene blue, whichever comes first. [Venlafaxine](#) can be resumed 24 hours after the last dose of IV methylene blue [123]. While the risk of concurrent [venlafaxine](#) 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

3.5.1.EPJ Metoclopramide

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

2J) Summary: A risk of [serotonin syndrome](#) with serious extrapyramidal reactions may occur with concomitant use of [venlafaxine](#) and [metoclopramide](#). In a case report, a 32-year-old woman developed extrapyramidal symptoms after [metoclopramide](#) was added to a regimen of [venlafaxine](#)[197]. Concomitant use of [venlafaxine](#) with [metoclopramide](#) is contraindicated [194]. If concurrent therapy is required, monitor patients for signs and symptoms of extrapyramidal reactions or [neuroleptic malignant syndrome](#) (fever, sweating, confusion, muscle stiffness). Discontinue [metoclopramide](#) if patient develops signs and symptoms of extrapyramidal reactions or [neuroleptic malignant syndrome](#). Injection of [diphenhydramine](#)

50 mg intramuscularly or [benztropine](#) 1 to 2 mg intramuscularly may reverse the extrapyramidal reactions [195].

3) Severity: contraindicated

4) Onset: unspecified

5) Substantiation: probable

6) Clinical Management: Concomitant use of [venlafaxine](#) with [metoclopramide](#) is contraindicated[194]. If concurrent therapy is required, monitor patients for signs and symptoms of extrapyramidal reactions or [neuroleptic malignant syndrome](#) (fever, sweating, confusion, muscle stiffness). Discontinue [metoclopramide](#) if patient develops signs and symptoms of extrapyramidal reactions or [neuroleptic malignant syndrome](#). Injection of [diphenhydramine](#) 50 mg intramuscularly or [benztropine](#) 1 to 2 mg intramuscularly may reverse the extrapyramidal reactions [195].

7) Probable Mechanism: synergistic dopaminergic inhibition

8) Literature Reports

a) [Metoclopramide](#) interacts with [venlafaxine](#) resulting in [serotonin syndrome](#) with serious dystonic-dyskinetic reactions. A 32-year-old female with [major depressive disorder](#) was admitted to the hospital after falling. She had been treated with [venlafaxine](#) 150 mg am and 75 mg pm for 3 years. The patient developed generalized shaking, jerking movements of all limbs, twitching of the jaw, and clenching of the teeth after receiving [metoclopramide](#) intravenously. She was unresponsive for less than a minute. Thirty minutes after the second dose of [metoclopramide](#), given 10 hours later, the patient developed myoclonic jerks and muscle rigidity and she became diaphoretic, confused and agitated. Additionally, she had involuntary twitching of the face, [horizontal nystagmus](#), and dilated pupils. Her temperature rose to 37.9 degrees Celsius, heart rate was 115 beats/min, respiratory rate 24 breaths/min, and blood pressure 137/95 mmHg (normal 115 to 120/80 to 85). Her laboratory values were normal. There was improvement in symptoms after intravenous [diazepam](#) was administered. All drugs were withheld. Two hours later the patient started shivering and demonstrated increased muscle rigidity with intermittent forceful extensions of her legs and jerking of her arms. Two or more of these episodes occurred with resolution after [diazepam](#) administration. Complete resolution of symptoms occurred on hospital day 3. [Venlafaxine](#) was reinstated without problems. According to the Naranjo probability scale, the combination of [metoclopramide](#) and [venlafaxine](#) was considered a probable cause of [serotonin syndrome](#) [196].

3.5.1.EQ| [Metoprolol](#)

1) Interaction Effect: increased [metoprolol](#) plasma concentrations, but decreased [metoprolol](#) efficacy

2) Summary: Concomitant use of [metoprolol](#) and [venlafaxine](#) may increase the plasma concentration of [metoprolol](#) but may also reduce the efficacy of [metoprolol](#). In healthy men (n=18), concomitant administration led to a 30% to 40% increase in [metoprolol](#) plasma concentrations, but the active alpha hydroxymetoprolol metabolite, [venlafaxine](#), and O-desmethylvenlafaxine metabolite were unaltered. Control of preexisting [hypertension](#) before [venlafaxine](#) treatment and regular blood pressure monitoring during concurrent treatment are recommended[60][400].

3) Severity: moderate

4) Onset: unspecified

5) Substantiation: established

6) Clinical Management: Concurrent administration of [metoprolol](#) and [venlafaxine](#) may increase plasma concentrations of [metoprolol](#), but also may decrease the effectiveness of [metoprolol](#) blood pressure control. Control of preexisting [hypertension](#) before [venlafaxine](#) treatment and regular blood pressure monitoring during concomitant treatment are recommended[60][400].

7) Probable Mechanism: unknown

8) Literature Reports

a) Following concomitant administration of [metoprolol](#) (100 mg every 24 hours for 5 days) and [venlafaxine](#) (50 mg every 8 hours for 5 days) in 18 healthy men, [metoprolol](#) plasma concentrations increased by approximately 30% to 40%; however, the plasma concentrations of the active alpha hydroxymetoprolol metabolite were unaltered. Similarly, the pharmacokinetic parameters of [venlafaxine](#) and the O-desmethylvenlafaxine metabolite were also unaltered. Notably in this study, [venlafaxine](#) reduced the blood pressure lowering effect of [metoprolol](#), but the clinical significance of reduction in [metoprolol](#) efficacy in hypertensive patients was not established [60][400].

3.5.1.ER] Metronidazole

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

2) Summary: Concurrent use of [metronidazole](#) with other QT-prolonging drugs was a probable cause of QT-interval prolongation in one study of cardiac ICU patients. Use caution with coadministration of [metronidazole](#) with other QT interval-prolonging drugs, as life-threatening additive effects on the QT interval, including [torsades de pointes](#), may occur. Consider close [ECG monitoring](#) at baseline and during concurrent therapy with QT-interval prolonging drugs[155].

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Use caution with coadministration of [metronidazole](#) with other QT interval-prolonging drugs, as life-threatening additive effects on the QT interval, including [torsades de pointes](#), may occur. Consider close [ECG monitoring](#) at baseline and during concurrent therapy with QT-interval prolonging drugs[155].

7) Probable Mechanism: additive QT-interval prolongation

8) Literature Reports

a) In a retrospective study, 164 of 501 patients admitted in cardiac ICUs (87.7%) developed QT-interval prolongation potentially linked to inhibition of CYP450-mediated metabolism. Out of 1027 total interactions that were potentially associated with QT-interval prolonging effects, interactions with [metronidazole](#) (n=22) were some of the most common. No patients developed [torsades de pointes](#) during their ICU stays. Close [ECG monitoring](#) at baseline and during concurrent therapy with drugs known to cause QT-interval prolongation is recommended [155].

b) A 71-year-old woman with antibiotic-induced [pseudomembranous colitis](#) developed ECG QTc interval prolongation and [torsades de pointes](#) with concurrent [amiodarone](#) 450 mg bolus followed by 900 mg/day IV and [metronidazole](#) 1500 mg/day oral administration. Baseline QTc interval was 440 msec. [Amiodarone](#) was added after trial fibrillation developed with 3 days of [amiodarone](#) therapy. Conversion to sinus rhythm occurred 2 days later; however, the follow-up ECG revealed a QTc interval of 625 msec. Symptoms progressed to sustained torsades de pointes-variant [ventricular tachycardia](#) that required emergent [cardioversion/defibrillation](#) to restore normal sinus rhythm. [Amiodarone](#) and [metronidazole](#) were immediately withdrawn, and the QTc interval slowly returned to baseline values without further clinically significant [arrhythmia](#) events [156].

3.5.1.ES] 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[315].

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[315].

7) Probable Mechanism: additive serotonergic effect

3.5.1.ET] Mirabegron

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

2) Summary: Patients concurrently treated with mirabegron, a moderate CYP2D6 inhibitor[401], and [venlafaxine](#), a CYP2D6 substrate [402][117], may have an increase in [venlafaxine](#) exposure and risk of adverse events. Inhibition of CYP2D6 leads to increased plasma concentrations of [venlafaxine](#) and decreased concentrations of its active metabolite, O-desmethylvenlafaxine (ODV). However, because both [venlafaxine](#) and ODV are pharmacologically active, changes in the relative concentrations of each did not result in clinically important differences when studied in CYP2D6 poor and extensive metabolizers [402][117]. Appropriate monitoring is advised when mirabegron is used concomitantly with a CYP2D6 substrate [401], but dose adjustments are not required when [venlafaxine](#) is coadministered with a CYP2D6 inhibitor [402][117].

3) Severity: moderate

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Concomitant use of mirabegron, a moderate CYP2D6 inhibitor[401], and [venlafaxine](#), a CYP2D6 substrate, may result in increased [venlafaxine](#) exposure. Dose adjustments to [venlafaxine](#) are not required when coadministered with CYP2D6 inhibitors [402][117], but monitoring is recommended [401].

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

3.5.1.EU] Mirtazapine

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

2) Summary: Concomitant use of [mirtazapine](#) with other serotonergic agents may increase the risk of [serotonin syndrome](#) due to additive serotonergic effects. Monitor for symptoms of [serotonin syndrome](#), especially during treatment initiation and dose increases, and if the patient shows symptoms, treatment with [mirtazapine](#) and any concomitant serotonergic agent should be discontinued[310]. 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 [119].

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: If concomitant use with other serotonergic drugs is clinically warranted, monitor for the emergence of [serotonin syndrome](#), particularly during treatment initiation and dose increases. Discontinue use of both agents if a patient shows symptoms of [serotonin syndrome](#)[310].

7) Probable Mechanism: additive serotonin effects**8) Literature Reports**

a) Within a few hours of starting [mirtazapine](#) and shortly after stopping [fluoxetine](#), a 75-year-old woman experienced symptoms consistent with [serotonin syndrome](#). Current medication for depression included [fluoxetine](#), [chlorpromazine](#), and [lorazepam](#). Due to lack of response, [fluoxetine](#) was discontinued and soon afterward [mirtazapine](#) 30 mg/day was started. Within a few hours of starting [mirtazapine](#), she experience dizziness, headache, nausea, dry mouth, intense anxiety and agitation with suicidal ideas. Other symptoms were difficulty walking, marked resting tremor of the hands, and insomnia. Over the next 3 days, she progressively worsened. [Mirtazapine](#) was discontinued on day 5. Her symptoms improved the following day. [Fluoxetine](#) 20 mg/day was restarted on day 7 with subsequent resolution of dizziness, nausea, headache, and agitation resolution over the following days. Over the next 10 days, tremor, anxiety, difficulty walking, dry mouth, and insomnia improved [311].

b) A 26-year-old woman with [anorexia nervosa](#) receiving [fluvoxamine](#) for 4 months developed symptoms of [serotonin syndrome](#) after [mirtazapine](#) was initiated. The symptoms of twitching, tremors, agitation, restlessness, and "feeling like she could crawl out of her skin" developed over a period of 4 days after starting [mirtazapine](#) 30 mg/day. Symptoms rapidly progressed to twitching, tremors, and restlessness. She was hospitalized with further symptoms of diaphoresis, flushing, fasciculations, and nausea and treated with [cyproheptadine](#), [acetaminophen](#), and IV fluids. She remained afebrile throughout the event. Symptoms completely resolved within 24 hours [312].

3.5.1.EV] Moclobemide

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

2) Summary: Concurrent administration or overlapping therapy with [venlafaxine](#) 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[165][166][167][168][169]. Concomitant use is contraindicated.

3) Severity: contraindicated

4) Onset: rapid

5) Substantiation: probable

6) Clinical Management: Concurrent use of [venlafaxine](#) and a MAO inhibitor is contraindicated. Wait at least 14 days after discontinuing a MAO inhibitor before initiating therapy with [venlafaxine](#). Wait at least seven days after discontinuing [venlafaxine](#) 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](#) [160]. [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) Two cases suggestive of an interaction between [fluoxetine](#) and [selegiline](#), a selective monoamine oxidase B inhibitor, have been reported [161]. One case involved a first episode of mania being observed approximately one month after adding [selegiline](#) to [fluoxetine](#) therapy. The patient improved two months after both drugs were discontinued, and no further details were provided. The second case involved diaphoresis, vasoconstriction, and cyanosis of the hands which occurred in close temporal relationship to adding [fluoxetine](#) and [selegiline](#). Both drugs were discontinued, with relatively quick resolution of symptoms. Rechallenge with [fluoxetine](#) alone occurred without incident.

c) Five fatal overdose cases due to [serotonin syndrome](#) have been reported [162]. In three of the five cases, the drug combination that induced the fatal syndrome was moclobemide, a selective monoamine oxidase inhibitor, and [citalopram](#). Of the three patients, blood concentrations of moclobemide ranged from five times the therapeutic level to 50 times the therapeutic level, and [citalopram](#) concentrations ranged from normal therapeutic levels to five times the therapeutic level.

d) A 34-year-old man experienced [serotonin syndrome](#) after ingesting [venlafaxine](#) 2.625 g and moclobemide 3 g with an unknown amount of alcohol. The patient displayed [tachycardia](#) (126 beats/min), tachypnea (26 breaths/min), altered mental status, hypertonia, and had a creatine phosphokinase (CPK) of 1006 U/L. Moclobemide, which is a reversible MAOI in therapeutic doses, may act like an irreversible MAOI with large doses, increasing the level of serotonin in the synaptic cleft [163].

e) A 32-year-old man taking moclobemide 20 mg twice daily and [diazepam](#) 15 mg daily was given [venlafaxine](#) 150 mg by a friend. Approximately 40 minutes afterward, he developed dizziness, vomiting, diaphoresis, hallucination and agitation. He also demonstrated muscle rigidity and ocular oscillation. Blood pressure was noted to be 162/107 mm Hg. He was treated with [diazepam](#) 10 mg and [chlorpromazine](#) 12.5 mg and his condition improved significantly [164].

3.5.1.EW] Morniflumate

1) Interaction Effect: an increased risk of bleeding

2) Summary: Use caution when coadministering NSAIDs and serotonin [norepinephrine](#) reuptake inhibitors (SNRI) as this may cause an increased risk of bleeding[318]. During clinical trials, concomitant use of NSAIDs and antidepressants, including tricyclic antidepressants, SSRIs, selective serotonin-norepinephrine reuptake inhibitors, and MAOIs, resulted in an increased risk of [intracranial hemorrhage](#) within 30 days of concomitant use compared with antidepressant use alone [319]. When NSAIDs and SNRIs are given concurrently, monitor the patient for signs of increased bleeding.

3) Severity: major

4) Onset: unspecified

5) Substantiation: established

6) Clinical Management: Serotonin [norepinephrine](#) reuptake inhibitors (SNRI) increase bleeding risk, especially with concomitant use of NSAIDs[318]. When NSAIDs and SNRIs are given concurrently, monitor the patient for signs of increased bleeding.

7) Probable Mechanism: unknown

8) Literature Reports

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

alone. There was no significant difference between the antidepressant drug classes and the increased risk; however, there was an increased risk associated with male patients compared with female patients [319].

3.5.1.EX] Moxifloxacin

- 1) Interaction Effect: increased risk of QT-interval prolongation
- 2) Summary: **Moxifloxacin** has been associated with QT-interval prolongation. Coadministration with another drug known to prolong the QT-interval should be avoided because of risk for additive effects on the QT-interval that can lead to serious cardiac adverse effects, including **torsade de pointes**. Elderly patients receiving treatment with IV **moxifloxacin** may be at an increased risk for QT prolongation. If concurrent use is not avoidable, do not exceed the recommended dose or infusion rate of **moxifloxacin**[317] and monitor for changes in the QT-interval.
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: **Moxifloxacin** has been associated with QT-interval prolongation. Coadministration with another drug known to prolong the QT-interval should be avoided because of risk for additive effects on the QT-interval that can lead to serious cardiac adverse effects, including **torsade de pointes**. Elderly patients receiving treatment with IV **moxifloxacin** may be at an increased risk for QT prolongation. If concurrent use is not avoidable, do not exceed the recommended dose or infusion rate of **moxifloxacin**[317] and monitor for changes in the QT-interval.
- 7) Probable Mechanism: additive effects on QT-interval

3.5.1.EY] Nabumetone

- 1) Interaction Effect: an increased risk of bleeding
- 2) Summary: Use caution when coadministering NSAIDs and serotonin **norepinephrine** reuptake inhibitors (SNRI) as this may cause an increased risk of bleeding[318]. During clinical trials, concomitant use of NSAIDs and antidepressants, including tricyclic antidepressants, SSRIs, selective serotonin-norepinephrine reuptake inhibitors, and MAOIs, resulted in an increased risk of **intracranial hemorrhage** within 30 days of concomitant use compared with antidepressant use alone [319]. When NSAIDs and SNRIs are given concurrently, monitor the patient for signs of increased bleeding.
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: established
- 6) Clinical Management: Serotonin **norepinephrine** reuptake inhibitors (SNRI) increase bleeding risk, especially with concomitant use of NSAIDs[318]. When NSAIDs and SNRIs are given concurrently, monitor the patient for signs of increased bleeding.
- 7) Probable Mechanism: unknown
- 8) Literature Reports

a) Concomitant use of NSAIDs and antidepressants, including tricyclic antidepressants, SSRIs, serotonin-norepinephrine reuptake inhibitors, and MAOIs, resulted in an increased risk of **intracranial hemorrhage** within 30 days of concomitant use compared with antidepressant use alone. There was no significant difference between the antidepressant drug classes and the increased risk; however, there was an increased risk associated with male patients compared with female patients [319].

3.5.1.EZ] Nafarelin

- 1) Interaction Effect: increased risk of QT-interval prolongation
- 2) Summary: Use caution with coadministration of gonadotropin-releasing hormone (GnRH) agonists with QT-interval prolonging drugs. Androgen deprivation caused by GnRH agonists may prolong the QT interval and cause additive effects when administered with QT-interval prolonging drugs[377][378][379]. If concurrent therapy is necessary, monitor patients closely for signs and symptoms of [cardiac toxicity](#), including changes in the ECG.
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Use caution with coadministration of gonadotropin-releasing hormone (GnRH) agonists with QT-interval prolonging drugs, as additive effects on the QT interval may occur[377][378][379].
- 7) Probable Mechanism: additive effects on the QT interval

3.5.1.FA] [Naproxen](#)

- 1) Interaction Effect: an increased risk of bleeding
- 2) Summary: Use caution when coadministering NSAIDs and serotonin [norepinephrine](#) reuptake inhibitors (SNRI) as this may cause an increased risk of bleeding[318]. During clinical trials, concomitant use of NSAIDs and antidepressants, including tricyclic antidepressants, SSRIs, selective serotonin-norepinephrine reuptake inhibitors, and MOAIs, resulted in an increased risk of [intracranial hemorrhage](#) within 30 days of concomitant use compared with antidepressant use alone [319]. When NSAIDs and SNRIs are given concurrently, monitor the patient for signs of increased bleeding.
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: established
- 6) Clinical Management: Serotonin [norepinephrine](#) reuptake inhibitors (SNRI) increase bleeding risk, especially with concomitant use of NSAIDs[318]. When NSAIDs and SNRIs are given concurrently, monitor the patient for signs of increased bleeding.
- 7) Probable Mechanism: unknown
- 8) Literature Reports

a) Concomitant use of NSAIDs and antidepressants, including tricyclic antidepressants, SSRIs, serotonin-norepinephrine reuptake inhibitors, and MAOIs, resulted in an increased risk of [intracranial hemorrhage](#) within 30 days of concomitant use compared with antidepressant use alone. There was no significant difference between the antidepressant drug classes and the increased risk; however, there was an increased risk associated with male patients compared with female patients [319].

3.5.1.FB] [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[259]. 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](#) [258].

- 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.FC| [Nefazodone](#)

- 1) Interaction Effect: increased plasma concentrations of [venlafaxine](#)
- 2) Summary: Caution is advised if a CYP3A4 inhibitor, such as [nefazodone](#), is administered with [venlafaxine](#), due to a possible increase in plasma concentration levels of both [venlafaxine](#) and O-desvenlafaxine (ODV)[6]. Patients should be monitored for [venlafaxine](#) toxicity.
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Patients should be monitored for signs of [venlafaxine](#) toxicity such as nausea, drowsiness, and dizziness; a decrease in dosage may be required with concomitant therapy.
- 7) Probable Mechanism: decreased [venlafaxine](#) clearance
- 8) Literature Reports

a) Caution is warranted with the concurrent use of CYP3A4 inhibitors, such as [nefazodone](#), and [venlafaxine](#) due to possible increases in plasma concentration levels of both [venlafaxine](#) and O-desvenlafaxine (ODV) [6].

3.5.1.FD| [Nelfinavir](#)

- 1) Interaction Effect: increased plasma concentrations of [venlafaxine](#)
- 2) Summary: Caution is advised if a CYP3A4 inhibitor, such as [nelfinavir](#), is administered with [venlafaxine](#), due to a possible increase in plasma concentration levels of both [venlafaxine](#) and O-desvenlafaxine (ODV)[6]. Patients should be monitored for [venlafaxine](#) toxicity.
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Patients should be monitored for signs of [venlafaxine](#) toxicity such as nausea, drowsiness, and dizziness; a decrease in dosage may be required with concomitant therapy.
- 7) Probable Mechanism: decreased [venlafaxine](#) clearance
- 8) Literature Reports

a) Caution is warranted with the concurrent use of CYP3A4 inhibitors, such as [nelfinavir](#), and [venlafaxine](#) due to possible increases in plasma concentration levels of both [venlafaxine](#) and O-desvenlafaxine (ODV) [6].

3.5.1.FE| [Nepafenac](#)

- 1) Interaction Effect: an increased risk of bleeding
- 2) Summary: Use caution when coadministering NSAIDs and serotonin [norepinephrine](#) reuptake inhibitors (SNRI) as this may cause an increased risk of bleeding[318]. During clinical trials, concomitant

use of NSAIDs and antidepressants, including tricyclic antidepressants, SSRIs, selective serotonin-norepinephrine reuptake inhibitors, and MOAIs, resulted in an increased risk of [intracranial hemorrhage](#) within 30 days of concomitant use compared with antidepressant use alone [319]. When NSAIDs and SNRIs are given concurrently, monitor the patient for signs of increased bleeding.

3) Severity: major

4) Onset: unspecified

5) Substantiation: established

6) Clinical Management: Serotonin [norepinephrine](#) reuptake inhibitors (SNRI) increase bleeding risk, especially with concomitant use of NSAIDs[318]. When NSAIDs and SNRIs are given concurrently, monitor the patient for signs of increased bleeding.

7) Probable Mechanism: unknown

8) Literature Reports

a) Concomitant use of NSAIDs and antidepressants, including tricyclic antidepressants, SSRIs, serotonin-norepinephrine reuptake inhibitors, and MAOIs, resulted in an increased risk of [intracranial hemorrhage](#) within 30 days of concomitant use compared with antidepressant use alone. There was no significant difference between the antidepressant drug classes and the increased risk; however, there was an increased risk associated with male patients compared with female patients [319].

3.5.1.FF] Nialamide

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

2) Summary: Concurrent administration or overlapping therapy with [venlafaxine](#) 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[290][291][292][293]. A 60-year old woman developed a serious case of [serotonin syndrome](#) after the inadvertent ingestion of a single dose of [venlafaxine](#) while on chronic [tranlycypromine](#) therapy [294]. Concomitant use is contraindicated.

3) Severity: contraindicated

4) Onset: rapid

5) Substantiation: probable

6) Clinical Management: Concurrent use of [venlafaxine](#) and a MAO inhibitor is contraindicated. Wait at least 14 days after discontinuing a MAO inhibitor before initiating therapy with [venlafaxine](#). Wait at least seven days after discontinuing [venlafaxine](#) 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](#) [285]. [Serotonin syndrome](#) is a condition of serotonergic hyperstimulation and manifests as restlessness, myoclonus, changes in mental status, hyperreflexia, diaphoresis, shivering, and tremor. If the syndrome is not recognized and correctly treated, death can result.

b) A 26-year old woman who had been taking [isocarboxazid](#) for eight weeks stopped taking the drug for 11 days before beginning therapy with [sertraline](#). After a single 100 mg [sertraline](#) dose, the patient became restless and developed leg twitches. The patient was later admitted to the emergency room with diaphoresis, [tachycardia](#), hyperreflexia, and various neuromuscular disturbances. After treatment with [diazepam](#) and [propranolol](#) the patient did not improve. The

patient was then given two 4 mg doses of [cyproheptadine](#) an hour apart, with notable improvement in symptoms after the second dose [286].

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 [287].

d) Two cases reports suggested a possible interaction between [fluoxetine](#) and [selegiline](#) [288]. One case involved a first episode of mania being observed approximately one month after adding [selegiline](#) to [fluoxetine](#) therapy. The patient improved two months after both drugs were discontinued, and no further details were provided. The second case involved diaphoresis, vasoconstriction, and cyanosis of the hands which occurred in close temporal relationship to adding [fluoxetine](#) and [selegiline](#). Both drugs were discontinued, with relatively quick resolution of symptoms. Rechallenge with [fluoxetine](#) alone occurred without incident.

e) A case of a 60-year old female who developed [serotonin syndrome](#) after the inadvertent ingestion of a single dose of [venlafaxine](#) while on chronic [tranylcypromine](#) therapy was reported. Approximately four hours after taking the [venlafaxine](#), the patient became weak, confused, and collapsed. Upon examination, the patient exhibited [tachycardia](#), restlessness, tremor, fever, hyperreflexia, and diaphoresis. After treatment with [diazepam](#), [dantrolene](#), and other supportive therapy, the patient's condition returned to normal over the next four days [289].

3.5.1.FG] Niflumic Acid

1) Interaction Effect: an increased risk of bleeding

2) Summary: Use caution when coadministering NSAIDs and serotonin [norepinephrine](#) reuptake inhibitors (SNRI) as this may cause an increased risk of bleeding[318]. During clinical trials, concomitant use of NSAIDs and antidepressants, including tricyclic antidepressants, SSRIs, selective serotonin-norepinephrine reuptake inhibitors, and MOAIs, resulted in an increased risk of [intracranial hemorrhage](#) within 30 days of concomitant use compared with antidepressant use alone [319]. When NSAIDs and SNRIs are given concurrently, monitor the patient for signs of increased bleeding.

3) Severity: major

4) Onset: unspecified

5) Substantiation: established

6) Clinical Management: Serotonin [norepinephrine](#) reuptake inhibitors (SNRI) increase bleeding risk, especially with concomitant use of NSAIDs[318]. When NSAIDs and SNRIs are given concurrently, monitor the patient for signs of increased bleeding.

7) Probable Mechanism: unknown

8) Literature Reports

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

increased risk; however, there was an increased risk associated with male patients compared with female patients [319].

3.5.1.FH] Nimesulide

- 1) Interaction Effect: an increased risk of bleeding
- 2) Summary: Use caution when coadministering NSAIDs and serotonin [norepinephrine](#) reuptake inhibitors (SNRI) as this may cause an increased risk of bleeding[318]. During clinical trials, concomitant use of NSAIDs and antidepressants, including tricyclic antidepressants, SSRIs, selective serotonin-norepinephrine reuptake inhibitors, and MAOIs, resulted in an increased risk of [intracranial hemorrhage](#) within 30 days of concomitant use compared with antidepressant use alone [319]. When NSAIDs and SNRIs are given concurrently, monitor the patient for signs of increased bleeding.
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: established
- 6) Clinical Management: Serotonin [norepinephrine](#) reuptake inhibitors (SNRI) increase bleeding risk, especially with concomitant use of NSAIDs[318]. When NSAIDs and SNRIs are given concurrently, monitor the patient for signs of increased bleeding.
- 7) Probable Mechanism: unknown
- 8) Literature Reports

a) Concomitant use of NSAIDs and antidepressants, including tricyclic antidepressants, SSRIs, serotonin-norepinephrine reuptake inhibitors, and MAOIs, resulted in an increased risk of [intracranial hemorrhage](#) within 30 days of concomitant use compared with antidepressant use alone. There was no significant difference between the antidepressant drug classes and the increased risk; however, there was an increased risk associated with male patients compared with female patients [319].

3.5.1.FI] Nimesulide Beta Cyclodextrin

- 1) Interaction Effect: an increased risk of bleeding
- 2) Summary: Use caution when coadministering NSAIDs and serotonin [norepinephrine](#) reuptake inhibitors (SNRI) as this may cause an increased risk of bleeding[318]. During clinical trials, concomitant use of NSAIDs and antidepressants, including tricyclic antidepressants, SSRIs, selective serotonin-norepinephrine reuptake inhibitors, and MAOIs, resulted in an increased risk of [intracranial hemorrhage](#) within 30 days of concomitant use compared with antidepressant use alone [319]. When NSAIDs and SNRIs are given concurrently, monitor the patient for signs of increased bleeding.
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: established
- 6) Clinical Management: Serotonin [norepinephrine](#) reuptake inhibitors (SNRI) increase bleeding risk, especially with concomitant use of NSAIDs[318]. When NSAIDs and SNRIs are given concurrently, monitor the patient for signs of increased bleeding.
- 7) Probable Mechanism: unknown
- 8) Literature Reports

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

increased risk; however, there was an increased risk associated with male patients compared with female patients [319].

3.5.1.FJ] Nortriptyline

- 1) Interaction Effect: an increased risk of **cardiotoxicity** (QT prolongation, **torsades de pointes**, **cardiac arrest**) and adverse effects of both drugs
- 2) Summary: Tricyclic antidepressants (TCAs) and **venlafaxine** have been shown to prolong the QTc interval at the recommended therapeutic dose[297][298]. Even though no formal drug interaction studies have been done, the coadministration of tricyclic antidepressants and other drugs known to prolong the QTc interval, such as **venlafaxine**, is not recommended [299]. In addition, **venlafaxine** and tricyclic antidepressants (TCAs) may competitively inhibit each other's metabolism which may increase side effects of both drugs [300][297][301]. **Venlafaxine** increased the AUC, Cmax, and Cmin of **desipramine** by approximately 35%. The AUCs of 2-OH-desipramine increased by 2.5 and 4.5 fold when administered with **venlafaxine** 37.5 mg and 75 mg every 12 hours, respectively. The pharmacokinetics of **imipramine** and the 2-hydroxy metabolite were not affected [6].
- 3) Severity: major
- 4) Onset: rapid
- 5) Substantiation: theoretical
- 6) Clinical Management: Due to the potential for additive effects on the QT interval, the concurrent administration of **venlafaxine** and tricyclic antidepressants is not recommended.
- 7) Probable Mechanism: decreased TCA and **venlafaxine** metabolism; additive effects on QT prolongation
- 8) Literature Reports

a) When administered with **imipramine**, the pharmacokinetics of **imipramine** and the 2-hydroxy metabolite were not affected. **Venlafaxine** increased the area under the concentration-time curve (AUC), maximum concentration (Cmax), and minimum concentration (Cmin) of **desipramine** by approximately 35%. The 2-OH-desipramine AUCs increased by 2.5-fold (**venlafaxine** 37.5 mg every 12 hours) and by 4.5-fold (**venlafaxine** 75 mg every 12 hours). The clinical significance of this finding is unknown [6].

3.5.1.FK] Ondansetron

- 1) Interaction Effect: an increased risk of QT interval prolongation
- 2) Summary: **Ondansetron** prolongs the QT interval in a dose-dependent manner and postmarketing cases of **torsade de pointes** have been reported. Concomitant use of **ondansetron** with other QT-prolonging drugs may result in additive prolongation of the QT interval. If coadministration is necessary, **ECG monitoring** is recommended[357][358].
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: **Ondansetron** prolongs the QT interval in a dose-dependent manner. Use caution with concomitant use of **ondansetron** and drugs known to prolong the QT interval. If coadministration is necessary, **ECG monitoring** is recommended[357][358].
- 7) Probable Mechanism: additive effects on QT interval prolongation

3.5.1.FL] Oxaprozin

- 1) Interaction Effect: an increased risk of bleeding
- 2) Summary: Use caution when coadministering NSAIDs and serotonin **norepinephrine** reuptake inhibitors (SNRI) as this may cause an increased risk of bleeding[318]. During clinical trials, concomitant

use of NSAIDs and antidepressants, including tricyclic antidepressants, SSRIs, selective serotonin-norepinephrine reuptake inhibitors, and MOAIs, resulted in an increased risk of [intracranial hemorrhage](#) within 30 days of concomitant use compared with antidepressant use alone [319]. When NSAIDs and SNRIs are given concurrently, monitor the patient for signs of increased bleeding.

3) Severity: major

4) Onset: unspecified

5) Substantiation: established

6) Clinical Management: Serotonin [norepinephrine](#) reuptake inhibitors (SNRI) increase bleeding risk, especially with concomitant use of NSAIDs[318]. When NSAIDs and SNRIs are given concurrently, monitor the patient for signs of increased bleeding.

7) Probable Mechanism: unknown

8) Literature Reports

a) Concomitant use of NSAIDs and antidepressants, including tricyclic antidepressants, SSRIs, serotonin-norepinephrine reuptake inhibitors, and MAOIs, resulted in an increased risk of [intracranial hemorrhage](#) within 30 days of concomitant use compared with antidepressant use alone. There was no significant difference between the antidepressant drug classes and the increased risk; however, there was an increased risk associated with male patients compared with female patients [319].

3.5.1.FM] [Oxycodone](#)

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

2) Summary: Coadministration of [oxycodone](#) and another serotonergic agent may result in [serotonin syndrome](#), because both drugs affect the serotonergic neurotransmitter system. If concomitant use of [oxycodone](#) and such an agent is clinically required, monitor patients carefully, especially during treatment initiation and dosage adjustment. Discontinue [oxycodone](#) if [serotonin syndrome](#) is suspected[309].

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Coadministration of [oxycodone](#) and another serotonergic agent may result in [serotonin syndrome](#), because both drugs affect the serotonergic neurotransmitter system. If concomitant use of [oxycodone](#) and such an agent is clinically required, monitor patients carefully, especially during treatment initiation and dosage adjustment. Discontinue [oxycodone](#) if [serotonin syndrome](#) is suspected[309].

7) Probable Mechanism: additive serotonergic effect

3.5.1.FN] [Oxyphenbutazone](#)

1) Interaction Effect: an increased risk of bleeding

2) Summary: Use caution when coadministering NSAIDs and serotonin [norepinephrine](#) reuptake inhibitors (SNRI) as this may cause an increased risk of bleeding[318]. During clinical trials, concomitant use of NSAIDs and antidepressants, including tricyclic antidepressants, SSRIs, selective serotonin-norepinephrine reuptake inhibitors, and MOAIs, resulted in an increased risk of [intracranial hemorrhage](#) within 30 days of concomitant use compared with antidepressant use alone [319]. When NSAIDs and SNRIs are given concurrently, monitor the patient for signs of increased bleeding.

3) Severity: major

4) Onset: unspecified

5) Substantiation: established

6) Clinical Management: Serotonin [norepinephrine](#) reuptake inhibitors (SNRI) increase bleeding risk, especially with concomitant use of NSAIDs[318]. When NSAIDs and SNRIs are given concurrently, monitor the patient for signs of increased bleeding.

7) Probable Mechanism: unknown

8) Literature Reports

a) Concomitant use of NSAIDs and antidepressants, including tricyclic antidepressants, SSRIs, serotonin-norepinephrine reuptake inhibitors, and MAOIs, resulted in an increased risk of [intracranial hemorrhage](#) within 30 days of concomitant use compared with antidepressant use alone. There was no significant difference between the antidepressant drug classes and the increased risk; however, there was an increased risk associated with male patients compared with female patients [319].

3.5.1.FO] [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](#)[356].

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](#)[356].

7) Probable Mechanism: unknown

3.5.1.FP] [Panobinostat](#)

1) Interaction Effect: increased risk of QT interval prolongation; increased CYP2D6 substrate exposure

2) Summary: Avoid coadministration of panobinostat (a CYP2D6 inhibitor and QT prolonging drug) and drugs that are QT-prolonging CYP2D6 substrates as this may result in increased plasma concentrations of the substrate and an increased risk of QT interval prolongation. If concomitant use cannot be avoided, monitor frequently for adverse reactions. [ECG monitoring](#) may be warranted[369].

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Coadministration of panobinostat (a CYP2D6 inhibitor and QT prolonging drug) and drugs that are QT-prolonging CYP2D6 substrates should be avoided as this may result in increased plasma concentrations of the substrate and an increased risk of QT interval prolongation. If concomitant use cannot be avoided, monitor frequently for adverse reactions. [ECG monitoring](#) may be warranted[369].

7) Probable Mechanism: additive QT-prolonging effects; inhibition of CYP2D6-mediated metabolism by panobinostat

3.5.1.FQ] [Parecoxib](#)

- 1) Interaction Effect: an increased risk of bleeding
- 2) Summary: Use caution when coadministering NSAIDs and serotonin [norepinephrine](#) reuptake inhibitors (SNRI) as this may cause an increased risk of bleeding[318]. During clinical trials, concomitant use of NSAIDs and antidepressants, including tricyclic antidepressants, SSRIs, selective serotonin-norepinephrine reuptake inhibitors, and MOAIs, resulted in an increased risk of [intracranial hemorrhage](#) within 30 days of concomitant use compared with antidepressant use alone [319]. When NSAIDs and SNRIs are given concurrently, monitor the patient for signs of increased bleeding.
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: established
- 6) Clinical Management: Serotonin [norepinephrine](#) reuptake inhibitors (SNRI) increase bleeding risk, especially with concomitant use of NSAIDs[318]. When NSAIDs and SNRIs are given concurrently, monitor the patient for signs of increased bleeding.
- 7) Probable Mechanism: unknown
- 8) Literature Reports

a) Concomitant use of NSAIDs and antidepressants, including tricyclic antidepressants, SSRIs, serotonin-norepinephrine reuptake inhibitors, and MAOIs, resulted in an increased risk of [intracranial hemorrhage](#) within 30 days of concomitant use compared with antidepressant use alone. There was no significant difference between the antidepressant drug classes and the increased risk; however, there was an increased risk associated with male patients compared with female patients [319].

3.5.1.FR] Pargyline

- 1) Interaction Effect: CNS toxicity or [serotonin syndrome](#) (hypertension, hyperthermia, myoclonus, mental status changes)
- 2) Summary: Concurrent administration or overlapping therapy with [venlafaxine](#) 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[229][230][231][232]. A 60-year old woman developed a serious case of [serotonin syndrome](#) after the inadvertent ingestion of a single dose of [venlafaxine](#) while on chronic [tranlycypromine](#) therapy [233]. Concomitant use is contraindicated.
- 3) Severity: contraindicated
- 4) Onset: rapid
- 5) Substantiation: probable
- 6) Clinical Management: Concurrent use of [venlafaxine](#) and a MAO inhibitor is contraindicated. Wait at least 14 days after discontinuing a MAO inhibitor before initiating therapy with [venlafaxine](#). Wait at least seven days after discontinuing [venlafaxine](#) 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](#) [224]. [Serotonin syndrome](#) is a condition of serotonergic hyperstimulation and manifests as restlessness, myoclonus, changes in mental status, hyperreflexia, diaphoresis, shivering, and tremor. If the syndrome is not recognized and correctly treated, death can result.

b) A 26-year old woman who had been taking [isocarboxazid](#) for eight weeks stopped taking the drug for 11 days before beginning therapy with [sertraline](#). After a single 100 mg [sertraline](#)

dose, the patient became restless and developed leg twitches. The patient was later admitted to the emergency room with diaphoresis, [tachycardia](#), hyperreflexia, and various neuromuscular disturbances. After treatment with [diazepam](#) and [propranolol](#) the patient did not improve. The patient was then given two 4 mg doses of [cyproheptadine](#) an hour apart, with notable improvement in symptoms after the second dose [225].

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 [226].

d) Two cases reports suggested a possible interaction between [fluoxetine](#) and [selegiline](#) [227]. One case involved a first episode of mania being observed approximately one month after adding [selegiline](#) to [fluoxetine](#) therapy. The patient improved two months after both drugs were discontinued, and no further details were provided. The second case involved diaphoresis, vasoconstriction, and cyanosis of the hands which occurred in close temporal relationship to adding [fluoxetine](#) and [selegiline](#). Both drugs were discontinued, with relatively quick resolution of symptoms. Rechallenge with [fluoxetine](#) alone occurred without incident.

e) A case of a 60-year old female who developed [serotonin syndrome](#) after the inadvertent ingestion of a single dose of [venlafaxine](#) while on chronic [tranylcypromine](#) therapy was reported. Approximately four hours after taking the [venlafaxine](#), the patient became weak, confused, and collapsed. Upon examination, the patient exhibited [tachycardia](#), restlessness, tremor, fever, hyperreflexia, and diaphoresis. After treatment with [diazepam](#), [dantrolene](#), and other supportive therapy, the patient's condition returned to normal over the next four days [228].

3.5.1.FS] [Paroxetine](#)

1) Interaction Effect: increased risk of QT interval prolongation; increased risk of [serotonin syndrome](#); increased CYP2D6 substrate exposure

2) Summary: Coadminister [paroxetine](#) (a CYP2D6 inhibitor) cautiously with drugs that are QT-prolonging, serotonergic CYP2D6 substrates. Monitor for [serotonin syndrome](#) with concurrent use, especially during treatment initiation or dose increases, and immediately discontinue and immediately discontinue [paroxetine](#) and other serotonergic agents if symptoms occur. Dose reduction of either [paroxetine](#) or a CYP2D6 substrate may be required, as Cmax and AUC of a single dose of [desipramine](#) (a CYP2D6 substrate), rose by 2- and 5-fold, respectively, when added to an existing regimen with [paroxetine](#). [Paroxetine](#) is also associated with [ventricular tachycardia](#) and [torsade de pointes](#)[199]; monitor for signs of additive prolongation of the QT interval during concurrent use.

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Coadminister cautiously with drugs that are QT-prolonging, serotonergic CYP2D6 substrates. Monitor for [serotonin syndrome](#) with concurrent use, especially during treatment initiation or dose increases, and immediately discontinue [paroxetine](#) and other serotonergic agents if symptoms occur. Dose reduction of either [paroxetine](#) (a CYP2D6 inhibitor) or a CYP2D6 substrate may

be required. [Paroxetine](#) is also associated with [ventricular tachycardia](#) and [torsade de pointes](#)[199]; monitor for signs of additive prolongation of the QT interval during concurrent use.

7J) Probable Mechanism: additive QT-prolonging effects; additive serotonergic effects; inhibition of CYP2D6 substrate metabolism by [paroxetine](#)

8J) Literature Reports

aJ) Following a single dose of [desipramine](#) 100 mg (a CYP2D6 substrate) added to steady state dosing of [paroxetine](#) 20 mg/day, the [desipramine](#) C_{max}, AUC, and t(1/2) increased by a mean of 2-, 5-, and 3-fold [199].

3.5.1.FT] Pasireotide

1J) Interaction Effect: increased risk of QT prolongation

2J) Summary: Pasireotide is associated with QT-interval prolongation. In 2 studies, QT prolongation occurred at both therapeutic and supratherapeutic doses of pasireotide. Concomitant administration of pasireotide with other drugs that prolong the QT interval, including antiarrhythmic medications, may have additive prolonging effects on the QT interval. ECGs at baseline and at 21 days after treatment initiation are recommended when pasireotide is coadministered with other QT-prolonging agents[332].

3J) Severity: major

4J) Onset: unspecified

5J) Substantiation: theoretical

6J) Clinical Management: Concomitant administration of pasireotide and QT-prolonging drugs, including antiarrhythmic medications, may result in additive prolongation of the QT interval. ECGs at baseline and 21 days after treatment initiation are recommended when pasireotide is coadministered with other QT-prolonging agents[332].

7J) Probable Mechanism: additive QT-interval prolongation

3.5.1.FU] Pazopanib

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

2J) Summary: Due to the potential for additive effects on QT-interval prolongation and increased risk of [torsade de pointes](#), coadministration of pazopanib with drugs that prolong the QT interval should be done cautiously. Baseline and periodic [monitoring of ECG](#) and electrolyte maintenance (eg, [calcium](#), [magnesium](#), [potassium](#)) within the normal range is recommended[335].

3J) Severity: major

4J) Onset: unspecified

5J) Substantiation: theoretical

6J) Clinical Management: Coadministration of pazopanib with this drugs that prolong the QT interval should be done cautiously due to the potential for additive effects on the QT interval and increased risk of [torsade de pointes](#). Baseline and periodic [monitoring of ECG](#) and electrolyte maintenance (eg, [calcium](#), [magnesium](#), [potassium](#)) within the normal range is recommended[335].

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

3.5.1.FV] [Pentosan](#) Polysulfate Sodium

1J) Interaction Effect: an increased risk of bleeding

2J) Summary: Case reports and epidemiological studies have shown that use of selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs), including [venlafaxine](#), is associated with [gastrointestinal bleeding](#). Bleeding events with SSRIs and SNRIs included cases of ecchymoses, [hematomas](#), [epistaxis](#), and [petechiae](#); life-threatening hemorrhages have also occurred. Coadministration with [warfarin](#) or other anticoagulants may potentiate the risk of bleeding. A population-

based, case-controlled study of new coumarin users (acenocoumarol and phenprocoumon) with concomitant selective serotonin reuptake inhibitors (SSRIs) resulted in an increased risk of hospitalization due to nongastrointestinal bleeding[354]. Increases in prothrombin time, partial thromboplastin time, or INR have been reported when [venlafaxine](#) was administered to patients receiving [warfarin](#). Therefore, concomitant use of [venlafaxine](#) with [warfarin](#) or other drugs affecting coagulation should be undertaken with caution. Whenever [venlafaxine](#) is initiated or discontinued in patients receiving an anticoagulant, close monitoring of coagulation parameters is recommended [321].

3) Severity: major

4) Onset: unspecified

5) Substantiation: probable

6) Clinical Management: Use caution when [venlafaxine](#) is used concomitantly with [warfarin](#) or other drugs affecting coagulation. Closely monitor coagulation parameters when [venlafaxine](#) is initiated or discontinued in patients receiving anticoagulants, such as [warfarin](#)[321].

7) Probable Mechanism: additive adverse events

8) Literature Reports

a) A population-based, case-controlled study of new coumarin users (acenocoumarol and phenprocoumon) with concomitant selective serotonin reuptake inhibitors (SSRIs) resulted in an increased risk of hospitalization due to nongastrointestinal bleeding. Using national pharmacy and hospitalization records, Netherlands researchers identified 1848 cases that were admitted for abnormal bleeding and compared them with 5818 control subjects also taking coumarins. Median duration of treatment in patients was 220 days (range, 1 to 4690 days). Patients on SSRIs showed greater risk for hospitalization for nongastrointestinal bleeding (adjusted odds ratio (OR) 1.7, 95% confidence interval (CI), 1.1 to 2.5), however, the rate of [gastrointestinal bleeding](#) (adjusted OR 0.8, 95% CI, 0.4 to 1.5) was not significantly different [354].

3.5.1.FW] [Phenelzine](#)

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

2) Summary: Serious, sometimes fatal, reactions have been seen with the combination of [venlafaxine](#) and monoamine oxidase inhibitors (MAOIs) and concurrent use is contraindicated[187]. Reports of adverse effects have included [hyperthermia](#), rigidity, myoclonus, instability of vital signs, and extreme agitation progressing to [delirium](#) and coma. Concurrent use of MAOIs and [venlafaxine](#) has also been reported to result in a condition termed [serotonin syndrome](#) [188][189][190]. [Serotonin syndrome](#) is a rare but potentially fatal condition of serotonergic hyperstimulation characterized by changes in mental status, restlessness, myoclonus, hyperreflexia, diaphoresis, shivering, and tremor [191]. In one case [serotonin syndrome](#) occurred with initiation of [venlafaxine](#) therapy 16 days after discontinuation of [phenelzine](#), suggesting that a longer waiting period may be necessary [192]. In another report, two additional patients were started on [venlafaxine](#) at least 14 days after discontinuation of [phenelzine](#) and experienced significant [serotonin syndrome](#) symptoms [193].

3) Severity: contraindicated

4) Onset: rapid

5) Substantiation: probable

6) Clinical Management: Concurrent use of [venlafaxine](#) and a MAO inhibitor is contraindicated. Wait at least 14 days after discontinuing a MAO inhibitor before initiating therapy with [venlafaxine](#). Wait at least seven days after discontinuing [venlafaxine](#) before initiating therapy with a MAO inhibitor. Even if initiating [venlafaxine](#) therapy two weeks after discontinuation of [phenelzine](#), monitor patients for development of [serotonin syndrome](#).

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](#) [181]. [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 46-year old man with depression was taking a regimen of [phenelzine](#) 30 mg three times daily and [divalproex](#) 500 mg twice daily. The patient was then told to taper [phenelzine](#) before initiating therapy with [venlafaxine](#). The exact tapering regimen was not available. One day after the patient's last dose of [phenelzine](#), the patient took one 37.5 mg tablet of [venlafaxine](#). After 30 to 60 minutes, the patient was confused, twitching, and had a full body tremor. The patient was also having difficulty speaking and was experiencing visual hallucinations. The patient was given [propranolol](#), [diphenhydramine](#), and [lorazepam](#) in the emergency room, with subsequent improvement in symptoms. The patient was diagnosed with [serotonin syndrome](#) and was transferred to the intensive care unit with resolution of symptoms over the next day without further complications [182].

c) A 39-year old woman developed symptoms similar to [serotonin syndrome](#) due to an interaction between [phenelzine](#) and [venlafaxine](#). The patient, who had discontinued a regimen of [phenelzine](#) 45 mg daily seven days earlier, took a single 37.5 mg dose of [venlafaxine](#). The patient then experienced diaphoresis, lethargy, lightheadedness, dizziness, agitation, and an elevated [creatinine](#) kinase level. After treatment with [lorazepam](#) and other supportive therapy, the patient's symptoms resolved. [Venlafaxine](#) therapy was successfully initiated a week later at the same dose [183].

d) A case of [serotonin syndrome](#) was reported in a 34-year old man due to an interaction between [venlafaxine](#) and [phenelzine](#). The patient had previously been taking [phenelzine](#) which was discontinued 16 days before the initiation of therapy with [venlafaxine](#). Shortly after the first [venlafaxine](#) dose of 75 mg, the patient experienced symptoms such as agitation, diaphoresis, [tachycardia](#), and muscular rigidity. The patient had a temperature of 98.1 degrees F, a pulse of 115, and a respiratory rate of 16 breaths per minute. After examination revealed hyperreflexia, rigidity, and myoclonus in both feet, the patient was diagnosed with [serotonin syndrome](#). The patient's symptoms resolved over the next 12 hours, and he was prescribed [cyproheptadine](#) 8 mg three times daily for two days upon discharge. This case may be of major importance since [phenelzine](#) had been discontinued for more than the recommended two weeks before initiation of [venlafaxine](#). A longer washout period may be necessary [184].

e) A 44-year-old female was stabilized on [phenelzine](#) 30 mg twice daily and [alprazolam](#) 0.5 mg three times daily when she inadvertently ingested 150 mg of [venlafaxine](#) mg along with a dose of [phenelzine](#) and [alprazolam](#). Within 45 minutes she began to experience extremity shaking and rapid respirations. On arrival at the hospital, she was agitated, had increased muscle rigidity, increased muscle tone, and diminished verbal responsiveness. Vital signs included blood pressure of 130/58 mm Hg, pulse 148/minute, respirations 24/minute, and a rectal temperature of 38 degrees Celsius. The diagnosis of [serotonin syndrome](#) was made. Following intubation and seven days in the intensive care unit, she recovered without any evidence of long-term complications [185].

f) In a case report on four patients, symptoms of [serotonin syndrome](#) were noted, even in two cases where the patients waited 14 days between [phenelzine](#) and [venlafaxine](#) treatment. The patients ranged in age from 25 to 49 years, and all had been on [phenelzine](#) for co-existing migraine and tension-type headaches. The [phenelzine](#) was discontinued for various reasons, and three of the four

patients had been advised to wait 14 days after stopping [phenelzine](#) to start taking [venlafaxine](#). The fourth patient had a hiatus from [phenelzine](#) for six days. All the patients experienced symptoms including agitation, shaking, diaphoresis, [hyperthermia](#), slight [hypertension](#), dizziness, weakness, palpitations, and muscle tremors. The onset of the symptoms was within one hour of administration of [venlafaxine](#), and all the patients were returned to baseline within 24 hours of discontinuing the medication [186].

3.5.1.FX] Phenindione

1J) Interaction Effect: an increased risk of bleeding

2J) Summary: Case reports and epidemiological studies have shown that use of selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs), including [venlafaxine](#), is associated with [gastrointestinal bleeding](#). Bleeding events with SSRIs and SNRIs included cases of ecchymoses, [hematomas](#), [epistaxis](#), and [petechiae](#); life-threatening hemorrhages have also occurred. Coadministration with [warfarin](#) or other anticoagulants may potentiate the risk of bleeding. A population-based, case-controlled study of new coumarin users (acenocoumarol and phenprocoumon) with concomitant selective serotonin reuptake inhibitors (SSRIs) resulted in an increased risk of hospitalization due to nongastrointestinal bleeding[354]. Increases in prothrombin time, partial thromboplastin time, or INR have been reported when [venlafaxine](#) was administered to patients receiving [warfarin](#). Therefore, concomitant use of [venlafaxine](#) with [warfarin](#) or other drugs affecting coagulation should be undertaken with caution. Whenever [venlafaxine](#) is initiated or discontinued in patients receiving an anticoagulant, close monitoring of coagulation parameters is recommended [321].

3J) Severity: major

4J) Onset: unspecified

5J) Substantiation: probable

6J) Clinical Management: Use caution when [venlafaxine](#) is used concomitantly with [warfarin](#) or other drugs affecting coagulation. Closely monitor coagulation parameters when [venlafaxine](#) is initiated or discontinued in patients receiving anticoagulants, such as [warfarin](#)[321].

7J) Probable Mechanism: additive adverse events

8J) Literature Reports

aJ) A population-based, case-controlled study of new coumarin users (acenocoumarol and phenprocoumon) with concomitant selective serotonin reuptake inhibitors (SSRIs) resulted in an increased risk of hospitalization due to nongastrointestinal bleeding. Using national pharmacy and hospitalization records, Netherlands researchers identified 1848 cases that were admitted for abnormal bleeding and compared them with 5818 control subjects also taking coumarins. Median duration of treatment in patients was 220 days (range, 1 to 4690 days). Patients on SSRIs showed 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 [354].

3.5.1.FY] Phenprocoumon

1J) Interaction Effect: an increased risk of bleeding

2J) Summary: Case reports and epidemiological studies have shown that use of selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs), including [venlafaxine](#), is associated with [gastrointestinal bleeding](#). Bleeding events with SSRIs and SNRIs included cases of ecchymoses, [hematomas](#), [epistaxis](#), and [petechiae](#); life-threatening hemorrhages have also occurred. Coadministration with [warfarin](#) or other anticoagulants may potentiate the risk of bleeding. A population-based, case-controlled study of new coumarin users (acenocoumarol and phenprocoumon) with concomitant selective serotonin reuptake inhibitors (SSRIs) resulted in an increased risk of hospitalization

due to nongastrointestinal bleeding[354]. Increases in prothrombin time, partial thromboplastin time, or INR have been reported when [venlafaxine](#) was administered to patients receiving [warfarin](#). Therefore, concomitant use of [venlafaxine](#) with [warfarin](#) or other drugs affecting coagulation should be undertaken with caution. Whenever [venlafaxine](#) is initiated or discontinued in patients receiving an anticoagulant, close monitoring of coagulation parameters is recommended [321].

3J) Severity: major

4J) Onset: unspecified

5J) Substantiation: probable

6J) Clinical Management: Use caution when [venlafaxine](#) is used concomitantly with [warfarin](#) or other drugs affecting coagulation. Closely monitor coagulation parameters when [venlafaxine](#) is initiated or discontinued in patients receiving anticoagulants, such as [warfarin](#)[321].

7J) Probable Mechanism: additive adverse events

8J) Literature Reports

aJ) A population-based, case-controlled study of new coumarin users (acenocoumarol and phenprocoumon) with concomitant selective serotonin reuptake inhibitors (SSRIs) resulted in an increased risk of hospitalization due to nongastrointestinal bleeding. Using national pharmacy and hospitalization records, Netherlands researchers identified 1848 cases that were admitted for abnormal bleeding and compared them with 5818 control subjects also taking coumarins. Median duration of treatment in patients was 220 days (range, 1 to 4690 days). Patients on SSRIs showed 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 [354].

3.5.1.FZJ [Phenylbutazone](#)

1J) Interaction Effect: an increased risk of bleeding

2J) Summary: Use caution when coadministering NSAIDs and serotonin [norepinephrine](#) reuptake inhibitors (SNRI) as this may cause an increased risk of bleeding[318]. During clinical trials, concomitant use of NSAIDs and antidepressants, including tricyclic antidepressants, SSRIs, selective serotonin-norepinephrine reuptake inhibitors, and MOAIs, resulted in an increased risk of [intracranial hemorrhage](#) within 30 days of concomitant use compared with antidepressant use alone [319]. When NSAIDs and SNRIs are given concurrently, monitor the patient for signs of increased bleeding.

3J) Severity: major

4J) Onset: unspecified

5J) Substantiation: established

6J) Clinical Management: Serotonin [norepinephrine](#) reuptake inhibitors (SNRI) increase bleeding risk, especially with concomitant use of NSAIDs[318]. When NSAIDs and SNRIs are given concurrently, monitor the patient for signs of increased bleeding.

7J) Probable Mechanism: unknown

8J) Literature Reports

aJ) Concomitant use of NSAIDs and antidepressants, including tricyclic antidepressants, SSRIs, serotonin-norepinephrine reuptake inhibitors, and MAOIs, resulted in an increased risk of [intracranial hemorrhage](#) within 30 days of concomitant use compared with antidepressant use alone. There was no significant difference between the antidepressant drug classes and the increased risk; however, there was an increased risk associated with male patients compared with female patients [319].

3.5.1.GAJ [Piketopifen](#)

- 1) Interaction Effect: an increased risk of bleeding
- 2) Summary: Use caution when coadministering NSAIDs and serotonin [norepinephrine](#) reuptake inhibitors (SNRI) as this may cause an increased risk of bleeding[318]. During clinical trials, concomitant use of NSAIDs and antidepressants, including tricyclic antidepressants, SSRIs, selective serotonin-norepinephrine reuptake inhibitors, and MAOIs, resulted in an increased risk of [intracranial hemorrhage](#) within 30 days of concomitant use compared with antidepressant use alone [319]. When NSAIDs and SNRIs are given concurrently, monitor the patient for signs of increased bleeding.
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: established
- 6) Clinical Management: Serotonin [norepinephrine](#) reuptake inhibitors (SNRI) increase bleeding risk, especially with concomitant use of NSAIDs[318]. When NSAIDs and SNRIs are given concurrently, monitor the patient for signs of increased bleeding.
- 7) Probable Mechanism: unknown
- 8) Literature Reports

a) Concomitant use of NSAIDs and antidepressants, including tricyclic antidepressants, SSRIs, serotonin-norepinephrine reuptake inhibitors, and MAOIs, resulted in an increased risk of [intracranial hemorrhage](#) within 30 days of concomitant use compared with antidepressant use alone. There was no significant difference between the antidepressant drug classes and the increased risk; however, there was an increased risk associated with male patients compared with female patients [319].

3.5.1.GB| Pimavanserin

- 1) Interaction Effect: increased risk of QT-interval prolongation
- 2) Summary: Clinically significant QT-interval prolongation has occurred at the usual pimavanserin dosage. Avoid concomitant use of pimavanserin with other agents that prolong the QT interval due to the potential for additive effects on the QT interval and an increased risk of [cardiac arrhythmia](#)[121].
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Concomitant use of pimavanserin with other agents that prolong the QT interval should be avoided due to the potential for additive effects on the QT interval and an increased risk of [cardiac arrhythmia](#)[121].
- 7) Probable Mechanism: additive effects on the QT interval

3.5.1.GC| Pimozide

- 1) Interaction Effect: increased risk of QT-interval prolongation
- 2) Summary: The concomitant use of [pimozide](#) with drugs that cause QT-interval prolongation is contraindicated, as coadministration may increase the risk of QT prolongation and serious [ventricular arrhythmias](#)[212].
- 3) Severity: contraindicated
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: The concomitant use of [pimozide](#) with drugs that cause QT-interval prolongation is contraindicated, as coadministration may increase the risk of QT prolongation and serious [ventricular arrhythmias](#)[212].
- 7) Probable Mechanism: additive QT-interval prolongation

3.5.1.GD] Piperaquine

- 1) Interaction Effect: increased risk of QT-interval prolongation
- 2) Summary: Concomitant administration of piperazine (a QT-interval prolonging drug) with other drugs that cause QT-interval prolongation, including antiarrhythmic medications, is contraindicated. Additionally, recent use of QT-interval prolonging drugs, that may still be circulating (based on the half-life) at the time of piperazine administration, is contraindicated[324].
- 3) Severity: contraindicated
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Concomitant administration of piperazine (a QT-interval prolonging drug) with other drugs that cause QT-interval prolongation, including antiarrhythmic medications, is contraindicated. Additionally, recent use of QT-interval prolonging drugs, that may still be circulating (based on the half-life) at the time of piperazine administration, is contraindicated[324].
- 7) Probable Mechanism: additive QT-interval prolongation

3.5.1.GE] Piroxicam

- 1) Interaction Effect: an increased risk of bleeding
- 2) Summary: Use caution when coadministering NSAIDs and serotonin [norepinephrine](#) reuptake inhibitors (SNRI) as this may cause an increased risk of bleeding[318]. During clinical trials, concomitant use of NSAIDs and antidepressants, including tricyclic antidepressants, SSRIs, selective serotonin-norepinephrine reuptake inhibitors, and MOAIs, resulted in an increased risk of [intracranial hemorrhage](#) within 30 days of concomitant use compared with antidepressant use alone [319]. When NSAIDs and SNRIs are given concurrently, monitor the patient for signs of increased bleeding.
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: established
- 6) Clinical Management: Serotonin [norepinephrine](#) reuptake inhibitors (SNRI) increase bleeding risk, especially with concomitant use of NSAIDs[318]. When NSAIDs and SNRIs are given concurrently, monitor the patient for signs of increased bleeding.
- 7) Probable Mechanism: unknown
- 8) Literature Reports

a) Concomitant use of NSAIDs and antidepressants, including tricyclic antidepressants, SSRIs, serotonin-norepinephrine reuptake inhibitors, and MAOIs, resulted in an increased risk of [intracranial hemorrhage](#) within 30 days of concomitant use compared with antidepressant use alone. There was no significant difference between the antidepressant drug classes and the increased risk; however, there was an increased risk associated with male patients compared with female patients [319].

3.5.1.GF] Pitolisant

- 1) Interaction Effect: increased risk of QT-interval prolongation
- 2) Summary: The concomitant administration of pitolisant and another drug that prolongs the QT interval should be done with careful monitoring[346].
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical

- 6) Clinical Management: The concomitant administration of pitolisant and another drug that prolongs the QT interval should be done with careful monitoring[346].
- 7) Probable Mechanism: additive QT prolongation

3.5.1.GG] Pranoprofen

- 1) Interaction Effect: an increased risk of bleeding
- 2) Summary: Use caution when coadministering NSAIDs and serotonin [norepinephrine](#) reuptake inhibitors (SNRI) as this may cause an increased risk of bleeding[318]. During clinical trials, concomitant use of NSAIDs and antidepressants, including tricyclic antidepressants, SSRIs, selective serotonin-norepinephrine reuptake inhibitors, and MOAIs, resulted in an increased risk of [intracranial hemorrhage](#) within 30 days of concomitant use compared with antidepressant use alone [319]. When NSAIDs and SNRIs are given concurrently, monitor the patient for signs of increased bleeding.
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: established
- 6) Clinical Management: Serotonin [norepinephrine](#) reuptake inhibitors (SNRI) increase bleeding risk, especially with concomitant use of NSAIDs[318]. When NSAIDs and SNRIs are given concurrently, monitor the patient for signs of increased bleeding.
- 7) Probable Mechanism: unknown
- 8) Literature Reports

a) Concomitant use of NSAIDs and antidepressants, including tricyclic antidepressants, SSRIs, serotonin-norepinephrine reuptake inhibitors, and MAOIs, resulted in an increased risk of [intracranial hemorrhage](#) within 30 days of concomitant use compared with antidepressant use alone. There was no significant difference between the antidepressant drug classes and the increased risk; however, there was an increased risk associated with male patients compared with female patients [319].

3.5.1.GH] Procarbazine

- 1) Interaction Effect: CNS toxicity or [serotonin syndrome](#) ([hypertension](#), [hyperthermia](#), myoclonus, mental status changes)
- 2) Summary: Concurrent administration or overlapping therapy with [venlafaxine](#) 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[270][271][272][273]. A 60-year old woman developed a serious case of [serotonin syndrome](#) after the inadvertent ingestion of a single dose of [venlafaxine](#) while on chronic [tranylecypromine](#) therapy [274]. Concomitant use is contraindicated.
- 3) Severity: contraindicated
- 4) Onset: rapid
- 5) Substantiation: probable
- 6) Clinical Management: Concurrent use of [venlafaxine](#) and a MAO inhibitor is contraindicated. Wait at least 14 days after discontinuing a MAO inhibitor before initiating therapy with [venlafaxine](#). Wait at least seven days after discontinuing [venlafaxine](#) 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](#) [265]. [Serotonin syndrome](#) is a

condition of serotonergic hyperstimulation and manifests as restlessness, myoclonus, changes in mental status, hyperreflexia, diaphoresis, shivering, and tremor. If the syndrome is not recognized and correctly treated, death can result.

b)) A 26-year old woman who had been taking [isocarboxazid](#) for eight weeks stopped taking the drug for 11 days before beginning therapy with [sertraline](#). After a single 100 mg [sertraline](#) dose, the patient became restless and developed leg twitches. The patient was later admitted to the emergency room with diaphoresis, [tachycardia](#), hyperreflexia, and various neuromuscular disturbances. After treatment with [diazepam](#) and [propranolol](#) the patient did not improve. The patient was then given two 4 mg doses of [cyproheptadine](#) an hour apart, with notable improvement in symptoms after the second dose [266].

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 [267].

d)) Two cases reports suggested a possible interaction between [fluoxetine](#) and [selegiline](#) [268]. One case involved a first episode of mania being observed approximately one month after adding [selegiline](#) to [fluoxetine](#) therapy. The patient improved two months after both drugs were discontinued, and no further details were provided. The second case involved diaphoresis, vasoconstriction, and cyanosis of the hands which occurred in close temporal relationship to adding [fluoxetine](#) and [selegiline](#). Both drugs were discontinued, with relatively quick resolution of symptoms. Rechallenge with [fluoxetine](#) alone occurred without incident.

e)) A case of a 60-year old female who developed [serotonin syndrome](#) after the inadvertent ingestion of a single dose of [venlafaxine](#) while on chronic [tranylcypromine](#) therapy was reported. Approximately four hours after taking the [venlafaxine](#), the patient became weak, confused, and collapsed. Upon examination, the patient exhibited [tachycardia](#), restlessness, tremor, fever, hyperreflexia, and diaphoresis. After treatment with [diazepam](#), [dantrolene](#), and other supportive therapy, the patient's condition returned to normal over the next four days [269].

3.5.1.GI] Proglumetacin

1)) Interaction Effect: an increased risk of bleeding

2)) Summary: Use caution when coadministering NSAIDs and serotonin [norepinephrine](#) reuptake inhibitors (SNRI) as this may cause an increased risk of bleeding[318]. During clinical trials, concomitant use of NSAIDs and antidepressants, including tricyclic antidepressants, SSRIs, selective serotonin-norepinephrine reuptake inhibitors, and MOAIs, resulted in an increased risk of [intracranial hemorrhage](#) within 30 days of concomitant use compared with antidepressant use alone [319]. When NSAIDs and SNRIs are given concurrently, monitor the patient for signs of increased bleeding.

3)) Severity: major

4)) Onset: unspecified

5)) Substantiation: established

6) Clinical Management: Serotonin [norepinephrine](#) reuptake inhibitors (SNRI) increase bleeding risk, especially with concomitant use of NSAIDs[318]. When NSAIDs and SNRIs are given concurrently, monitor the patient for signs of increased bleeding.

7) Probable Mechanism: unknown

8) Literature Reports

a) Concomitant use of NSAIDs and antidepressants, including tricyclic antidepressants, SSRIs, serotonin-norepinephrine reuptake inhibitors, and MAOIs, resulted in an increased risk of [intracranial hemorrhage](#) within 30 days of concomitant use compared with antidepressant use alone. There was no significant difference between the antidepressant drug classes and the increased risk; however, there was an increased risk associated with male patients compared with female patients [319].

3.5.1.GJ] Propyphenazone

1) Interaction Effect: an increased risk of bleeding

2) Summary: Use caution when coadministering NSAIDs and serotonin [norepinephrine](#) reuptake inhibitors (SNRI) as this may cause an increased risk of bleeding[318]. During clinical trials, concomitant use of NSAIDs and antidepressants, including tricyclic antidepressants, SSRIs, selective serotonin-norepinephrine reuptake inhibitors, and MOAIs, resulted in an increased risk of [intracranial hemorrhage](#) within 30 days of concomitant use compared with antidepressant use alone [319]. When NSAIDs and SNRIs are given concurrently, monitor the patient for signs of increased bleeding.

3) Severity: major

4) Onset: unspecified

5) Substantiation: established

6) Clinical Management: Serotonin [norepinephrine](#) reuptake inhibitors (SNRI) increase bleeding risk, especially with concomitant use of NSAIDs[318]. When NSAIDs and SNRIs are given concurrently, monitor the patient for signs of increased bleeding.

7) Probable Mechanism: unknown

8) Literature Reports

a) Concomitant use of NSAIDs and antidepressants, including tricyclic antidepressants, SSRIs, serotonin-norepinephrine reuptake inhibitors, and MAOIs, resulted in an increased risk of [intracranial hemorrhage](#) within 30 days of concomitant use compared with antidepressant use alone. There was no significant difference between the antidepressant drug classes and the increased risk; however, there was an increased risk associated with male patients compared with female patients [319].

3.5.1.GK] Proquazone

1) Interaction Effect: an increased risk of bleeding

2) Summary: Use caution when coadministering NSAIDs and serotonin [norepinephrine](#) reuptake inhibitors (SNRI) as this may cause an increased risk of bleeding[318]. During clinical trials, concomitant use of NSAIDs and antidepressants, including tricyclic antidepressants, SSRIs, selective serotonin-norepinephrine reuptake inhibitors, and MOAIs, resulted in an increased risk of [intracranial hemorrhage](#) within 30 days of concomitant use compared with antidepressant use alone [319]. When NSAIDs and SNRIs are given concurrently, monitor the patient for signs of increased bleeding.

3) Severity: major

4) Onset: unspecified

5) Substantiation: established

6) Clinical Management: Serotonin [norepinephrine](#) reuptake inhibitors (SNRI) increase bleeding risk, especially with concomitant use of NSAIDs[318]. When NSAIDs and SNRIs are given concurrently, monitor the patient for signs of increased bleeding.

7) Probable Mechanism: unknown

8) Literature Reports

a) Concomitant use of NSAIDs and antidepressants, including tricyclic antidepressants, SSRIs, serotonin-norepinephrine reuptake inhibitors, and MAOIs, resulted in an increased risk of [intracranial hemorrhage](#) within 30 days of concomitant use compared with antidepressant use alone. There was no significant difference between the antidepressant drug classes and the increased risk; however, there was an increased risk associated with male patients compared with female patients [319].

3.5.1.GL] Protein C

1) Interaction Effect: an increased risk of bleeding

2) Summary: Case reports and epidemiological studies have shown that use of selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs), including [venlafaxine](#), is associated with [gastrointestinal bleeding](#). Bleeding events with SSRIs and SNRIs included cases of ecchymoses, [hematomas](#), [epistaxis](#), and [petechiae](#); life-threatening hemorrhages have also occurred. Coadministration with [warfarin](#) or other anticoagulants may potentiate the risk of bleeding. A population-based, case-controlled study of new coumarin users (acenocoumarol and phenprocoumon) with concomitant selective serotonin reuptake inhibitors (SSRIs) resulted in an increased risk of hospitalization due to nongastrointestinal bleeding[354]. Increases in prothrombin time, partial thromboplastin time, or INR have been reported when [venlafaxine](#) was administered to patients receiving [warfarin](#). Therefore, concomitant use of [venlafaxine](#) with [warfarin](#) or other drugs affecting coagulation should be undertaken with caution. Whenever [venlafaxine](#) is initiated or discontinued in patients receiving an anticoagulant, close monitoring of coagulation parameters is recommended [321].

3) Severity: major

4) Onset: unspecified

5) Substantiation: probable

6) Clinical Management: Use caution when [venlafaxine](#) is used concomitantly with [warfarin](#) or other drugs affecting coagulation. Closely monitor coagulation parameters when [venlafaxine](#) is initiated or discontinued in patients receiving anticoagulants, such as [warfarin](#)[321].

7) Probable Mechanism: additive adverse events

8) Literature Reports

a) A population-based, case-controlled study of new coumarin users (acenocoumarol and phenprocoumon) with concomitant selective serotonin reuptake inhibitors (SSRIs) resulted in an increased risk of hospitalization due to nongastrointestinal bleeding. Using national pharmacy and hospitalization records, Netherlands researchers identified 1848 cases that were admitted for abnormal bleeding and compared them with 5818 control subjects also taking coumarins. Median duration of treatment in patients was 220 days (range, 1 to 4690 days). Patients on SSRIs showed greater risk for hospitalization for nongastrointestinal bleeding (adjusted odds ratio (OR) 1.7, 95% confidence interval (CI), 1.1 to 2.5), however, the rate of [gastrointestinal bleeding](#) (adjusted OR 0.8, 95% CI, 0.4 to 1.5) was not significantly different [354].

3.5.1.GM] [Protriptyline](#)

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

2) Summary: Tricyclic antidepressants (TCAs) and [venlafaxine](#) have been shown to prolong the QTc interval at the recommended therapeutic dose[297][298]. Even though no formal drug interaction studies have been done, the coadministration of tricyclic antidepressants and other drugs known to prolong the QTc interval, such as [venlafaxine](#), is not recommended [299]. In addition, [venlafaxine](#) and tricyclic antidepressants (TCAs) may competitively inhibit each other's metabolism which may increase side effects of both drugs [300][297][301]. [Venlafaxine](#) increased the AUC, Cmax, and Cmin of [desipramine](#) by approximately 35%. The AUCs of 2-OH-desipramine increased by 2.5 and 4.5 fold when administered with [venlafaxine](#) 37.5 mg and 75 mg every 12 hours, respectively. The pharmacokinetics of [imipramine](#) and the 2-hydroxy metabolite were not affected [6].

3) Severity: major

4) Onset: rapid

5) Substantiation: theoretical

6) Clinical Management: Due to the potential for additive effects on the QT interval, the concurrent administration of [venlafaxine](#) and tricyclic antidepressants is not recommended.

7) Probable Mechanism: decreased TCA and [venlafaxine](#) metabolism; additive effects on QT prolongation

8) Literature Reports

a) When administered with [imipramine](#), the pharmacokinetics of [imipramine](#) and the 2-hydroxy metabolite were not affected. [Venlafaxine](#) increased the area under the concentration-time curve (AUC), maximum concentration (Cmax), and minimum concentration (Cmin) of [desipramine](#) by approximately 35%. The 2-OH-desipramine AUCs increased by 2.5-fold ([venlafaxine](#) 37.5 mg every 12 hours) and by 4.5-fold ([venlafaxine](#) 75 mg every 12 hours). The clinical significance of this finding is unknown [6].

3.5.1.GN] [Quetiapine](#)

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

2) Summary: The concomitant use of [quetiapine](#) and a QT-prolonging drug should be avoided. [Quetiapine](#) is known to increase the QT interval and concurrent use with another drug known to prolong the QT interval may lead to an increased risk of serious cardiac adverse events[234].

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: The coadministration of [quetiapine](#) and a drug known to prolong the QT interval should be avoided, as concurrent use of such agents may lead to an increased risk of serious cardiac adverse events[234].

7) Probable Mechanism: additive effects on QT interval

3.5.1.GO] [Rasagiline](#)

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

2) Summary: Concurrent use of [rasagiline](#), an MAOI, and [venlafaxine](#) is contraindicated. Wait at least 14 days after discontinuing [rasagiline](#) before initiating therapy with [venlafaxine](#). Wait at least 7 days after discontinuing [venlafaxine](#) before initiating therapy with [rasagiline](#)[123].

3) Severity: contraindicated

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Concurrent use of [rasagiline](#) (an MAOI) and [venlafaxine](#) is contraindicated. Wait at least 14 days after discontinuing [rasagiline](#) before initiating therapy with [venlafaxine](#). Wait at least 7 days after discontinuing [venlafaxine](#) before initiating therapy with [rasagiline](#)[123].

7J) Probable Mechanism: additive serotonergic effect

3.5.1.GP] Ritonavir

1J) Interaction Effect: increased plasma concentrations of [venlafaxine](#)

2J) Summary: Caution is advised if a CYP3A4 inhibitor, such as [ritonavir](#), is administered with [venlafaxine](#), due to a possible increase in plasma concentration levels of both [venlafaxine](#) and O-desvenlafaxine (ODV) [6]. Patients should be monitored for [venlafaxine](#) toxicity.

3J) Severity: major

4J) Onset: unspecified

5J) Substantiation: theoretical

6J) Clinical Management: Patients should be monitored for signs of [venlafaxine](#) toxicity such as nausea, drowsiness, and dizziness; a decrease in dosage may be required with concomitant therapy.

7J) Probable Mechanism: decreased [venlafaxine](#) clearance

8J) Literature Reports

aJ) Caution is warranted with the concurrent use of CYP3A4 inhibitors, such as [ritonavir](#), and [venlafaxine](#) due to possible increases in plasma concentration levels of both [venlafaxine](#) and O-desvenlafaxine (ODV) [6].

3.5.1.GQ] Rivaroxaban

1J) Interaction Effect: an increased risk of bleeding

2J) Summary: Case reports and epidemiological studies have shown that use of selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs), including [venlafaxine](#), is associated with [gastrointestinal bleeding](#). Bleeding events with SSRIs and SNRIs included cases of ecchymoses, [hematomas](#), [epistaxis](#), and [petechiae](#); life-threatening hemorrhages have also occurred. Coadministration with [warfarin](#) or other anticoagulants may potentiate the risk of bleeding. A population-based, case-controlled study of new coumarin users (acenocoumarol and phenprocoumon) with concomitant selective serotonin reuptake inhibitors (SSRIs) resulted in an increased risk of hospitalization due to nongastrointestinal bleeding[354]. Increases in prothrombin time, partial thromboplastin time, or INR have been reported when [venlafaxine](#) was administered to patients receiving [warfarin](#). Therefore, concomitant use of [venlafaxine](#) with [warfarin](#) or other drugs affecting coagulation should be undertaken with caution. Whenever [venlafaxine](#) is initiated or discontinued in patients receiving an anticoagulant, close monitoring of coagulation parameters is recommended [321].

3J) Severity: major

4J) Onset: unspecified

5J) Substantiation: probable

6J) Clinical Management: Use caution when [venlafaxine](#) is used concomitantly with [warfarin](#) or other drugs affecting coagulation. Closely monitor coagulation parameters when [venlafaxine](#) is initiated or discontinued in patients receiving anticoagulants, such as [warfarin](#)[321].

7J) Probable Mechanism: additive adverse events

8J) Literature Reports

aJ) A population-based, case-controlled study of new coumarin users (acenocoumarol and phenprocoumon) with concomitant selective serotonin reuptake inhibitors (SSRIs) resulted in an increased risk of hospitalization due to nongastrointestinal bleeding. Using national pharmacy and hospitalization records, Netherlands researchers identified 1848 cases that were admitted for abnormal bleeding and compared them with 5818 control subjects also taking coumarins. Median duration of treatment in patients was 220 days (range, 1 to 4690 days). Patients on SSRIs showed 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 [354].

3.5.1.GR| [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)[263]. Because [rizatriptan](#) is a 5HT 1B/1D receptor agonist, a similar interaction between SSRIs and [rizatriptan](#) may occur [264]. 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](#) [258].

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](#) [262].

3.5.1.GS| [Rofecoxib](#)

1) Interaction Effect: an increased risk of bleeding

2) Summary: Use caution when coadministering NSAIDs and serotonin [norepinephrine](#) reuptake inhibitors (SNRI) as this may cause an increased risk of bleeding[318]. During clinical trials, concomitant use of NSAIDs and antidepressants, including tricyclic antidepressants, SSRIs, selective serotonin-norepinephrine reuptake inhibitors, and MOAIs, resulted in an increased risk of [intracranial hemorrhage](#) within 30 days of concomitant use compared with antidepressant use alone [319]. When NSAIDs and SNRIs are given concurrently, monitor the patient for signs of increased bleeding.

3) Severity: major

4) Onset: unspecified

5) Substantiation: established

6) Clinical Management: Serotonin [norepinephrine](#) reuptake inhibitors (SNRI) increase bleeding risk, especially with concomitant use of NSAIDs[318]. When NSAIDs and SNRIs are given concurrently, monitor the patient for signs of increased bleeding.

7) Probable Mechanism: unknown

8) Literature Reports

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

[intracranial hemorrhage](#) within 30 days of concomitant use compared with antidepressant use alone. There was no significant difference between the antidepressant drug classes and the increased risk; however, there was an increased risk associated with male patients compared with female patients [319].

3.5.1.GT] 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[260].
- 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[260].
- 7) Probable Mechanism: Additive serotonergic effects

3.5.1.GU] Salicylic Acid

- 1) Interaction Effect: an increased risk of bleeding
- 2) Summary: Use caution when coadministering NSAIDs and serotonin [norepinephrine](#) reuptake inhibitors (SNRI) as this may cause an increased risk of bleeding[318]. During clinical trials, concomitant use of NSAIDs and antidepressants, including tricyclic antidepressants, SSRIs, selective serotonin-norepinephrine reuptake inhibitors, and MOAIs, resulted in an increased risk of [intracranial hemorrhage](#) within 30 days of concomitant use compared with antidepressant use alone [319]. When NSAIDs and SNRIs are given concurrently, monitor the patient for signs of increased bleeding.
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: established
- 6) Clinical Management: Serotonin [norepinephrine](#) reuptake inhibitors (SNRI) increase bleeding risk, especially with concomitant use of NSAIDs[318]. When NSAIDs and SNRIs are given concurrently, monitor the patient for signs of increased bleeding.
- 7) Probable Mechanism: unknown
- 8) Literature Reports

a) Concomitant use of NSAIDs and antidepressants, including tricyclic antidepressants, SSRIs, serotonin-norepinephrine reuptake inhibitors, and MAOIs, resulted in an increased risk of [intracranial hemorrhage](#) within 30 days of concomitant use compared with antidepressant use alone. There was no significant difference between the antidepressant drug classes and the increased risk; however, there was an increased risk associated with male patients compared with female patients [319].

3.5.1.GV] Salsalate

- 1) Interaction Effect: an increased risk of bleeding
- 2) Summary: Use caution when coadministering NSAIDs and serotonin [norepinephrine](#) reuptake inhibitors (SNRI) as this may cause an increased risk of bleeding[318]. During clinical trials, concomitant use of NSAIDs and antidepressants, including tricyclic antidepressants, SSRIs, selective serotonin-norepinephrine reuptake inhibitors, and MOAIs, resulted in an increased risk of [intracranial hemorrhage](#)

within 30 days of concomitant use compared with antidepressant use alone [319]. When NSAIDs and SNRIs are given concurrently, monitor the patient for signs of increased bleeding.

3) Severity: major

4) Onset: unspecified

5) Substantiation: established

6) Clinical Management: Serotonin [norepinephrine](#) reuptake inhibitors (SNRI) increase bleeding risk, especially with concomitant use of NSAIDs[318]. When NSAIDs and SNRIs are given concurrently, monitor the patient for signs of increased bleeding.

7) Probable Mechanism: unknown

8) Literature Reports

a) Concomitant use of NSAIDs and antidepressants, including tricyclic antidepressants, SSRIs, serotonin-norepinephrine reuptake inhibitors, and MAOIs, resulted in an increased risk of [intracranial hemorrhage](#) within 30 days of concomitant use compared with antidepressant use alone. There was no significant difference between the antidepressant drug classes and the increased risk; however, there was an increased risk associated with male patients compared with female patients [319].

3.5.1.GW| [Saquinavir](#)

1) Interaction Effect: increased risk of QT interval prolongation; increased plasma concentrations of [venlafaxine](#)

2) Summary: Both ritonavir-boosted [saquinavir](#) and [venlafaxine](#) prolong the QT interval. The concomitant use of ritonavir-boosted [saquinavir](#) with drugs that both increase [saquinavir](#) plasma concentrations and cause QT-interval prolongation is contraindicated. If concurrent use of ritonavir-boosted [saquinavir](#) and [venlafaxine](#) is required, perform a baseline ECG. Do not initiate coadministration if QT interval exceeds 450 msec. Perform an on-treatment ECG after 3 to 4 days of concurrent use; if the QT interval exceeds 480 msec or has increased more than 20 msec from baseline, discontinue one or both therapies[382]. Additionally, the concomitant use of ritonavir-boosted [saquinavir](#) (a strong CYP3A inhibitor) and [venlafaxine](#) (a CYP3A substrate) may increase the exposure of [venlafaxine](#) [382][6]. If concomitant administration is required, monitor for [venlafaxine](#) adverse effects and consider [venlafaxine](#) dose reductions [382].

3) Severity: contraindicated

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Both ritonavir-boosted [saquinavir](#) and [venlafaxine](#) prolong the QT interval. The concomitant use of ritonavir-boosted [saquinavir](#) with drugs that both increase [saquinavir](#) plasma concentrations and cause QT-interval prolongation is contraindicated. If concurrent use of ritonavir-boosted [saquinavir](#) and [venlafaxine](#) is required, perform a baseline ECG. Do not initiate coadministration if QT interval exceeds 450 msec. Perform an on-treatment ECG after 3 to 4 days of concurrent use; if the QT interval exceeds 480 msec or has increased more than 20 msec from baseline, discontinue one or both therapies[382]. Additionally, the concomitant use of ritonavir-boosted [saquinavir](#) (a strong CYP3A inhibitor) and [venlafaxine](#) (a CYP3A substrate) may increase the exposure of [venlafaxine](#) [382][6]. If concomitant administration is required, monitor for [venlafaxine](#) adverse effects and consider [venlafaxine](#) dose reductions [382].

7) Probable Mechanism: additive effects on the QT interval; decreased [venlafaxine](#) clearance

3.5.1.GX| [Selegiline](#)

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

2) Summary: Concurrent administration or overlapping therapy with [venlafaxine](#) 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[175][176][177][178]. Concomitant administration of [venlafaxine](#) and [selegiline](#) is contraindicated, and a minimum of 14 days should elapse after discontinuing [selegiline](#) before initiating therapy with [venlafaxine](#) or a minimum of 7 days should elapse after discontinuing [venlafaxine](#) before initiating therapy with [selegiline](#) [179]. However, [serotonin syndrome](#) has been reported 15 days after discontinuation of [selegiline](#) therapy and initiation of [venlafaxine](#) therapy, indicating that some patients may need a longer washout period [180].

3) Severity: contraindicated

4) Onset: rapid

5) Substantiation: probable

6) Clinical Management: Concurrent use of [venlafaxine](#) and [selegiline](#) is contraindicated. Wait at least 14 days after discontinuing [selegiline](#) before initiating therapy with [venlafaxine](#). Wait at least seven days after discontinuing [venlafaxine](#) 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](#) [170]. [Serotonin syndrome](#) is a condition of serotonergic hyperstimulation and manifests as restlessness, myoclonus, changes in mental status, hyperreflexia, diaphoresis, shivering, and tremor. If the syndrome is not recognized and correctly treated, death can result.

b) A 26-year old woman who had been taking [isocarboxazid](#) for eight weeks stopped taking the drug for 11 days before beginning therapy with [sertraline](#). After a single 100 mg [sertraline](#) dose, the patient became restless and developed leg twitches. The patient was later admitted to the emergency room with diaphoresis, [tachycardia](#), hyperreflexia, and various neuromuscular disturbances. After treatment with [diazepam](#) and [propranolol](#) the patient did not improve. The patient was then given two 4 mg doses of [cyproheptadine](#) an hour apart, with notable improvement in symptoms after the second dose [171].

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 5 half-lives of the parent drug and any active metabolites [172].

d) Two cases reports suggested a possible interaction between [fluoxetine](#) and [selegiline](#) [173]. One case involved a first episode of mania being observed approximately one month after adding [selegiline](#) to [fluoxetine](#) therapy. The patient improved two months after both drugs were discontinued, and no further details were provided. The second case involved diaphoresis, vasoconstriction, and cyanosis of the hands which occurred in close temporal relationship to

adding [fluoxetine](#) and [selegiline](#). Both drugs were discontinued, with relatively quick resolution of symptoms. Rechallenge with [fluoxetine](#) alone occurred without incident.

e) Although it has been suggested that MAOIs be discontinued for at least 14 days before the initiation of a SSRI, [serotonin syndrome](#) has been reported in a 39-year old man upon initiation of [venlafaxine](#) 15 days after cessation of [selegiline](#). The patient had been treated previously with multiple antidepressants, and had been taking [valproic acid](#), [nortriptyline](#), [thioridazine](#), and [selegiline](#) 50 mg. All medications were discontinued due to poor response and [venlafaxine](#) 37.5 mg was started 15 days later. The patient then experienced symptoms consistent with [serotonin syndrome](#), including profound anxiety, diarrhea, myoclonic jerks, shivering, tremor, and diaphoresis. These symptoms resolved in six hours. One week later, [venlafaxine](#) was successfully started without further complications. The authors suggested that some patients may need a longer washout period between discontinuation of the MAOI and initiation of the SSRI [174].

3.5.1.GY] [Sertraline](#)

1) Interaction Effect: increased exposure of CYP2D6 substrate and risk of [serotonin syndrome](#)

2) Summary: Caution is advised with concomitant administration of [sertraline](#) and drugs that are CYP2D6 substrates and serotonergic agents. [Sertraline](#) is a CYP2D6 inhibitor and has been associated with [serotonin syndrome](#) during monotherapy. Risk of this event is increased when [sertraline](#) is coadministered with other serotonergic agents. If coadministration is necessary, monitor for symptoms of [serotonin syndrome](#), especially with treatment initiation and dose increases. If [serotonin syndrome](#) is suspected, immediately discontinue [sertraline](#) and other serotonergic agents and provide supportive treatment[320].

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[320].

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

3.5.1.GZ] [Sevoflurane](#)

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

2) Summary: [Sevoflurane](#) is a QT-interval-prolonging drug. Use caution with concurrent use of other QT-interval-prolonging agents, due to increased risk of additive QT-interval prolongation and [torsade de pointes](#)[200].

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: [Sevoflurane](#) is a QT-interval-prolonging drug. Use caution with concurrent use of other QT-interval-prolonging agents, due to increased risk of additive QT-interval prolongation and [torsade de pointes](#)[200].

7) Probable Mechanism: additive effects on QT interval

3.5.1.HA| Sibrafiban

- 1) Interaction Effect: an increased risk of bleeding
- 2) Summary: The release of serotonin by [platelets](#) is important for maintaining hemostasis. Case reports and epidemiological studies have shown that use of selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs), including [venlafaxine](#), is associated with [gastrointestinal bleeding](#). Bleeding events with SSRIs and SNRIs included cases of ecchymoses, [hematomas](#), [epistaxis](#), and [petechiae](#); life-threatening hemorrhages have also occurred. Coadministration with drugs that affect coagulation, such as antiplatelet agents, may potentiated the risk of bleeding[321].
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: probable
- 6) Clinical Management: Use caution when [venlafaxine](#) is used concomitantly with antiplatelet agents. Closely monitor patient for signs of bleeding when [venlafaxine](#) is initiated or discontinued in patients receiving antiplatelet agents concomitantly[321].
- 7) Probable Mechanism: unknown

3.5.1.HB| 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[348].
- 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 [347].

3.5.1.HC| Sodium Salicylate

- 1) Interaction Effect: an increased risk of bleeding
- 2) Summary: Use caution when coadministering NSAIDs and serotonin [norepinephrine](#) reuptake inhibitors (SNRI) as this may cause an increased risk of bleeding[318]. During clinical trials, concomitant use of NSAIDs and antidepressants, including tricyclic antidepressants, SSRIs, selective serotonin-norepinephrine reuptake inhibitors, and MOAIs, resulted in an increased risk of [intracranial hemorrhage](#) within 30 days of concomitant use compared with antidepressant use alone [319]. When NSAIDs and SNRIs are given concurrently, monitor the patient for signs of increased bleeding.
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: established

6) Clinical Management: Serotonin [norepinephrine](#) reuptake inhibitors (SNRI) increase bleeding risk, especially with concomitant use of NSAIDs[318]. When NSAIDs and SNRIs are given concurrently, monitor the patient for signs of increased bleeding.

7) Probable Mechanism: unknown

8) Literature Reports

a) Concomitant use of NSAIDs and antidepressants, including tricyclic antidepressants, SSRIs, serotonin-norepinephrine reuptake inhibitors, and MAOIs, resulted in an increased risk of [intracranial hemorrhage](#) within 30 days of concomitant use compared with antidepressant use alone. There was no significant difference between the antidepressant drug classes and the increased risk; however, there was an increased risk associated with male patients compared with female patients [319].

3.5.1.HD) [Sotalol](#)

1) Interaction Effect: increased risk for [torsade de pointes](#)

2) Summary: Avoid use of [sotalol](#) with agents that prolong the QT interval. If use is unavoidable, monitor the ECG for excessive increases in the QT interval[204][205]. There have been isolated reports of QTc prolongation and [torsade de pointes](#) temporally related to the concomitant administration of [ciprofloxacin](#) and [sotalol](#) [207][206].

3) Severity: major

4) Onset: rapid

5) Substantiation: theoretical

6) Clinical Management: Avoid use of [sotalol](#) with agents that prolong the QT interval. If use is unavoidable, monitor the ECG for excessive increases in the QT interval[204][205].

7) Probable Mechanism: additive effects on the QT interval

8) Literature Reports

a) A 70-year-old female receiving [sotalol](#) therapy experienced [torsade de pointes](#) following coadministration of [ciprofloxacin](#). The patient was admitted with new onset [atrial fibrillation](#) with rapid ventricular response and was given IV [amiodarone](#) (loading dose, 450 mg; followed by 24-hour infusion, 650 mg) and [digoxin](#) (0.25 mg/day). The patient converted to sinus rhythm within 48 hours of admission. Both [amiodarone](#) and [digoxin](#) were discontinued and [sotalol](#) (40 mg twice daily) was initiated. The next day the patient presented with [jaundice](#), fever, and [cholecystitis](#), and was treated with IV [ciprofloxacin](#) 400 mg twice daily. Within 12 hours of [ciprofloxacin](#) administration, the patient developed syncope with documented [torsade de pointes](#) that necessitated [defibrillation](#). Her QTc interval, which was 0.38 seconds prior to [ciprofloxacin](#) initiation, was significantly (0.62 seconds) increased following resuscitation. Within 3 days of [ciprofloxacin](#) and [sotalol](#) discontinuation, the QTc interval decreased to 0.42 seconds [206].

b) [Torsade de pointes](#) temporally related to [ciprofloxacin](#) administration was reported in a 44-year-old female who was stable on [sotalol](#) 160 mg twice a day for the treatment of [supraventricular arrhythmia](#). [Pyelonephritis](#) was treated with [ciprofloxacin](#) 1 g in the emergency room (ER). At that time, the QTc interval measured 405 milliseconds. The patient was discharged on [ciprofloxacin](#) 500 mg twice a day. Within hours of discharge, she experienced several presyncopal and syncopal episodes and returned to the ER. Torsade-induced syncope was diagnosed and [defibrillation](#) was required. The QTc interval following resuscitation was 590 milliseconds which was compared with previous normal or slightly increased intervals (maximum, 460 milliseconds) during [sotalol](#) maintenance therapy. Upon discontinuation of both medications, the QTc interval normalized within 2 days [207].

3.5.1.HE] Sparfloxacin

- 1) Interaction Effect: increased risk of QT-interval prolongation
- 2) Summary: The concomitant use of [sparfloxacin](#) with drugs that cause QT-interval prolongation is contraindicated, as coadministration may increase the risk of QT prolongation and serious [ventricular arrhythmias](#)[296].
- 3) Severity: contraindicated
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: The concomitant use of [sparfloxacin](#) with drugs that cause QT-interval prolongation is contraindicated, as coadministration may increase the risk of QT prolongation and serious [ventricular arrhythmias](#)[296].
- 7) Probable Mechanism: additive QT interval effects

3.5.1.HF] St John's Wort

- 1) Interaction Effect: an increased risk of [serotonin syndrome](#) ([hypertension](#), [hyperthermia](#), myoclonus, mental status changes)
- 2) Summary: One case of [serotonin syndrome](#) likely resulting from concomitant use of St. John's Wort and [venlafaxine](#) has been reported[386]. Several case reports describe the onset of serotonin syndrome-like symptoms following the addition of St. John's Wort to [sertraline](#) or [nefazodone](#) therapy [387]. St. John's Wort is thought to inhibit serotonin reuptake and may have mild monoamine oxidase inhibitory activity [388][389], which when added to selective serotonin reuptake inhibitors may result in [serotonin syndrome](#). [Serotonin syndrome](#) is a condition of serotonergic hyperstimulation and manifests as restlessness, myoclonus, changes in mental status, hyperreflexia, diaphoresis, shivering, and tremor. Although St. John's Wort was initially characterized as a monoamine oxidase inhibitor (MAOI), it is now believed that insufficient MAO inhibition occurs to explain the clinical activity of St. John's Wort as an antidepressant [390]. It remains possible that the mild MAOI property of St. John's Wort may contribute to an interaction with drugs which inhibit serotonin reuptake leading to [serotonin syndrome](#) [391]. Concomitant administration of monoamine oxidase inhibitors (MAOIs) with SSRIs has been considered an absolute contraindication in the past and still is listed as such by the manufacturers. This contraindication may be extended to [venlafaxine](#) which, though not an SSRI, inhibits serotonin and [norepinephrine](#) reuptake. A two-week washout period is suggested after discontinuing St. John's Wort before starting a SSRI [392], and may be applied to [venlafaxine](#) as well.
- 3) Severity: moderate
- 4) Onset: delayed
- 5) Substantiation: probable
- 6) Clinical Management: Avoid concomitant use. Given the half-life of [venlafaxine](#) of up to 11 hours, St. John's Wort should be avoided for at least 5 half-lives (one to two days) following [venlafaxine](#) discontinuation. A two-week washout period is suggested after discontinuing St. John's Wort before starting a SSRI, and may be applied to [venlafaxine](#) as well.
- 7) Probable Mechanism: additive serotonergic effect
- 8) Literature Reports

- a) A 32-year-old male experienced symptoms of [serotonin syndrome](#) (malaise, anxiety, diaphoresis, tremor, [tachycardia](#)) after 3 days of comedication with [venlafaxine](#) 250 milligrams (mg) daily and St. John's Wort tincture 200 drops three times daily (usual dose stated as 160 drops daily). The patient had been taking [venlafaxine](#) for several months for depression and self-medicated with St. John's Wort after hearing of its benefits. St. John's Wort was discontinued on day 4 while [venlafaxine](#) was continued, and symptoms improved over 3 days [385].

3.5.1.HG| Sulfinpyrazone

- 1) Interaction Effect: an increased risk of bleeding
- 2) Summary: The release of serotonin by [platelets](#) is important for maintaining hemostasis. Case reports and epidemiological studies have shown that use of selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs), including [venlafaxine](#), is associated with [gastrointestinal bleeding](#). Bleeding events with SSRIs and SNRIs included cases of ecchymoses, [hematomas](#), [epistaxis](#), and [petechiae](#); life-threatening hemorrhages have also occurred. Coadministration with drugs that affect coagulation, such as antiplatelet agents, may potentiated the risk of bleeding[321].
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: probable
- 6) Clinical Management: Use caution when [venlafaxine](#) is used concomitantly with antiplatelet agents. Closely monitor patient for signs of bleeding when [venlafaxine](#) is initiated or discontinued in patients receiving antiplatelet agents concomitantly[321].
- 7) Probable Mechanism: unknown

3.5.1.HH| Sulindac

- 1) Interaction Effect: an increased risk of bleeding
- 2) Summary: Use caution when coadministering NSAIDs and serotonin [norepinephrine](#) reuptake inhibitors (SNRI) as this may cause an increased risk of bleeding[318]. During clinical trials, concomitant use of NSAIDs and antidepressants, including tricyclic antidepressants, SSRIs, selective serotonin-norepinephrine reuptake inhibitors, and MOAIs, resulted in an increased risk of [intracranial hemorrhage](#) within 30 days of concomitant use compared with antidepressant use alone [319]. When NSAIDs and SNRIs are given concurrently, monitor the patient for signs of increased bleeding.
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: established
- 6) Clinical Management: Serotonin [norepinephrine](#) reuptake inhibitors (SNRI) increase bleeding risk, especially with concomitant use of NSAIDs[318]. When NSAIDs and SNRIs are given concurrently, monitor the patient for signs of increased bleeding.
- 7) Probable Mechanism: unknown
- 8) Literature Reports

a) Concomitant use of NSAIDs and antidepressants, including tricyclic antidepressants, SSRIs, serotonin-norepinephrine reuptake inhibitors, and MAOIs, resulted in an increased risk of [intracranial hemorrhage](#) within 30 days of concomitant use compared with antidepressant use alone. There was no significant difference between the antidepressant drug classes and the increased risk; however, there was an increased risk associated with male patients compared with female patients [319].

3.5.1.HI| Sulodexide

- 1) Interaction Effect: an increased risk of bleeding
- 2) Summary: The release of serotonin by [platelets](#) is important for maintaining hemostasis. Case reports and epidemiological studies have shown that use of selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs), including [venlafaxine](#), is associated with [gastrointestinal bleeding](#). Bleeding events with SSRIs and SNRIs included cases of ecchymoses,

hematomas, epistaxis, and petechiae; life-threatening hemorrhages have also occurred. Coadministration with drugs that affect coagulation, such as antiplatelet agents, may potentiated the risk of bleeding[321].

3) Severity: major

4) Onset: unspecified

5) Substantiation: probable

6) Clinical Management: Use caution when [venlafaxine](#) is used concomitantly with antiplatelet agents. Closely monitor patient for signs of bleeding when [venlafaxine](#) is initiated or discontinued in patients receiving antiplatelet agents concomitantly[321].

7) Probable Mechanism: unknown

3.5.1.HJ] Sulpiride

1) Interaction Effect: increased risk of QT interval prolongation and [torsades de pointes](#)

2) Summary: Use caution with the concomitant use of sulpiride with other agents that prolong the QT interval. Because sulpiride by itself prolongs the QT interval, coadministration with another medication that prolongs the QT interval increases the risk of serious [ventricular arrhythmias](#) such [torsade de pointes](#) and is not recommended. If administration cannot be avoided, [monitoring of heart rate](#) and correction of any electrolyte disturbances is warranted[126].

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Use caution with the concomitant use of sulpiride with other agents that prolong the QT interval. Because sulpiride by itself prolongs the QT interval, coadministration with another medication that prolongs the QT interval increases the risk of serious [ventricular arrhythmias](#) such [torsade de pointes](#) and is not recommended. If administration cannot be avoided, [monitoring of heart rate](#) and correction of any electrolyte disturbances is warranted[126].

7) Probable Mechanism: additive effects on the QT interval

3.5.1.HK] Sumatriptan

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

2) Summary: Concurrent use of a serotonin [norepinephrine](#) reuptake inhibitor, such as [venlafaxine](#), and [sumatriptan](#) 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](#)[258] [5][4][380].

3) Severity: major

4) Onset: delayed

5) Substantiation: theoretical

6) Clinical Management: Coadministration of a triptan, such as [sumatriptan](#), and a serotonergic agent, such as [venlafaxine](#), 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)[258].

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

3.5.1.HL] Tacrolimus

- 1) Interaction Effect: increased risk of QT-interval prolongation
- 2) Summary: Concomitant use of [tacrolimus](#) with a drug that has additive effects on the QT interval may increase the risk of serious [cardiac toxicity](#), including [torsade de pointes](#). If coadministered, observe patients for signs and symptoms of QT interval prolongation, and consider obtaining an ECG and monitoring magnesium, potassium, and [calcium](#) blood levels[338][339].
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Concomitant use of [tacrolimus](#) with a drug that has additive effects on the QT interval may increase the risk of serious [cardiac toxicity](#), including [torsade de pointes](#). If coadministered, observe patients for signs and symptoms of QT interval prolongation, and consider obtaining an ECG and monitoring magnesium, potassium, and [calcium](#) blood levels[338][339].
- 7) Probable Mechanism: additive effects on QT interval

3.5.1.HM] Tapentadol

- 1) Interaction Effect: increased risk of [serotonin syndrome](#) ([hypertension](#), [hyperthermia](#), myoclonus, mental status changes)
- 2) Summary: Concurrent use of tapentadol and [venlafaxine](#) 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[344].
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Coadministration of tapentadol and [venlafaxine](#) 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[344].
- 7) Probable Mechanism: additive serotonergic effect

3.5.1.HN] Telithromycin

- 1) Interaction Effect: increased plasma concentrations of [venlafaxine](#)
- 2) Summary: Caution is advised if a CYP3A4 inhibitor, such as [telithromycin](#), is administered with [venlafaxine](#), due to a possible increase in plasma concentration levels of both [venlafaxine](#) and O-desvenlafaxine (ODV)[6]. Patients should be monitored for [venlafaxine](#) toxicity.
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Patients should be monitored for signs of [venlafaxine](#) toxicity such as nausea, drowsiness, and dizziness; a decrease in dosage may be required with concomitant therapy.
- 7) Probable Mechanism: decreased [venlafaxine](#) clearance
- 8) Literature Reports

- a) Caution is warranted with the concurrent use of CYP3A4 inhibitors, such as [telithromycin](#), and [venlafaxine](#) due to possible increases in plasma concentration levels of both [venlafaxine](#) and O-desvenlafaxine (ODV) [6].

3.5.1.HO| Tenoxicam

- 1) Interaction Effect: an increased risk of bleeding
- 2) Summary: Use caution when coadministering NSAIDs and serotonin [norepinephrine](#) reuptake inhibitors (SNRI) as this may cause an increased risk of bleeding[318]. During clinical trials, concomitant use of NSAIDs and antidepressants, including tricyclic antidepressants, SSRIs, selective serotonin-norepinephrine reuptake inhibitors, and MOAIs, resulted in an increased risk of [intracranial hemorrhage](#) within 30 days of concomitant use compared with antidepressant use alone [319]. When NSAIDs and SNRIs are given concurrently, monitor the patient for signs of increased bleeding.
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: established
- 6) Clinical Management: Serotonin [norepinephrine](#) reuptake inhibitors (SNRI) increase bleeding risk, especially with concomitant use of NSAIDs[318]. When NSAIDs and SNRIs are given concurrently, monitor the patient for signs of increased bleeding.
- 7) Probable Mechanism: unknown
- 8) Literature Reports

a) Concomitant use of NSAIDs and antidepressants, including tricyclic antidepressants, SSRIs, serotonin-norepinephrine reuptake inhibitors, and MAOIs, resulted in an increased risk of [intracranial hemorrhage](#) within 30 days of concomitant use compared with antidepressant use alone. There was no significant difference between the antidepressant drug classes and the increased risk; however, there was an increased risk associated with male patients compared with female patients [319].

3.5.1.HP| Terfenadine

- 1) Interaction Effect: increased risk of QT-interval prolongation
- 2) Summary: The concomitant use of [terfenadine](#) with drugs that cause QT-interval prolongation is contraindicated, as coadministration may increase the risk of QT prolongation and serious [ventricular arrhythmias](#)[295].
- 3) Severity: contraindicated
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: The concomitant use of [terfenadine](#) with drugs that cause QT-interval prolongation is contraindicated, as coadministration may increase the risk of QT prolongation and serious [ventricular arrhythmias](#)[295].
- 7) Probable Mechanism: additive QT interval effects

3.5.1.HQ| Thioridazine

- 1) Interaction Effect: increased risk of QT-interval prolongation
- 2) Summary: The concomitant use of [thioridazine](#) with drugs that cause QT-interval prolongation is contraindicated, as coadministration may increase the risk of QT prolongation and serious [ventricular arrhythmias](#)[131].
- 3) Severity: contraindicated
- 4) Onset: unspecified
- 5) Substantiation: theoretical

6) Clinical Management: The concomitant use of [thioridazine](#) with drugs that cause QT-interval prolongation is contraindicated, as coadministration may increase the risk of QT prolongation and serious [ventricular arrhythmias](#)[131].

7) Probable Mechanism: additive QT interval effects

3.5.1.HR] Tiaprofenic Acid

1) Interaction Effect: an increased risk of bleeding

2) Summary: Use caution when coadministering NSAIDs and serotonin [norepinephrine](#) reuptake inhibitors (SNRI) as this may cause an increased risk of bleeding[318]. During clinical trials, concomitant use of NSAIDs and antidepressants, including tricyclic antidepressants, SSRIs, selective serotonin-norepinephrine reuptake inhibitors, and MOAIs, resulted in an increased risk of [intracranial hemorrhage](#) within 30 days of concomitant use compared with antidepressant use alone [319]. When NSAIDs and SNRIs are given concurrently, monitor the patient for signs of increased bleeding.

3) Severity: major

4) Onset: unspecified

5) Substantiation: established

6) Clinical Management: Serotonin [norepinephrine](#) reuptake inhibitors (SNRI) increase bleeding risk, especially with concomitant use of NSAIDs[318]. When NSAIDs and SNRIs are given concurrently, monitor the patient for signs of increased bleeding.

7) Probable Mechanism: unknown

8) Literature Reports

a) Concomitant use of NSAIDs and antidepressants, including tricyclic antidepressants, SSRIs, serotonin-norepinephrine reuptake inhibitors, and MAOIs, resulted in an increased risk of [intracranial hemorrhage](#) within 30 days of concomitant use compared with antidepressant use alone. There was no significant difference between the antidepressant drug classes and the increased risk; however, there was an increased risk associated with male patients compared with female patients [319].

3.5.1.HS] Ticlopidine

1) Interaction Effect: an increased risk of bleeding

2) Summary: The release of serotonin by [platelets](#) is important for maintaining hemostasis. Case reports and epidemiological studies have shown that use of selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs), including [venlafaxine](#), is associated with [gastrointestinal bleeding](#). Bleeding events with SSRIs and SNRIs included cases of ecchymoses, [hematomas](#), [epistaxis](#), and [petechiae](#); life-threatening hemorrhages have also occurred. Coadministration with drugs that affect coagulation, such as antiplatelet agents, may potentiated the risk of bleeding[321].

3) Severity: major

4) Onset: unspecified

5) Substantiation: probable

6) Clinical Management: Use caution when [venlafaxine](#) is used concomitantly with antiplatelet agents. Closely monitor patient for signs of bleeding when [venlafaxine](#) is initiated or discontinued in patients receiving antiplatelet agents concomitantly[321].

7) Probable Mechanism: unknown

3.5.1.HT] Tinzaparin

1) Interaction Effect: an increased risk of bleeding

2j) Summary: Case reports and epidemiological studies have shown that use of selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs), including [venlafaxine](#), is associated with [gastrointestinal bleeding](#). Bleeding events with SSRIs and SNRIs included cases of ecchymoses, [hematomas](#), [epistaxis](#), and [petechiae](#); life-threatening hemorrhages have also occurred. Coadministration with [warfarin](#) or other anticoagulants may potentiate the risk of bleeding. A population-based, case-controlled study of new coumarin users (acenocoumarol and phenprocoumon) with concomitant selective serotonin reuptake inhibitors (SSRIs) resulted in an increased risk of hospitalization due to nongastrointestinal bleeding[354]. Increases in prothrombin time, partial thromboplastin time, or INR have been reported when [venlafaxine](#) was administered to patients receiving [warfarin](#). Therefore, concomitant use of [venlafaxine](#) with [warfarin](#) or other drugs affecting coagulation should be undertaken with caution. Whenever [venlafaxine](#) is initiated or discontinued in patients receiving an anticoagulant, close monitoring of coagulation parameters is recommended [321].

3j) Severity: major

4j) Onset: unspecified

5j) Substantiation: probable

6j) Clinical Management: Use caution when [venlafaxine](#) is used concomitantly with [warfarin](#) or other drugs affecting coagulation. Closely monitor coagulation parameters when [venlafaxine](#) is initiated or discontinued in patients receiving anticoagulants, such as [warfarin](#)[321].

7j) Probable Mechanism: additive adverse events

8j) Literature Reports

a)j) A population-based, case-controlled study of new coumarin users (acenocoumarol and phenprocoumon) with concomitant selective serotonin reuptake inhibitors (SSRIs) resulted in an increased risk of hospitalization due to nongastrointestinal bleeding. Using national pharmacy and hospitalization records, Netherlands researchers identified 1848 cases that were admitted for abnormal bleeding and compared them with 5818 control subjects also taking coumarins. Median duration of treatment in patients was 220 days (range, 1 to 4690 days). Patients on SSRIs showed greater risk for hospitalization for nongastrointestinal bleeding (adjusted odds ratio (OR) 1.7, 95% confidence interval (CI), 1.1 to 2.5), however, the rate of [gastrointestinal bleeding](#) (adjusted OR 0.8, 95% CI, 0.4 to 1.5) was not significantly different [354].

3.5.1.HU] [Tirofiban](#)

1j) Interaction Effect: an increased risk of bleeding

2j) Summary: The release of serotonin by [platelets](#) is important for maintaining hemostasis. Case reports and epidemiological studies have shown that use of selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs), including [venlafaxine](#), is associated with [gastrointestinal bleeding](#). Bleeding events with SSRIs and SNRIs included cases of ecchymoses, [hematomas](#), [epistaxis](#), and [petechiae](#); life-threatening hemorrhages have also occurred. Coadministration with drugs that affect coagulation, such as antiplatelet agents, may potentiated the risk of bleeding[321].

3j) Severity: major

4j) Onset: unspecified

5j) Substantiation: probable

6j) Clinical Management: Use caution when [venlafaxine](#) is used concomitantly with antiplatelet agents. Closely monitor patient for signs of bleeding when [venlafaxine](#) is initiated or discontinued in patients receiving antiplatelet agents concomitantly[321].

7j) Probable Mechanism: unknown

3.5.1.HV] [Tolfenamic Acid](#)

1j) Interaction Effect: an increased risk of bleeding

2) Summary: Use caution when coadministering NSAIDs and serotonin [norepinephrine](#) reuptake inhibitors (SNRI) as this may cause an increased risk of bleeding[318]. During clinical trials, concomitant use of NSAIDs and antidepressants, including tricyclic antidepressants, SSRIs, selective serotonin-norepinephrine reuptake inhibitors, and MAOIs, resulted in an increased risk of [intracranial hemorrhage](#) within 30 days of concomitant use compared with antidepressant use alone [319]. When NSAIDs and SNRIs are given concurrently, monitor the patient for signs of increased bleeding.

3) Severity: major

4) Onset: unspecified

5) Substantiation: established

6) Clinical Management: Serotonin [norepinephrine](#) reuptake inhibitors (SNRI) increase bleeding risk, especially with concomitant use of NSAIDs[318]. When NSAIDs and SNRIs are given concurrently, monitor the patient for signs of increased bleeding.

7) Probable Mechanism: unknown

8) Literature Reports

a) Concomitant use of NSAIDs and antidepressants, including tricyclic antidepressants, SSRIs, serotonin-norepinephrine reuptake inhibitors, and MAOIs, resulted in an increased risk of [intracranial hemorrhage](#) within 30 days of concomitant use compared with antidepressant use alone. There was no significant difference between the antidepressant drug classes and the increased risk; however, there was an increased risk associated with male patients compared with female patients [319].

3.5.1.HW] Tolmetin

1) Interaction Effect: an increased risk of bleeding

2) Summary: Use caution when coadministering NSAIDs and serotonin [norepinephrine](#) reuptake inhibitors (SNRI) as this may cause an increased risk of bleeding[318]. During clinical trials, concomitant use of NSAIDs and antidepressants, including tricyclic antidepressants, SSRIs, selective serotonin-norepinephrine reuptake inhibitors, and MAOIs, resulted in an increased risk of [intracranial hemorrhage](#) within 30 days of concomitant use compared with antidepressant use alone [319]. When NSAIDs and SNRIs are given concurrently, monitor the patient for signs of increased bleeding.

3) Severity: major

4) Onset: unspecified

5) Substantiation: established

6) Clinical Management: Serotonin [norepinephrine](#) reuptake inhibitors (SNRI) increase bleeding risk, especially with concomitant use of NSAIDs[318]. When NSAIDs and SNRIs are given concurrently, monitor the patient for signs of increased bleeding.

7) Probable Mechanism: unknown

8) Literature Reports

a) Concomitant use of NSAIDs and antidepressants, including tricyclic antidepressants, SSRIs, serotonin-norepinephrine reuptake inhibitors, and MAOIs, resulted in an increased risk of [intracranial hemorrhage](#) within 30 days of concomitant use compared with antidepressant use alone. There was no significant difference between the antidepressant drug classes and the increased risk; however, there was an increased risk associated with male patients compared with female patients [319].

3.5.1.HX] Toloxatone

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

2j) Summary: Concurrent administration or overlapping therapy with [venlafaxine](#) 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[244][245][246][247]. A 60-year old woman developed a serious case of [serotonin syndrome](#) after the inadvertent ingestion of a single dose of [venlafaxine](#) while on chronic [tranylcypromine](#) therapy [248]. 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 [venlafaxine](#) and a MAO inhibitor is contraindicated. Wait at least 14 days after discontinuing a MAO inhibitor before initiating therapy with [venlafaxine](#). Wait at least seven days after discontinuing [venlafaxine](#) before initiating therapy with a MAO inhibitor.

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

8j) Literature Reports

a) Concomitant use of selective serotonin reuptake inhibitors and monoamine oxidase inhibitors can produce a toxic reaction known as [serotonin syndrome](#) [239]. [Serotonin syndrome](#) is a condition of serotonergic hyperstimulation and manifests as restlessness, myoclonus, changes in mental status, hyperreflexia, diaphoresis, shivering, and tremor. If the syndrome is not recognized and correctly treated, death can result.

b) A 26-year old woman who had been taking [isocarboxazid](#) for eight weeks stopped taking the drug for 11 days before beginning therapy with [sertraline](#). After a single 100 mg [sertraline](#) dose, the patient became restless and developed leg twitches. The patient was later admitted to the emergency room with diaphoresis, [tachycardia](#), hyperreflexia, and various neuromuscular disturbances. After treatment with [diazepam](#) and [propranolol](#) the patient did not improve. The patient was then given two 4 mg doses of [cyproheptadine](#) an hour apart, with notable improvement in symptoms after the second dose [240].

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 [241].

d) Two cases reports suggested a possible interaction between [fluoxetine](#) and [selegiline](#) [242]. One case involved a first episode of mania being observed approximately one month after adding [selegiline](#) to [fluoxetine](#) therapy. The patient improved two months after both drugs were discontinued, and no further details were provided. The second case involved diaphoresis, vasoconstriction, and cyanosis of the hands which occurred in close temporal relationship to

adding [fluoxetine](#) and [selegiline](#). Both drugs were discontinued, with relatively quick resolution of symptoms. Rechallenge with [fluoxetine](#) alone occurred without incident.

e) A case of a 60-year old female who developed [serotonin syndrome](#) after the inadvertent ingestion of a single dose of [venlafaxine](#) while on chronic [tranylcypromine](#) therapy was reported. Approximately four hours after taking the [venlafaxine](#), the patient became weak, confused, and collapsed. Upon examination, the patient exhibited [tachycardia](#), restlessness, tremor, fever, hyperreflexia, and diaphoresis. After treatment with [diazepam](#), [dantrolene](#), and other supportive therapy, the patient's condition returned to normal over the next four days [243].

3.5.1.HY] [Toremifene](#)

- 1) Interaction Effect: an increased risk of [Torsade de pointes](#)
- 2) Summary: Due to the potential for additive effects on the QT interval and increased risk of [torsade de pointes](#), the concomitant use of [toremifene](#) with [venlafaxine](#) should be avoided. If treatment with [venlafaxine](#) is warranted, interrupt [toremifene](#) therapy; however, if coadministration of [toremifene](#) with [venlafaxine](#) can not be avoided, monitor for QT prolongation. Consider [monitoring ECG](#) at baseline and during treatment as indicated in patients at increased risk of QT prolongation[368].
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Concomitant use of [toremifene](#) with [venlafaxine](#) may result in additive effects on the QT interval and should be avoided. If treatment with [venlafaxine](#) is required, interruption of [toremifene](#) is recommended; however, if concomitant use is necessary, closely monitor for QT prolongation. Consider [monitoring ECG](#) at baseline and during treatment as indicated in patients at increased risk of QT prolongation[368].
- 7) Probable Mechanism: additive effects on the QT interval prolongation

3.5.1.HZ] [Tramadol](#)

- 1) Interaction Effect: an increased risk of [serotonin syndrome](#)
- 2) Summary: The use of [tramadol](#) concurrently with other serotonergic drugs may result in [serotonin syndrome](#)[128]. Concurrent use of [tramadol](#) with [mirtazapine](#) and [venlafaxine](#) resulted in symptoms of [serotonin syndrome](#) in 47-year-old male. He experienced agitation, confusion, severe shivering, diaphoresis, myoclonus, hyperreflexia, and mydriasis [129]. If [tramadol](#) is used concomitantly with [venlafaxine](#), monitor closely for symptoms of [serotonin syndrome](#). [Serotonin syndrome](#) can be life-threatening. If [serotonin syndrome](#) develops, discontinue the offending agents and provide supportive care and other therapy as necessary [119].
- 3) Severity: major
- 4) Onset: delayed
- 5) Substantiation: probable
- 6) Clinical Management: There is potential for [serotonin syndrome](#) with the concomitant use of [tramadol](#) and other serotonergic drugs, such as [venlafaxine](#)[128]. A case of [serotonin syndrome](#) was reported with coadministration of [tramadol](#) with [venlafaxine](#) and [mirtazapine](#) and therefore, concomitant use is discouraged [129]. If the use of [tramadol](#) concomitantly with [venlafaxine](#) is clinically warranted, monitor closely for symptoms of [serotonin syndrome](#) such as neuromuscular abnormalities (including hyperreflexia, tremor, muscle rigidity, clonus, peripheral hypertonicity, and shivering), autonomic hyperactivity (including [tachycardia](#), mydriasis, diaphoresis, the presence of bowel sounds, and diarrhea), and mental status changes (including agitation and [delirium](#)). [Serotonin syndrome](#) can be life-threatening. If [serotonin syndrome](#) develops, discontinue the offending agents and provide supportive care and other therapy as necessary [119].

7J) Probable Mechanism: additive serotonergic pharmacologic effects

8J) Literature Reports

aJ) **Serotonin syndrome** developed in a 47-year-old male when **tramadol** was added to a regimen of **venlafaxine** and **mirtazapine**. He was previously on extended-release **venlafaxine** 300 mg/day and **mirtazapine** 30 mg/day for 4 months. **Tramadol** was added and over 4 weeks the dose was titrated up to 300 mg/day without any adverse outcomes. A few weeks after a dose increase to 400 mg/day of **tramadol**, he experienced agitation, confusion, severe shivering, diaphoresis, myoclonus, hyperreflexia, and mydriasis. **Tramadol**, **mirtazapine**, and **venlafaxine** were discontinued. Over the next 4 hours, **tachycardia** and a fever (39.2 degrees Celsius) developed. Intravenous fluids were administered. Symptoms resolved over the following 36 hours. **Venlafaxine** and **mirtazapine** were restarted with dose titrations to original doses over 1 week without any recurrence of **serotonin syndrome** [129].

3.5.1.IA] **Tranlycypromine**

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

2J) Summary: Concurrent administration or overlapping therapy with **venlafaxine** 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[137][138][139][140]. A 60-year old woman developed a serious case of **serotonin syndrome** after the inadvertent ingestion of a single dose of **venlafaxine** while on chronic **tranlycypromine** therapy [141]. Concomitant use is contraindicated.

3J) Severity: contraindicated

4J) Onset: rapid

5J) Substantiation: probable

6J) Clinical Management: Concurrent use of **venlafaxine** and a MAO inhibitor is contraindicated. Wait at least 14 days after discontinuing a MAO inhibitor before initiating therapy with **venlafaxine**. Wait at least seven days after discontinuing **venlafaxine** before initiating therapy with a MAO inhibitor.

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

8J) Literature Reports

aJ) Concomitant use of serotonin specific reuptake inhibitors and monoamine oxidase inhibitors can produce a toxic reaction known as **serotonin syndrome** [133]. **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.

bJ) 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 5 half-lives of the parent drug and any active metabolites [134].

c) Two cases reports suggested a possible interaction between [fluoxetine](#) and [selegiline](#) [135]. One case involved a first episode of mania being observed approximately one month after adding [selegiline](#) to [fluoxetine](#) therapy. The patient improved two months after both drugs were discontinued, and no further details were provided. The second case involved diaphoresis, vasoconstriction, and cyanosis of the hands which occurred in close temporal relationship to adding [fluoxetine](#) and [selegiline](#). Both drugs were discontinued, with relatively quick resolution of symptoms. Rechallenge with [fluoxetine](#) alone occurred without incident.

d) A case of a 60-year old female who developed [serotonin syndrome](#) after the inadvertent ingestion of a single dose of [venlafaxine](#) while on chronic [tranylcypromine](#) therapy has been reported. Approximately four hours after taking the [venlafaxine](#), the patient became weak, confused, and collapsed. Upon examination, the patient exhibited [tachycardia](#), restlessness, tremor, fever, hyperreflexia, and diaphoresis. After treatment with [diazepam](#), [dantrolene](#), and other supportive therapy, the patient's condition returned to normal over the next four days [136].

3.5.1.1B] [Trazodone](#)

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

2) Summary: Concurrent use of [trazodone](#) and [venlafaxine](#) resulted in symptoms of [serotonin syndrome](#) in a 50-year-old man who was also taking [methadone](#)[120]. Both [trazodone](#) and [venlafaxine](#) affect the serotonergic neurotransmitter systems. Concomitant use should be approached with caution due to the additive effects and the potential for increased risk of [serotonin syndrome](#) [117][118]. If [trazodone](#) and [venlafaxine](#) are used concomitantly, monitor closely for symptoms of [serotonin syndrome](#), particularly during treatment initiation and dose increases [117][119]. 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 [119].

3) Severity: major

4) Onset: delayed

5) Substantiation: probable

6) Clinical Management: Use caution with concomitant administration of [trazodone](#) and [venlafaxine](#), a selective serotonin reuptake inhibitor[117], as this may result in additive serotonergic effects and may increase the risk of [serotonin syndrome](#). If coadministration is required, appropriate monitoring may be warranted, particularly during treatment initiation and dose increases [118][117][119]

7) Probable Mechanism: additive serotonergic effects

8) Literature Reports

a) A 50-year-old man experienced [serotonin syndrome](#) 18 days after starting [venlafaxine](#) and [trazodone](#). [Venlafaxine](#) extended release for depression, [trazodone](#) for insomnia, [methadone](#) for [opioid dependence](#), and [docusate](#) were started after he was admitted to the hospital for depressed mood, [anhedonia](#), hopelessness, insomnia, and [suicidal ideation](#). The dose of [venlafaxine](#) was increased over 7 days to 225 mg/day. Eighteen days after hospitalization, he became disoriented, restless and experienced myoclonic jerking, gross tremulousness, and diaphoresis. He was afebrile. His other vital signs were unremarkable. All his drugs were discontinued because his symptoms progressively worsened. Intravenous hydration was initiated. He significantly improved within 24 hours. [Methadone](#) and [docusate](#) were restarted and [mirtazapine](#) was started. He experienced no

further episodes. Significant past medical history includes selective serotonin reuptake inhibitors (SSRIs) while on [methadone](#), without any similar symptoms [120].

3.5.1.IC] [Trifluoperazine](#)

- 1) Interaction Effect: an increased risk of [neuroleptic malignant syndrome](#) and an increased risk of [cardiotoxicity](#) (QT prolongation, [torsades de pointes](#), cardiac arrest)
- 2) Summary: Q and T wave distortions have been observed in patients taking phenothiazines[372]. Although citing no data, the manufacturers of some phenothiazines state that concomitant use with other drugs which prolong the QT interval is contraindicated [373][374]. [Venlafaxine](#) has been shown to prolong the QTc interval at the recommended therapeutic dose [375]. In addition, concomitant use of [venlafaxine](#) and [trifluoperazine](#) has resulted in [neuroleptic malignant syndrome](#) [376].
- 3) Severity: contraindicated
- 4) Onset: rapid
- 5) Substantiation: probable
- 6) Clinical Management: The concurrent administration of [venlafaxine](#) and [trifluoperazine](#) is contraindicated.
- 7) Probable Mechanism: dopamine-inhibition effect of [venlafaxine](#) augments dopamine-receptor inhibition by [trifluoperazine](#); additive effects on QT prolongation
- 8) Literature Reports

a) A 44-year-old male who had been receiving [trifluoperazine](#) 1 mg three times daily for ten years as an anxiolytic was prescribed [venlafaxine](#) 75 mg once daily for depression. Twelve hours following his first dose, he presented with profound sweating, anxiety, tremor, and rigidity. Vital signs revealed a blood pressure ranging from 130/80 mm Hg to 165/100 mm Hg and a pulse of 163 beats per minute. Urine and blood panels were within normal limits, with the exception of an elevated creatine phosphokinase concentration of 11,320 IU/L and a white-cell count of $23.5 \times 10^9/L$. [Neuroleptic malignant syndrome](#) was diagnosed, and the patient was treated with [dantrolene](#) and [bromocriptine](#). Within 24 hours the patient recovered completely. [Trifluoperazine](#) was reintroduced without complications. [Neuroleptic malignant syndrome](#) may have developed in this patient because of a pharmacodynamic interaction of a dopamine-inhibition effect induced by [venlafaxine](#) which augmented dopamine-receptor inhibition by [trifluoperazine](#) [371].

3.5.1.ID] [Trimipramine](#)

- 1) Interaction Effect: an increased risk of [cardiotoxicity](#) (QT prolongation, [torsades de pointes](#), cardiac arrest) and adverse effects of both drugs
- 2) Summary: Tricyclic antidepressants (TCAs) and [venlafaxine](#) have been shown to prolong the QTc interval at the recommended therapeutic dose[297][298]. Even though no formal drug interaction studies have been done, the coadministration of tricyclic antidepressants and other drugs known to prolong the QTc interval, such as [venlafaxine](#), is not recommended [299]. In addition, [venlafaxine](#) and tricyclic antidepressants (TCAs) may competitively inhibit each other's metabolism which may increase side effects of both drugs [300][297][301]. [Venlafaxine](#) increased the AUC, Cmax, and Cmin of [desipramine](#) by approximately 35%. The AUCs of 2-OH-desipramine increased by 2.5 and 4.5 fold when administered with [venlafaxine](#) 37.5 mg and 75 mg every 12 hours, respectively. The pharmacokinetics of [imipramine](#) and the 2-hydroxy metabolite were not affected [6].
- 3) Severity: major
- 4) Onset: rapid
- 5) Substantiation: theoretical
- 6) Clinical Management: Due to the potential for additive effects on the QT interval, the concurrent administration of [venlafaxine](#) and tricyclic antidepressants is not recommended.

7J) Probable Mechanism: decreased TCA and [venlafaxine](#) metabolism; additive effects on QT prolongation

8J) Literature Reports

aJ) When administered with [imipramine](#), the pharmacokinetics of [imipramine](#) and the 2-hydroxy metabolite were not affected. [Venlafaxine](#) increased the area under the concentration-time curve (AUC), maximum concentration (C_{max}), and minimum concentration (C_{min}) of [desipramine](#) by approximately 35%. The 2-OH-desipramine AUCs increased by 2.5-fold ([venlafaxine](#) 37.5 mg every 12 hours) and by 4.5-fold ([venlafaxine](#) 75 mg every 12 hours). The clinical significance of this finding is unknown [6].

3.5.1.IE] [Triptorelin](#)

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

2J) Summary: Use caution with coadministration of gonadotropin-releasing hormone (GnRH) agonists with QT-interval prolonging drugs. Androgen deprivation caused by GnRH agonists may prolong the QT interval and cause additive effects when administered with QT-interval prolonging drugs[377][378][379]. If concurrent therapy is necessary, monitor patients closely for signs and symptoms of [cardiac toxicity](#), including changes in the ECG.

3J) Severity: major

4J) Onset: unspecified

5J) Substantiation: theoretical

6J) Clinical Management: Use caution with coadministration of gonadotropin-releasing hormone (GnRH) agonists with QT-interval prolonging drugs, as additive effects on the QT interval may occur[377][378][379].

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

3.5.1.IF] [Valdecoxib](#)

1J) Interaction Effect: an increased risk of bleeding

2J) Summary: Use caution when coadministering NSAIDs and serotonin [norepinephrine](#) reuptake inhibitors (SNRI) as this may cause an increased risk of bleeding[318]. During clinical trials, concomitant use of NSAIDs and antidepressants, including tricyclic antidepressants, SSRIs, selective serotonin-norepinephrine reuptake inhibitors, and MOAIs, resulted in an increased risk of [intracranial hemorrhage](#) within 30 days of concomitant use compared with antidepressant use alone [319]. When NSAIDs and SNRIs are given concurrently, monitor the patient for signs of increased bleeding.

3J) Severity: major

4J) Onset: unspecified

5J) Substantiation: established

6J) Clinical Management: Serotonin [norepinephrine](#) reuptake inhibitors (SNRI) increase bleeding risk, especially with concomitant use of NSAIDs[318]. When NSAIDs and SNRIs are given concurrently, monitor the patient for signs of increased bleeding.

7J) Probable Mechanism: unknown

8J) Literature Reports

aJ) Concomitant use of NSAIDs and antidepressants, including tricyclic antidepressants, SSRIs, serotonin-norepinephrine reuptake inhibitors, and MAOIs, resulted in an increased risk of [intracranial hemorrhage](#) within 30 days of concomitant use compared with antidepressant use alone. There was no significant difference between the antidepressant drug classes and the increased risk; however, there was an increased risk associated with male patients compared with female patients [319].

3.5.1.IG| Vandetanib

- 1) Interaction Effect: increased risk of QT-interval prolongation
- 2) Summary: Vandetanib is associated with QT-interval prolongation. [Torsades de pointes](#), [ventricular tachycardia](#), and sudden death have also been reported in patients taking vandetanib. Therefore, avoid concurrent use of other QT-interval-prolonging agents as this may increase the risk of additive QT-interval prolongation and [torsade de pointes](#). If coadministration is required, monitor ECG more frequently than during vandetanib monotherapy[364].
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Concurrent use of vandetanib with another drug known to prolong QT interval should be avoided due to increased risk of additive QT-interval prolongation and [ventricular arrhythmias](#). Monitor ECG frequently if coadministration is required[364].
- 7) Probable Mechanism: additive effects on QT interval

3.5.1.IH| Vasopressin

- 1) Interaction Effect: an increased risk of [cardiotoxicity](#) (QT prolongation, [torsades de pointes](#), [cardiac arrest](#))
- 2) Summary: [Venlafaxine](#) and [vasopressin](#) have been shown to prolong the QTc interval at the recommended therapeutic dose[341][342]. Even though no formal drug interaction studies have been done, the coadministration of drugs known to prolong the QTc interval is not recommended.
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: The concurrent administration of [venlafaxine](#) and [vasopressin](#) is not recommended.
- 7) Probable Mechanism: additive effects on QT prolongation

3.5.1.II| Vemurafenib

- 1) Interaction Effect: increased risk of QT-interval prolongation
- 2) Summary: Do not start vemurafenib treatment in patients who are receiving another drug known to prolong the QT interval. Vemurafenib is known to increase the QT interval, which may lead to an increased risk of serious cardiac adverse events, including [torsade de pointes](#). Coadministration of vemurafenib with another drug that prolongs the QT interval may result in additive effects on the QT interval and further increase the risk of [torsade de pointes](#)[127].
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Do not start vemurafenib treatment in patients who are receiving another drug known to prolong the QT interval, as concurrent use of such agents may lead to an increased risk of serious cardiac adverse events, including [torsade de pointes](#)[127].
- 7) Probable Mechanism: additive effects on QT interval

3.5.1.IJ| 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](#)[132]. 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 [119]. 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 [132].

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[132].

7) Probable Mechanism: additive serotonergic effects

3.5.1.IK] Vinflunine

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

2) Summary: Vinflunine is associated with QT-interval prolongation. Concomitant administration of vinflunine with other drugs that prolong the QT interval may have additive prolonging effects on the QT interval and is not recommended[211]. If concomitant use is required, consider a baseline ECG and on-treatment monitoring when vinflunine is coadministered with other QT-prolonging agents.

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Concomitant administration of vinflunine and QT-prolonging drugs may result in additive QT-interval prolongation effects and is therefore not recommended[211]. If concomitant use is required, consider a baseline ECG and on-treatment monitoring.

7) Probable Mechanism: additive QT interval effects

3.5.1.IL] 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[383].

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[383].

7) Probable Mechanism: additive serotonergic effects

3.5.1.IM] [Warfarin](#)

1) Interaction Effect: an increased risk of bleeding

2) Summary: Case reports and epidemiological studies have shown that use of selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs), including [venlafaxine](#), is associated with [gastrointestinal bleeding](#). Bleeding events with SSRIs and SNRIs included cases of ecchymoses, [hematomas](#), [epistaxis](#), and [petechiae](#); life-threatening hemorrhages have also occurred. Coadministration with [warfarin](#) or other anticoagulants may potentiate the risk of bleeding. A population-based, case-controlled study of new coumarin users (acenocoumarol and phenprocoumon) with concomitant selective serotonin reuptake inhibitors (SSRIs) resulted in an increased risk of hospitalization due to nongastrointestinal bleeding[354]. Increases in prothrombin time, partial thromboplastin time, or INR have been reported when [venlafaxine](#) was administered to patients receiving [warfarin](#). Therefore, concomitant use of [venlafaxine](#) with [warfarin](#) or other drugs affecting coagulation should be undertaken with caution. Whenever [venlafaxine](#) is initiated or discontinued in patients receiving an anticoagulant, close monitoring of coagulation parameters is recommended [321].

3) Severity: major

4) Onset: unspecified

5) Substantiation: probable

6) Clinical Management: Use caution when [venlafaxine](#) is used concomitantly with [warfarin](#) or other drugs affecting coagulation. Closely monitor coagulation parameters when [venlafaxine](#) is initiated or discontinued in patients receiving anticoagulants, such as [warfarin](#)[321].

7) Probable Mechanism: additive adverse events

8) Literature Reports

a) A population-based, case-controlled study of new coumarin users (acenocoumarol and phenprocoumon) with concomitant selective serotonin reuptake inhibitors (SSRIs) resulted in an increased risk of hospitalization due to nongastrointestinal bleeding. Using national pharmacy and hospitalization records, Netherlands researchers identified 1848 cases that were admitted for abnormal bleeding and compared them with 5818 control subjects also taking coumarins. Median duration of treatment in patients was 220 days (range, 1 to 4690 days). Patients on SSRIs showed greater risk for hospitalization for nongastrointestinal bleeding (adjusted odds ratio (OR) 1.7, 95% confidence interval (CI), 1.1 to 2.5), however, the rate of [gastrointestinal bleeding](#) (adjusted OR 0.8, 95% CI, 0.4 to 1.5) was not significantly different [354].

3.5.1.IN] [Xemilofiban](#)

1) Interaction Effect: an increased risk of bleeding

2) Summary: The release of serotonin by [platelets](#) is important for maintaining hemostasis. Case reports and epidemiological studies have shown that use of selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs), including [venlafaxine](#), is associated with [gastrointestinal bleeding](#). Bleeding events with SSRIs and SNRIs included cases of ecchymoses, [hematomas](#), [epistaxis](#), and [petechiae](#); life-threatening hemorrhages have also occurred. Coadministration with drugs that affect coagulation, such as antiplatelet agents, may potentiated the risk of bleeding[321].

- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: probable
- 6) Clinical Management: Use caution when [venlafaxine](#) is used concomitantly with antiplatelet agents. Closely monitor patient for signs of bleeding when [venlafaxine](#) is initiated or discontinued in patients receiving antiplatelet agents concomitantly[321].
- 7) Probable Mechanism: unknown

3.5.1.IO| [Ziprasidone](#)

- 1) Interaction Effect: increased risk of QT-interval prolongation and increased risk of [serotonin syndrome](#) ([hypertension](#), [hyperthermia](#), myoclonus, mental status changes)
- 2) Summary: The concomitant use of [ziprasidone](#) with other drugs that prolong the QT interval is contraindicated because coadministration may result in additive risk for QT-interval prolongation. [Serotonin syndrome](#) has also been reported with [ziprasidone](#) monotherapy and in combination with other serotonergic drugs[313][314]; coadministration with another serotonergic drug may increase the risk for [serotonin syndrome](#).
- 3) Severity: contraindicated
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: The concomitant use of [ziprasidone](#) with other drugs that prolong the QT interval is contraindicated because coadministration may result in additive risk for QT-interval prolongation. [Serotonin syndrome](#) has also been reported with [ziprasidone](#) monotherapy and in combination with other serotonergic drugs[313][314]; coadministration with another serotonergic drug may increase the risk for [serotonin syndrome](#).
- 7) Probable Mechanism: additive QT interval effects; additive serotonergic effect

3.5.1.IP| [Zolmitriptan](#)

- 1) Interaction Effect: an increased risk of [serotonin syndrome](#)
- 2) Summary: Concurrent use of a triptan and a serotonin [norepinephrine](#) reuptake inhibitor (SNRI) has resulted in life-threatening [serotonin syndrome](#). Onset of symptoms is usually rapid, occurring within minutes to hours of initiation or dose escalation of a serotonergic agent[257]. Symptoms of [serotonin syndrome](#) may include restlessness, hallucinations, loss of coordination, fast heart beat, rapid changes in blood pressure, increased body temperature, overreactive reflexes, nausea, vomiting, and diarrhea. Clinicians should be aware that triptans may be commonly used intermittently and that either the triptan or the serotonergic agent may be prescribed by a different physician. Discuss the risks of [serotonin syndrome](#) with patients who are prescribed this combination and monitor them closely for symptoms of [serotonin syndrome](#) [258]. Discontinue use of [zolmitriptan](#) if [serotonin syndrome](#) is suspected [257].
- 3) Severity: major
- 4) Onset: rapid
- 5) Substantiation: probable
- 6) Clinical Management: Life-threatening [serotonin syndrome](#) has been reported with coadministration of triptans and serotonin [norepinephrine](#) reuptake inhibitors (SNRIs)[257]. Consider potential intermittent use of triptans in patients who receive SNRIs and closely monitor patients receiving both medications for symptoms of [serotonin syndrome](#) [258]. Discontinue [zolmitriptan](#) if [serotonin syndrome](#) is suspected [257].
- 7) Probable Mechanism: additive pharmacologic effects resulting in excessive serotonergic stimulation

3.5.1.IQ| [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](#)[237].

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 [236].

3.5.1.IR] Zuclopenthixol

1) Interaction Effect: increased risk of QT prolongation

2) Summary: Avoid the concomitant use of zuclopenthixol and other drugs known to significantly increase the QT interval. Additionally, drugs known to cause electrolyte disturbances (eg, hypokalemia) or drugs known to increase the plasma concentration of zuclopenthixol should be used cautiously. Cases of QT prolongation, [ventricular arrhythmias](#) and fibrillation, [ventricular tachycardia](#), [torsade de pointes](#), and sudden death have been reported with zuclopenthixol[349][350].

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Avoid the concomitant use of zuclopenthixol and other drugs known to significantly increase the QT interval. Additionally, drugs known to cause electrolyte disturbances (eg, hypokalemia) or drugs known to increase the plasma concentration of zuclopenthixol should be used cautiously. Cases of QT prolongation, [ventricular arrhythmias](#) and fibrillation, [ventricular tachycardia](#), [torsade de pointes](#), and sudden death have been reported with zuclopenthixol[349][350].

7) Probable Mechanism: additive QT prolongation

3.5.2] Drug-Food Combinations

3.5.2.A] Ethanol

1) Interaction Effect: an increased risk of CNS effects

2) Summary: Concomitant use of [venlafaxine](#) and ethanol did not potentiate psychomotor or psychometric effects associated with alcohol consumption[407][408]. However, the manufacturer of [venlafaxine](#) recommends that patients be advised to avoid alcohol while using [venlafaxine](#) [409].

3) Severity: minor

4) Onset: rapid

5) Substantiation: theoretical

6) Clinical Management: Patients receiving [venlafaxine](#) should be advised to avoid the use of alcohol.

7) Probable Mechanism: unknown

8) Literature Reports

a) The pharmacokinetic and pharmacodynamic effect of [venlafaxine](#) was tested in 16 healthy volunteers after receiving a 0.5 g/kg dose of ethanol or placebo. The dose of [venlafaxine](#) was 50 mg every eight hours for seven days. Ethanol or placebo was given on day 5 or 7 of [venlafaxine](#) administration with a randomized, blinded method. There was no significant difference in the pharmacokinetics of [venlafaxine](#) when given with ethanol or placebo. In addition, no significant difference was detected in eight objective performance tests when [venlafaxine](#) was given with ethanol or placebo. It is not known if repeated administration of ethanol would have had a significant effect [406].

3.5.3] Drug-Lab Modifications

3.5.3.A] [Amphetamine measurement](#)

- 1) Interaction Effect: a false-positive urine [amphetamine immunoassay](#) result
- 2) Summary: Use of [venlafaxine](#) has resulted in false-positive urine [amphetamine](#) test results as evaluated by [immunoassay](#). False-positive results may also occur for several days following discontinuation of [venlafaxine](#). It may be necessary to confirm positive urine [amphetamine](#) screens with more specific tests, such as [gas chromatography/mass spectrometry](#)[402][117].
- 3) Severity: moderate
- 4) Onset: unspecified
- 5) Substantiation: probable
- 6) Clinical Management: The administration of [venlafaxine](#) has resulted in false-positive urine [amphetamine immunoassay](#) results due to screening tests that lack specificity. False positive results may also occur for several days following the discontinuation of [venlafaxine](#). More specific tests, such as [gas chromatography/mass spectrometry](#), will be able to distinguish between [venlafaxine](#) and [amphetamine](#)[402][117].
- 7) Probable Mechanism: lack of specificity of the [immunoassay](#) screening test

3.5.3.B] [Phencyclidine measurement](#)

- 1) Interaction Effect: a false-positive urine phencyclidine [immunoassay](#) result
- 2) Summary: Use of [venlafaxine](#) has resulted in false-positive urine phencyclidine (PCP) test results as evaluated by [immunoassay](#). False-positive results may also occur several days following discontinuation of [venlafaxine](#). It may be necessary to confirm positive urine phencyclidine screens with more specific tests, such as [gas chromatography/mass spectrometry](#)[402][117].
- 3) Severity: moderate
- 4) Onset: unspecified
- 5) Substantiation: probable
- 6) Clinical Management: The administration of [venlafaxine](#) has resulted in a false-positive urine phencyclidine (PCP) [immunoassay](#) due to screening tests that lack specificity. False-positive results may also occur several days following discontinuation of [venlafaxine](#). More specific tests, such as [gas chromatography/mass spectrometry](#), will be able to distinguish between [venlafaxine](#) and phencyclidine[402][117].
- 7) Probable Mechanism: lack of specificity of the [immunoassay](#) 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)] Venlafaxine Hydrochloride

1)] Therapeutic

a)] Physical Findings

1)] Measures such as the Hamilton Depression Rating Scale, Hamilton depressed mood item, MADRS total score, Clinical Global Impression (CGI) Severity of Illness rating, and the CGI Global Improvement item may be used to assess efficacy in patients receiving venlafaxine for major depressive disorder [4][5].

2)] The Hamilton Rating Scale for Anxiety (HAM-A) total score, the HAM-A anxiety and tension items, and the Clinical Global Impressions (CGI) scale may be used to assess therapeutic efficacy of venlafaxine extended-release in generalized anxiety disorder [5].

3)] The Liebowitz Social Anxiety Scale (LSAS) may be used to assess therapeutic efficacy of venlafaxine extended-release in social anxiety disorder [5].

4)] The Panic and Anticipatory Anxiety Scale (PAAS), Panic Disorder Severity Scale (PDSS) total score, and the Clinical Global Impressions (CGI) Improvement scale may be used to assess therapeutic efficacy of venlafaxine extended-release in panic disorder [5].

2)] Toxic

a)] Laboratory Parameters

1)] Measurement of serum cholesterol levels should be considered during long-term treatment as clinically relevant increases in serum cholesterol were reported in patients being treated with venlafaxine for at least 3 months during placebo-controlled trials [4][5].

2)] Hyponatremia may occur as a result of treatment with SSRIs and serotonin-norepinephrine reuptake inhibitors, particularly in the elderly, volume-depleted patients, and patients receiving diuretics. Consider monitoring serum sodium levels in these patients [4][5].

3)] Liver function should be monitored as dosage adjustments are necessary in cases of cirrhosis of the liver [4][5].

4)] Patients receiving warfarin therapy should be carefully monitored when venlafaxine is initiated or discontinued as altered anticoagulant effects, including increased bleeding, have been reported when SSRIs and serotonin-norepinephrine reuptake inhibitors were co-administered with warfarin [4][5].

5j) Renal function should be monitored, particularly in the elderly, as dosage adjustments are necessary in cases of severe renal impairment and end stage renal disease [4][5].

bj) Physical Findings

1j) Cough, progressive dyspnea, or chest discomfort may be indicative of interstitial lung disease and eosinophilic pneumonia, which have been rarely reported with venlafaxine use. If these symptoms are observed, prompt medical evaluation and possible discontinuation of venlafaxine therapy is recommended [4][5].

2j) Increases in blood pressure have been reported in patients receiving venlafaxine. Preexisting hypertension should be controlled before initiating treatment with venlafaxine and regular monitoring of blood pressure should occur in patients receiving venlafaxine. Dose-reduction or discontinuation of venlafaxine should be considered in cases of sustained increases in blood pressure [4][5].

3j) Observe patients for discontinuation symptoms such as dysphoric mood, irritability, agitation, dizziness, sensory disturbances, anxiety, confusion, headache, lethargy, emotional lability, insomnia, hypomania, tinnitus, and seizures. Avoid abrupt discontinuation or dose-reduction of venlafaxine [4][5].

4j) Observe patients (particularly the elderly, volume-depleted, and those receiving diuretics) for signs and symptoms of hyponatremia including headache, difficulty concentrating, memory impairment, confusion, weakness, and unsteadiness. More severe and/or acute cases may lead to hallucination, syncope, seizure, coma, respiratory arrest, and death [4][5].

5j) Observe patients for signs and symptoms of serotonin syndrome. Symptoms may include mental status changes (agitation, hallucinations, coma), autonomic instability (tachycardia, labile blood pressure, hyperthermia), neuromuscular aberrations (hyperreflexia, incoordination), and/or gastrointestinal symptoms (nausea, vomiting, diarrhea) [4][5].

6j) Patients with depressive symptoms should be screened prior to initiating treatment with an antidepressant to determine if they are at risk for bipolar disorder. Screening should include a detailed psychiatric history, including a family history of suicide, bipolar disorder, and depression [4][5].

7j) Patients receiving antidepressants should be monitored 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 [4][5][109][457].

8j) Patients who experience symptoms of anxiety, agitation, panic attacks, insomnia, irritability, hostility, aggressiveness, 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 [109][457][4][5].

9) Patients with raised ocular pressure or at risk of acute narrow angle glaucoma should have ocular pressure measured while on venlafaxine [4][5].

4.2] Patient Instructions

A) Venlafaxine (By mouth)

Venlafaxine

Treats depression, [generalized anxiety disorder](#), [panic disorder](#), and [social anxiety disorder](#).

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 [venlafaxine](#) or desvenlafaxine succinate.

How to Use This Medicine:

Long Acting Capsule, Tablet, Long Acting Tablet

Take your medicine as directed. Your dose may need to be changed several times to find what works best for you.

It is best to take the extended-release capsule at the same time each day (either in the morning or evening).

It is best to take this medicine with food or milk.

Swallow the extended-release capsule whole. Do not crush, break, or chew it. Do not place the capsule in a liquid.

If you cannot swallow the extended-release capsule, you may open it and pour the medicine into a small amount of soft food such as pudding, yogurt, or applesauce. Stir this mixture well and swallow it without chewing.

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 if you have used an MAO inhibitor within the past 14 days. Do not take an MAO inhibitor for at least 7 days after you stop this medicine.

Some medicines can affect how [venlafaxine](#) works. Tell your doctor if you are using any of the following:

[Buspirone](#), [cimetidine](#), [fentanyl](#), [ketoconazole](#), [lithium](#), [metoprolol](#), [mirtazapine](#), St John's wort, [tramadol](#), or tryptophan supplements

[Amphetamines](#)

Blood thinner (including [warfarin](#))

Diuretic (water pill)

Medicine for migraine headaches

Medicine to lose weight (including [phentermine](#))

NSAID pain or [arthritis](#) medicine (including [aspirin](#), [celecoxib](#), [diclofenac](#), [ibuprofen](#), [naproxen](#))

Tricyclic antidepressant

Do not drink alcohol while you are using this medicine.

Tell your doctor if you use anything else that makes you sleepy. Some examples are allergy medicine, narcotic pain medicine, and alcohol.

Warnings While Using This Medicine:

Tell your doctor if you are pregnant or breastfeeding, or if you have [kidney disease](#), liver disease, [glaucoma](#), [heart disease](#), [high blood pressure](#), or [thyroid problems](#). Tell your doctor if you have a history of mania, seizures, [heart attack](#), or [stroke](#).

This medicine can increase thoughts of suicide. Tell your doctor right away if you start to feel depressed and have thoughts about hurting yourself.

This medicine may cause the following problems:

[Serotonin syndrome](#) (when used with certain medicines)

Increased cholesterol levels

[Increased blood pressure](#)

Increased risk of bleeding problems

Low sodium levels

[Interstitial lung disease](#) and [eosinophilic pneumonia](#)

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.

Tell any doctor or dentist who treats you that you are using this medicine. This medicine may affect certain medical test results.

Your doctor will do lab tests at regular visits to check on the effects of this medicine. Keep all appointments.

Keep all medicine out of the reach of children. Never share your medicine with anyone.

Possible Side Effects While Using This Medicine:

Call your doctor right away if you notice any of these side effects:

[Allergic reaction](#): Itching or hives, swelling in your face or hands, swelling or tingling in your mouth or throat, chest tightness, trouble breathing

Anxiety, restlessness, fever, sweating, muscle spasms, nausea, vomiting, diarrhea, seeing or hearing things that are not there

Blistering, [peeling](#), red skin rash

Chest pain, [cough](#), trouble breathing

Confusion, weakness, and muscle twitching

Eye pain, vision changes, seeing halos around lights

Fast or pounding heartbeat

Feeling more excited or energetic than usual

Headache, trouble concentrating, memory problems, unsteadiness

Seizures

Unusual behavior, thoughts of hurting yourself or others, trouble sleeping, nervousness, unusual dreams

Unusual bleeding or bruising

If you notice these less serious side effects, talk with your doctor:

Dry mouth

Mild nausea, constipation, vomiting, loss of appetite, weight loss

Sexual problems

Sleepiness or unusual drowsiness, dizziness

If you notice other side effects that you think are caused by this medicine, tell your doctor.

4.3] Place In Therapy

A) Venlafaxine Hydrochloride

1) Like the SSRIs, venlafaxine does not cause the anticholinergic, sedative, or cardiovascular adverse effects typical of "traditional" antidepressants. In fact, venlafaxine has been shown to cause an activating effect, at least with acute administration. Although its clinical significance is unclear, it inhibits synaptosomal dopamine reuptake, unlike most existing antidepressants. Clinical data involving patients with previous experience with tricyclic antidepressants indicate that venlafaxine has a different adverse effect profile from the tricyclic antidepressants but similar to SSRIs.

2) Despite availability of newer antidepressants, 30% to 40% of patients with severe depression fail to achieve complete remission; consequently, relapse and residual functional impairment remain. In limited clinical trials, venlafaxine was comparable to tricyclic antidepressants and superior to selective serotonin reuptake inhibitors for inducing remission in patients with severe depression. Improved response rates may result from the dual action of venlafaxine on the norepinephrine and serotonin system. Further evaluation of venlafaxine in severely depressed patients is needed [458]. Venlafaxine extended-release was superior to placebo in the prevention of recurrent episodes of depression in patients with major depressive disorder during two randomized, double-blind one-year maintenance phase trials [13][14].

3) One potential advantage of venlafaxine is its apparent rapid onset of action; significant improvement of depressive symptoms and induction of noradrenergic subsensitivity has been demonstrated after 2 weeks of therapy. However, it has not been established that venlafaxine clearly works faster than other antidepressants; rapid antidepressant effects may be a result of rapid up dosing during clinical trials, rather than a distinguishing characteristic of this drug. If additional research including comparative trials support the safety, efficacy, and rapid onset of action of venlafaxine, formulary inclusion should be considered.

4) Preliminary data suggest that venlafaxine may be useful in the treatment of obsessive-compulsive disorder and posttraumatic stress disorder; however, more research is required to determine its role in these disorders.

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

4.4] Mechanism of Action / Pharmacology

A) Venlafaxine Hydrochloride

1) MECHANISM OF ACTION

a) Venlafaxine hydrochloride is an antidepressant agent that potentiates the neurotransmitter activity in the central nervous system (CNS). It also inhibits neuronal serotonin activity, and norepinephrine and dopamine reuptake. Venlafaxine and its active metabolite, O-desmethylenlafaxine (ODV), are potent inhibitors of neuronal serotonin (5-hydroxytryptamine; 5-HT) reuptake, slightly less potent inhibitors of neuronal norepinephrine reuptake, and weak inhibitors of neuronal dopamine reuptake. Venlafaxine inhibits serotonin reuptake less potently than do the selective serotonin reuptake inhibitors [4][5][444][426][442][441][443][446].

b) Venlafaxine is a bicyclic antidepressant that has been referred to as an atypical or "second-generation" antidepressant. It selectively inhibits neuronal uptake of serotonin, norepinephrine, and dopamine in order of decreasing potency. It does not inhibit monoamine oxidase, and does not show the degree of anticholinergic, sedative, or cardiovascular effects other commonly

used antidepressants have been shown to exhibit. No affinity for central muscarinic-cholinergic, dopaminergic, histaminic, opioid (μ), benzodiazepine, or α -1-adrenergic receptors has been demonstrated for [venlafaxine](#) or its major active metabolite, O-desmethylvenlafaxine. In animal studies, [venlafaxine](#) has been shown to inhibit neuronal activity in the locus coeruleus of the brain. Other antidepressant properties include its ability to reverse [reserpine](#) hypothermia and to cause pineal beta-adrenergic subsensitivity [447][433][448][449][450].

c) [Venlafaxine](#) is a racemic mixture; while the pharmacologic profile of the levo(-) isomer is similar to that of the racemate, the dextro(+) isomer is primarily a serotonin uptake inhibitor [433].

2) ELECTROENCEPHALOGRAPHIC EFFECTS

a) Electroencephalographic (EEG) analysis in patients receiving [venlafaxine](#) has shown that it exerts significant effects on brain function. With doses of 12.5 to 50 mg, absolute power is reduced compared with placebo, alpha power is decreased, relative delta/theta and beta powers are increased, and the total centroid is accelerated. These effects are similar to those caused by other antidepressants such as [imipramine](#) [449].

3) NEUROPSYCHIATRIC EFFECTS

a) Administration of [venlafaxine](#) has been shown to cause significant improvement in attention, concentration, memory, fine motor ability, reaction time performance, drive, and wakefulness compared to placebo in healthy volunteers. This is thought to be due to activation of all 3 neurotransmitter systems (i.e., serotonin, [norepinephrine](#), and [dopamine](#)). However, deterioration in performance occurs with higher doses, most likely due to the drug's serotonergic activity [449].

4) REVIEW ARTICLES

a) Two reviews provide a discussion of the efficacy of selective serotonin reuptake inhibitors and other antidepressants for treatment of severe depression [451][452].

b) The efficacy of antidepressants in reducing panic attack frequency, symptoms of depression, social avoidance, and overall impairments from [panic disorder](#) are addressed [453].

c) A review article discussed the rational treatment of depression and included a discussion of each class of antidepressants [454].

d) The pharmacology and therapeutic potential of [venlafaxine](#) has been reviewed [455][432].

e) Drug-interactions of antidepressants are reviewed in German language [456].

4.5] Therapeutic Uses

4.5.1] FDA Uses

4.5.1.A] [Venlafaxine](#) Hydrochloride

4.5.1.A.1] Generalized anxiety disorder

FDA Labeled Indication

a) Overview

FDA Approval: Adult, yes (extended-release capsule only); **Pediatric, no**

Efficacy: Adult, Effective; Pediatric, Evidence favors efficacy

Recommendation: Adult, Class IIa; **Pediatric, Class IIb**

Strength of Evidence: Adult, Category B; Pediatric, Category B

See Drug Consult reference: **RECOMMENDATION AND EVIDENCE RATINGS**

b) Summary:

Venlafaxine extended-release is approved for treating **generalized anxiety disorder** (GAD), as defined in DSM-IV, in adults [5].

Extended-release **venlafaxine** was more effective than placebo for improving the symptoms of depression and anxiety in patients with **major depressive disorder** (MDD) and comorbid **generalized anxiety disorder**; however, time to response was greater in patients with comorbidity than in patients with MDD only [9].

Venlafaxine extended-release was safe and effective for long-term treatment (6 months) of **generalized anxiety disorder** in adults during a randomized, double-blind, placebo-controlled trial (n=251) [19].

Extended-release **venlafaxine** was superior to placebo for relieving **generalized anxiety disorder** in non-depressed patients during short-term treatment (2 months) in a randomized, double-blind trial (n=349) [20].

In two randomized, placebo-controlled, 8-week studies enrolling children with **generalized anxiety disorder**, extended-release **venlafaxine** (n=157) was more effective than placebo (n=163) in one individual trial and the pooled analysis [21].

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

c) Adult:

1) Extended release (XR) venlafaxine was more effective than placebo for improving the symptoms of depression and anxiety in patients with **major depressive disorder** and comorbid **generalized anxiety disorder** (GAD). However, time to response was greater in patients with comorbidity than in patients with **major depressive disorder** only. From the data of all the patients meeting DSM-IV criteria for **major depressive disorder** in a double-blind, randomized trial (n=368), results from the subset of patients who had comorbid GAD (n=92) were analyzed separately and compared to results of the noncomorbid patients. Patients took once-daily doses of **venlafaxine** XR 75 mg, **fluoxetine** 20 mg, or placebo for 12 weeks. **Venlafaxine** doses could be increased to a maximum of 225 mg. According to the criteria of more than 50% reduction (from baseline) in the Hamilton-Depression (HAM-D) and Hamilton-Anxiety (HAM-A) scores, improvement with **venlafaxine** was significantly greater (p less than 0.05) than with placebo by 12 weeks of treatment. About one third of patients with comorbidity showed response at 4 weeks; however, overall, there was no evident trend for a placebo-drug difference until after the eighth week of treatment. Among patients without comorbidity, the placebo-venlafaxine difference was evident as early as week 2. By week 12, response rate was 66% on HAM-D and 59% on HAM-A for those taking **venlafaxine** and 36% and 24% for those taking placebo [9].

2) Venlafaxine extended-release (XR) was safe and effective for the long-term treatment of **generalized anxiety disorder** (GAD) in a 6-month, double-blind, placebo-controlled

trial. Patients (n=251) who met DSM-IV criteria for GAD without a diagnosis of [major depressive disorder](#) were randomized to receive either [venlafaxine XR](#) 75, 150, or 225 mg/day (n=124; mean age, 41 years) or placebo (n=127; mean age, 38 years) for 28 weeks. Primary outcome measures included change from baseline in the Hamilton Rating Scale for Anxiety (HAM-A) total score, the HAM-A psychic anxiety factor score, and the Clinical Global Impressions (CGI) scale Severity of Illness and Global Improvement scores. Of the 251 patients randomized, 238 were considered evaluable for the efficacy analysis. The overall dropout rate was 59%, with 60 and 44 patients in the [venlafaxine XR](#) and placebo groups, respectively, completing the study. Using the last-observation-carried-forward (LOCF) method, the adjusted mean changes from baseline to week 28 for HAM-A were -13.4 for [venlafaxine XR](#) and -8.7 for placebo (p less than 0.001). The changes for HAM-A psychic anxiety score were -7.4 for [venlafaxine XR](#) and -4.2 for placebo (p less than 0.001), and the changes for CGI-Improvement were 2.2 and 3, respectively (p less than 0.001). Significant (p less than 0.01) changes in the HAM-A scores were seen as early as week 1 with [venlafaxine XR](#) when all patients received 75 mg daily and significant (p less than 0.001) differences between [venlafaxine XR](#) and placebo were maintained throughout the final assessment at week 28. Similar results were demonstrated for the HAM-A psychic anxiety factor scores, where significant reductions were noted with [venlafaxine XR](#) compared with placebo at week 1 (p=0.02) and at weeks 2 through 28 (p less than 0.001). The beneficial changes in CGI-Severity of Illness scores for [venlafaxine XR](#) compared to placebo became initially noted at week 2, but became more significant at week 6 through 28 (p less than 0.001). [Venlafaxine XR](#) therapy was also superior to placebo on the CGI-Global Improvement item at all times assessed beyond week 1. Response rates (defined as either a reduction in HAM-A total score of at least 40% from baseline or a CGI-Global Improvement score of 1 or 2) during weeks 6 through 28 were at least 69% in the [venlafaxine XR](#) group compared with 42% to 46% in the placebo group (p less than 0.001). The most common adverse events occurring with at least twice the frequency with [venlafaxine XR](#) were anorexia, constipation, dizziness, dry mouth, nausea, sexual dysfunction, somnolence, and sweating. Over time (days 57 to 196), these events subsided with continued therapy [19].

3j) Extended-release (XR) [venlafaxine](#) was superior to placebo for relieving [generalized anxiety disorder](#) in non-depressed patients during short-term treatment (2 months). In a randomized, double-blind trial, patients were given placebo (n=96) or [venlafaxine XR](#) (n=253) at one of 3 dose levels (75, 150, or 225 mg/day). All patients receiving [venlafaxine](#) started with 75 mg/day for the first week; during the second week, those assigned to the 150 and 225 mg/day groups were raised to 150 mg/day; those in the 225 mg/day group were raised to that dose in week 3. By the end of week 1 and throughout the 8 weeks of treatment, efficacy measures for all doses of [venlafaxine](#) were superior to those for placebo. By week 8, scores on the Hamilton anxiety scale were indistinguishable for the 2 highest doses of [venlafaxine](#), although, according to the Anxiety Subscale of the Hospital Anxiety and Depression Scale, improvement was greater with 225 mg/day. Most discontinuations (29% of patients) were caused by adverse reactions and occurred within the first week of treatment. The most common side effects with [venlafaxine XR](#) were nausea, insomnia, dry mouth, somnolence, dizziness, and asthenia [20].

d) Pediatric:

1j) Extended-release [venlafaxine](#) may improve [generalized anxiety disorder](#) in children as evaluated in two randomized, placebo-controlled, 8-week studies. These two flexible-dose studies were identical in design and were analyzed separately and in a pooled analysis. Children with [generalized anxiety disorder](#) received initial doses of extended-release

venlafaxine 37.5 mg once daily (n=157) or placebo (n=163) and were titrated up according to body weight for 8 weeks, followed by a taper down period for up to 14 days. The maximum extended-release venlafaxine dose was 225 mg/day for children weighing greater than or equal to 50 kg. Patients were stratified by age (6 to 11 years and 12 to 17 years) and had a total score of greater than or equal to 20 on the severity component of the generalized anxiety section of the Columbia Schedule for Affective Disorders and Schizophrenia for School-Age Children (Columbia K-SADS). Patients were excluded if they had major depressive disorder, acute suicidality, social anxiety, or other psychiatric disorders. In the first study, the adjusted mean change from baseline to 8 weeks in the composite score of nine delineated items from the Columbia K-SADS (primary endpoint) was greater in the extended-release venlafaxine group (-18.6) compared to the placebo group (-12.4; p less than or equal 0.001); however, there was not a significant difference between treatment groups in the second study (-15.8 versus -13, respectively; p=0.06). A greater number of patients responded (defined as at least a 50% decrease from baseline in the nine-item Columbia K-SADS or a clinical global impression (CGI) score of less than 3) to treatment in the venlafaxine group (38%) compared to the placebo group (17%; p-value not reported) in the first study, but not in the second study. In the pooled analysis, the adjusted mean decrease in the composite score of nine delineated items from the Columbia K-SADS generalized anxiety disorder section was 17.4 points in the extended-release venlafaxine group compared to 12.7 points in the placebo group (p < 0.001). In both studies, patients treated with extended-release venlafaxine experienced greater improvement in CGI severity of illness scores and adjusted mean improvement scores. The most common adverse events in the extended-release venlafaxine group that were twice as frequent as placebo were asthenia, pain, anorexia, and somnolence [21].

4.5.1.A.2] Major depressive disorder

FDA Labeled Indication

a) Overview

FDA Approval: Adult, yes; Pediatric, no

Efficacy: Adult, Effective; Pediatric, Evidence is inconclusive

Recommendation: Adult, Class IIa; Pediatric, Class IIb

Strength of Evidence: Adult, Category B; Pediatric, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:

The immediate-release and extended-release formulations of venlafaxine are indicated for the treatment of major depressive disorder [4][5][6].

Efficacy of venlafaxine immediate- and extended-release tablets for the treatment of major depressive disorder was demonstrated in multiple randomized, double-blind, controlled trials [7][8][9][10] and in an open, community-based study [11].

Results from the Prevention of Recurrent Episodes of Depression with Venlafaxine for Two Years (PREVENT) study indicated that maintenance therapy with venlafaxine extended release (ER) was effective in preventing recurrence of depression in patients who had been successfully treated with venlafaxine ER during acute (10 weeks), continuation (6 months), and maintenance (1 or 2 years) therapy [12][13][14].

Several open-label studies support the usefulness of [venlafaxine](#) as a possible therapy for patients with treatment-resistant depression [15][16].

[Venlafaxine](#) combined with [electroconvulsive therapy](#) was efficacious in patients with treatment-resistant depression, however, an adverse effect of the therapy was [asystole](#) in 4 of 13 patients [17].

Separate results of 2 similar placebo-controlled, double-blind, randomized trials did not demonstrate a significant clinical benefit of [venlafaxine](#) extended-release over placebo in pediatric patients with [major depressive disorder](#); pooled results showed greater improvement in adolescents (12 to 17 years) but not in children (7 to 11 years) [18].

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

c) Adult:

1) Extended-Release

a) In an 8-week, double-blind, parallel-group, active- and placebo-controlled, flexible-dose trial (n=591), extended release (XR) [venlafaxine](#) was more effective than placebo for improving symptoms of depression; however, [bupropion](#) XR did not demonstrate a significant difference from placebo. Patients who met DSM-IV criteria for [major depressive disorder](#) were randomized to receive [venlafaxine](#) XR 75 mg (n=198), [bupropion](#) XR 150 mg (n=204), or placebo (n=189) for an initial treatment period of 4 weeks. At week 5, an option to double the dose at the discretion of the investigator was allowed if response was inadequate. Based on the modified intent-to-treat population (n=581), the mean change in the Montgomery-Asberg Depression Rating Scale (MARDS) total score at week 8 (primary endpoint) was -17 points in the [venlafaxine](#) XR arm (baseline, 30.1), -14.7 points in the [bupropion](#) XR arm (baseline, 30.6), and -13.2 points in the placebo arm (baseline, 30.6). Relative to placebo, [venlafaxine](#) demonstrated significant difference in the primary endpoint (p less than 0.001), but not [bupropion](#) (p=0.146). The difference in mean change in MADRS total score between [venlafaxine](#) and placebo was significant (p less than 0.05) as early as week 2 after initiation of therapy, and was sustained for the remainder of the study. The average daily dose at the end of the study was 85 mg for [venlafaxine](#) XR and 180 mg for [bupropion](#) XR. [Venlafaxine](#) was associated with higher incidence of dry mouth (18% vs 7%), nausea (27% vs 9%), dizziness (14% vs 6%) compared with placebo [8].

b) Continuation of [venlafaxine](#) extended-release (ER) therapy following response to treatment appeared to be effective in preventing [relapse](#) in patients with [major depressive disorder](#). In a prospective, multicenter study, patients (n=318) who responded to 8 weeks of open-label treatment with [venlafaxine](#) ER (75, 150, or 225 mg/day; mean dose, 186 to 192 mg/day) entered a 6-month randomized, double-blind, continuation phase in which they either received placebo or continued on the same dose of [venlafaxine](#) ER (mean dose, 177 to 191 mg/day). During the 6-month relapse-prevention phase, significantly fewer patients treated with [venlafaxine](#) ER experienced [relapse](#) as compared with patients given placebo (p less than 0.001) and at study endpoint, the cumulative probability of [relapse](#) was higher for patients in the placebo group than in the [venlafaxine](#) ER group (52% vs 28%). Significant differences in favor of [venlafaxine](#) ER as compared with placebo (p less than 0.001) were also observed for secondary outcome measures (i.e., Hamilton Rating Scale for Depression (HAM-D) total score, HAM-D depressed mood item, Montgomery-

Asberg Depression Rating Scale total score, and Clinical Global Impression Scale-Severity of illness scores). Common adverse effects occurring significantly more often with [venlafaxine](#) than with placebo included [hypertension](#) and sweating ($p=0.018$ and $p=0.024$, respectively). In the [venlafaxine](#) group, four (2%) patients were withdrawn from the study due to increases in blood pressure [7].

c) Extended release (XR) [venlafaxine](#) was more effective than placebo for improving the symptoms of depression and anxiety in patients with [major depressive disorder](#) (MDD) and comorbid [generalized anxiety disorder](#) (GAD). However, time to response was greater in patients with comorbidity than in patients with MDD only. From the data of all the patients meeting DSM-IV criteria for MDD in a double-blind, randomized trial ($n=368$), results from the subset of patients who had comorbid GAD ($n=92$) were analyzed separately and compared to results of the noncomorbid patients. Patients took once-daily doses of [venlafaxine](#) XR 75 mg, [fluoxetine](#) 20 mg, or placebo for 12 weeks. [Venlafaxine](#) doses could be increased to a maximum of 225 mg. According to the criteria of more than 50% reduction (from baseline) in the Hamilton-Depression (HAM-D) and Hamilton- Anxiety (HAM-A) scores, improvement with [venlafaxine](#) was significantly greater (p less than 0.05) than with placebo by 12 weeks of treatment. About one third of patients with comorbidity showed response at 4 weeks; however, overall, there was no evident trend for a placebo-drug difference until after the eighth week of treatment. Among patients without comorbidity, the placebo-venlafaxine difference was evident as early as week 2. By week 12, response rate was 66% on HAM-D and 59% on HAM-A for those taking [venlafaxine](#) and 36% and 24% for those taking placebo [9].

2) Immediate-Release

a) In an open, community-based study, [venlafaxine](#) effectively treated depression in 62% of patients. This study ($n=880$) accrued patients from 211 community-based physicians of whom 149 were family physicians, and 62 were psychiatrists; each physician could enter a maximum of 5 patients. After confirming the diagnosis of [major depression](#) using a patient and physician scale, patients began treatment with [venlafaxine](#) 37.5 mg twice daily for about 2 weeks with dose titration to a maximum of 375 mg/day depending on response. Of the 198 patients who withdrew from the study, 134 (15%) withdrew due to adverse effects; whereas, only 17 withdrew due to lack of efficacy. The primary outcome was a score of 1 or 2 on the Clinical Global Impressions (CGI) assessment; 522 (62%) patients achieved this outcome based on intent-to-treat. Headache (15%) and nausea (32%) occurred frequently during the first week of treatment but declined over the remainder of the study [11].

b) Once versus twice daily administration of [venlafaxine](#) immediate-release resulted in comparable reductions in depressive symptoms in patients treated for [major depression](#). In this double-blind, randomized study ($n=48$), patients received the same dose of [venlafaxine](#) once or twice daily for 6 weeks. The initial starting dose was 37.5 mg daily for both groups. This dose was continued for 1 week in the once daily group; whereas, patients in the twice daily group progressed to 75 mg daily on days 4 to 7. Dose titration continued until a maximum dose of 225 mg daily was reached. At 2 weeks, a nonsignificant trend for greater improvement on the Hamilton Rating Scale for Depression (HAM-D) and Montgomery-Asberg Depression Rating scale (MADRS) were observed in the twice daily versus once daily group; however,

differences between treatment groups were not significant at 6 weeks. Adverse effects were similar between treatments. This study suggests that once daily versus twice daily administration of immediate-release [venlafaxine](#) provides comparable efficacy while avoiding the inconvenience of more frequent administration [10].

3) Relapse Prevention

a) Results of the double-blind, randomized PREVENT (Prevention of Recurrent Episodes of Depression with [Venlafaxine](#) for Two Years) study demonstrated that [venlafaxine](#) extended-release (ER) was effective for the prevention of recurrent depressive episodes when given as long-term maintenance therapy. Patients with recurrent major depressive disorder (MDD) who had depressive symptoms for at least 1 month prior to the start of the study and a score of at least 18 on the 17-item Hamilton Depression Rating Scale (HDRS) at the time of randomization were randomized to [venlafaxine](#) ER 75 to 300 mg per day (n=821) or [fluoxetine](#) 20 to 60 mg per day (n=275) for 10 weeks in the acute phase. Drug therapy was initiated at [venlafaxine](#) 37.5 mg per day or [fluoxetine](#) 10 mg per day and titrated based on response and tolerability. Patients who achieved response (defined as HDRS score of 12 or less or a decrease from baseline of 50% or more) or remission (defined as HDRS score of 7 or less), remained on double-blind [venlafaxine](#) ER or [fluoxetine](#) during the 6-month continuation phase. Patients who remained responders after the continuation phase were then enrolled into 2 consecutive 12-month maintenance phases. Response and remission for [venlafaxine](#) ER and [fluoxetine](#) were evaluated in the acute and continuation phases, while overall the study was powered for the primary endpoint of time to recurrence of depression (primary definition: HDRS score of greater than 12 and a reduction from acute phase baseline that was not more than 50% at 2 consecutive visits or at last valid visit; secondary definition: HDRS total score of greater than 12 or less than a 50% reduction in HDRS score from acute phase baseline) in the maintenance phase for [venlafaxine](#) ER compared to placebo. Patients in the different groups were similar with the exception of [fluoxetine](#)-treated patients being more severely depressed in the acute phase than [venlafaxine](#)-treated patients (p=0.047). At the end of the 10-week acute phase, the response rate for both [venlafaxine](#) ER and [fluoxetine](#) was 79% while remission rates were 49% and 50%, respectively (p=0.719 overall comparison). The continuation phase did not demonstrate any significant differences between treatment groups at end point with regard to the proportion of patients who maintained or improved response ([venlafaxine](#) ER, 82% and [fluoxetine](#), 84%; p=0.697). The response rates for [venlafaxine](#) ER and [fluoxetine](#) at the end of the continuation phase were 90% and 92%, respectively, while the remission rates were 72% and 69%, respectively (p=0.696 overall comparison). [Venlafaxine](#) ER responders after the 6-month continuation phase were then randomized to double-blind treatment with [venlafaxine](#) ER (mean daily dose, 220.8 mg) or placebo, while [fluoxetine](#) responders continued taking [fluoxetine](#) during the first one-year maintenance phase. The efficacy evaluable population for the first 12 months of maintenance included 129 patients receiving [venlafaxine](#) ER and 129 patients receiving placebo. At study endpoint, [venlafaxine](#) ER was associated with a significantly lower risk of recurrence based on both the primary and secondary definitions of recurrence (p=0.005 and p less than 0.001, respectively). The probability of recurrence, using the primary definition, at 12 months was 42% for placebo (95% confidence interval (CI), 31.8 to 52.2%) and

23.1% for [venlafaxine](#) ER (95% CI, 15.3 to 30.9%) ($p=0.005$ for the comparison). Again, responders after the first 12-month maintenance phase were enrolled in another 12-month maintenance phase, and [venlafaxine](#) responders were randomized to [venlafaxine](#) ER ($n=43$; mean daily dose, 213.5 mg) or placebo ($n=40$) while [fluoxetine](#) responders continued taking [fluoxetine](#). Placebo responders continued to receive placebo in the second maintenance phase. At study endpoint, [venlafaxine](#) ER was associated with a significantly longer time to recurrence compared with placebo (p less than 0.001). The probability of recurrence at month 12 was 44.8% for placebo (95% CI, 27.6 to 62%) and 8% for [venlafaxine](#) ER (95% CI, 0 to 16.8%) (p less than 0.001). The rate of response or remission at 12 months was also significantly higher in the [venlafaxine](#) group compared with the placebo group (93% and 63%, respectively; $p=0.002$) [12][13][14].

4j) Treatment-Resistant Depression

a) Nine out of 11 patients experienced a sustained improvement in depression with combined [venlafaxine](#) and tricyclic antidepressant treatment. In this open trial, 10 out of 11 patients had recurrent depression while 1 patient had a severe major depressive episode. Two patients also had comorbid [panic disorder with agoraphobia](#), and 1 had [obsessive-compulsive disorder](#). Nine patients had failed [fluoxetine](#) or [paroxetine](#) therapy, and 9 had failed augmentation with [lithium](#), [thyroxine](#), [citalopram](#), [pindolol](#), [methylphenidate](#), and [buspirone](#). Eight patients received [clomipramine](#) 150 to 375 mg/day, and 3 patients received [imipramine](#) 200 to 250 mg/day. Over 6.5 months, patients had [venlafaxine](#) added to their regimen titrated from 37.5 mg daily to 150 mg every 12 hours. Using the Hamilton Rating Scale for Depression (HAM-D), 9 patients had a sustained positive response while 7 patients attained a complete remission. The 2 patients with panic- agoraphobic symptoms also showed improvement; however, there was no improvement in the one patient's obsessive-compulsive symptoms. The dosage range of [venlafaxine](#) that allowed for maximum improvement was 75 to 300 mg/day [15].

b) In an 8-week, open trial ($n=159$), 58% and 28% of patients achieved a good response and remission, respectively. All patients had treatment-resistant depression defined by failure to respond to at least 1 other antidepressant; 45% of patients had used 3 or more medications for this episode of depression. [Venlafaxine](#) was initiated at 37.5 mg twice daily with titration to 375 mg/day over 4 weeks, if needed; the mean daily dose was 260 mg/day at 8 weeks. The mean Hamilton Rating Scale for Depression (HAM-D), Montgomery-Asberg Depression Rating Scale, and the Clinical Global Impression Scale scores were significantly lower at 8 weeks ($p=0.0001$). The mean HAM-D decreased from 25.6 at baseline to 11.4 at 8 weeks. Compared to many antidepressant trials, the number of patients who stopped treatment due to adverse effects was only 8% [16].

1j) With Electroconvulsive Therapy

a) [Venlafaxine](#) combined with electroconvulsive therapy (ECT) proved to be efficacious in patients with treatment-resistant depression; however, an adverse effect of the therapy was asystole in 4 of 13 patients. Mean score on the Hamilton Rating Scale for Depression (HAM-D) was 35.84 prior to combination treatment

compared with 15.30 at day 28 of treatment (p less than 0.004, posttreatment compared with baseline). Overall, 10 of 13 (76.9%) patients were considered responders by ratings of 'much improved' or 'very much improved' on the Clinical Global Impression (CGI) subscale for improvement and a 50% reduction of the HAM-D score from baseline. During the 28-day treatment period, mean doses of venlafaxine were 265.38 mg (range 150 to 375 mg) and were not changed during ECT. Mean number of ECT sessions per patients was 8.38 (range 6 to 12). Related to safety, rapid reduction in heart rate followed by asystole occurred in 4 of 110 sessions involving 4 different patients. Atropine treatment restored normal sinus rhythm in the 4 affected patients. None of the study subjects had a history of cardiovascular disease. All 4 who experienced asystole were taking daily venlafaxine doses of 300 mg or more (mean 337.5 mg, range 300 to 375 mg) compared with subjects in whom asystole did not occur (mean dose 265.38 mg, range 150 to 375 mg). Propofol, atropine, and succinylcholine were given immediately before ECT. No complications, such as prolonged seizures, were reported. The authors noted that subjects taking relatively low doses (150 to 225 mg/day) were as responsive to combination venlafaxine-ECT treatment as those who were receiving 300 mg/day or more [17].

d) Pediatric:

1) Separate results from two similar double-blind, randomized controlled trials indicated there was no significant difference between [venlafaxine](#) extended-release (ER) and placebo for the treatment of [major depressive disorder](#) (MDD) in pediatric patients aged 7 to 17 years, while pooled results demonstrated a greater improvement with [venlafaxine](#) XR over placebo in adolescents (aged 12 to 17 years) only. After a single-blind, placebo lead-in phase, study participants (mean age, approximately 12 years) were randomized to [venlafaxine](#) ER at a flexible dose based on body weight ($n=184$) or placebo ($n=183$) for up to 8 weeks. The primary efficacy measure was the change from baseline in the Childhood Depression Rating Scale-Revised (CDRS-R) score at 8 weeks. Secondary efficacy measures included the 21-Item Hamilton Rating Scale for Depression (HAM-D)-21, Montgomery-Asberg Depression Rating Scale (MADRS), Clinical Global Impression-Severity (CGI-S), and CGI-Improvement scales. Efficacy and safety data from both studies were analyzed separately and a post hoc subgroup analysis by age was completed on the pooled data from both studies. The combined study discontinuation rates were 27% and 32% for patients receiving placebo versus [venlafaxine](#) XR, respectively. Based on CDRS-R score changes from baseline, no statistically significant differences were seen between [venlafaxine](#) ER and placebo in either study at week 8 or at any other time period, nor were there any statistically significant differences in secondary outcome measures or response rates. In the post hoc subgroup analysis by age, children aged 7 to 11 years demonstrated no differences between treatment groups on any outcome measure. Adolescents aged 12 to 17 years who received [venlafaxine](#) XR experienced a greater decrease in CDRS-R score from an adjusted mean baseline score of 56.9 to 32.5 at week 8 compared to a decrease from 56.9 to 36.9 at week 8 for the placebo group ($p=0.022$); however, the effect size was small (0.28136), indicating minimal clinical relevance. Adjusted mean change scores at week 8 also demonstrated greater improvement with [venlafaxine](#) XR over placebo for CGI-S

($p=0.035$), MADRS total ($p=0.037$), HAM-D depressed mood item ($p=0.022$) but not HAM-D-21 total. Additionally, there was a difference in responder rates based on CDRS-R score (71% for [venlafaxine XR](#) versus 55% for placebo; $p=0.018$). Commonly reported adverse events for [venlafaxine XR](#) and placebo were abdominal pain (21% and 10%, respectively) and dizziness (12% and 6%, respectively). Serious adverse events (SAEs) were reported in 7% and 2% of patients receiving [venlafaxine XR](#) and placebo, respectively. Of the SAEs, [venlafaxine XR](#) patients experienced [suicidal ideation](#) ($n=4$), hostility ($n=3$), and manic reaction ($n=2$). There were no completed suicides [18].

4.5.1.A.3] [Panic disorder](#), With or without [agoraphobia](#)

FDA Labeled Indication

a) Overview

FDA Approval: Adult, yes (extended-release capsule only); [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:

[Venlafaxine](#) hydrochloride extended-release capsules are indicated for the treatment of [panic disorder](#), with or without [agoraphobia](#), as defined in DSM-IV [5].

Results of a double-blind, randomized, controlled trial ($n=664$) comparing [venlafaxine](#) extended-release (XR), [paroxetine](#), and placebo for the treatment of [panic disorder](#) in adults demonstrated greater improvement with [venlafaxine XR](#) and [paroxetine](#) than with placebo [24].

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

c) Adult:

1) Results of a double-blind, randomized, controlled trial which compared [venlafaxine](#) extended-release (XR), [paroxetine](#), and placebo for the treatment of [panic disorder](#) in adults demonstrated greater improvement with [venlafaxine XR](#) and [paroxetine](#) than with placebo. Although [paroxetine](#) was included, this study was powered to examine differences between [venlafaxine XR](#) and placebo only. Nondepressed outpatients with a diagnosis of [panic disorder](#) with or without [agoraphobia](#) were randomized to fixed-dose [venlafaxine XR](#) 75 mg/day ($n=166$; baseline median full-symptom panic attacks, 6), [venlafaxine XR](#) 150 mg/day ($n=168$; baseline median full-symptom panic attacks, 6.5), [paroxetine](#) 40 mg/day ($n=166$; baseline median full-symptom panic attacks, 6), or placebo ($n=163$; baseline median full-symptom panic attacks, 6.1) orally for 12 weeks. The primary efficacy measure was the percentage of patients free from full-symptom panic attacks in the last observation carried forward (LOCF) end point analysis, which was assessed using the Panic and Anticipatory Anxiety Scale (PAAS). Secondary efficacy measures included the [Panic Disorder Severity Scale](#), Clinical Global Impressions-Severity (CGI-S) and -Improvement (CGI-I) scales, response (CGI-I of 1 (very much improved) or 2 (much improved)), and remission (no full-symptom panic attacks on the PAAS and CGI-S scores of 1 (not at all ill) or 2 (borderline ill)). Results of the LOCF end point analysis on the intent-to-treat population (ITT) demonstrated

that patients who received [venlafaxine](#) XR or [paroxetine](#) experienced significantly greater improvement on most efficacy measures than those who received placebo. The three active treatment groups had a significantly higher percentage of patients (p less than 0.001 for each active treatment group relative to placebo) in the ITT population who were panic-free in the 2 weeks before study endpoint compared with the placebo group ([venlafaxine](#) XR 75 mg, 54.4%; [venlafaxine](#) XR 150 mg, 59.7%; [paroxetine](#), 60.9%; and placebo, 35.3%). The difference from baseline in median full-symptom panic attacks was also significantly greater in the three active treatment groups compared to placebo (-4.8) at week 12 ([venlafaxine](#) XR 75 mg, (-6) p less than or equal to 0.001; [venlafaxine](#) XR 150 mg, (-6.5) p less than or equal to 0.001, [paroxetine](#), (-6) p less than or equal to 0.01). Additionally, all three active treatment groups had significantly greater mean reductions in [Panic Disorder](#) Severity Scale total score compared with placebo at week 12 (p less than 0.001 for each active treatment group relative to placebo). At the LOCF end point, the percentage of patients who responded to active treatments were 76.6% ([venlafaxine](#) XR 75 mg), 79.2% ([venlafaxine](#) XR 150 mg), and 80.6% ([paroxetine](#)) compared with 55.8% of patients receiving placebo (p less than 0.001 for all three active treatment groups relative to placebo). The percentage of patients who achieved remission while receiving active treatments were 43.0% ([venlafaxine](#) XR 75 mg), 43.4% ([venlafaxine](#) XR 150 mg), and 44.4% ([paroxetine](#)) compared with 23.7% of patients receiving placebo (p less than 0.001 for each active treatment group relative to placebo). Adverse events were mild or moderate and similar between treatment groups. The most common adverse effects reported with [venlafaxine](#) at either dose were sweating, dry mouth, anorexia, and tremor [24].

2j) In 2 double-blind, multicenter, placebo-controlled studies, [venlafaxine](#) hydrochloride extended-release capsules were significantly more effective than placebo in improving the outcomes in patients with [panic disorder](#). The 12-week studies included adult outpatients who met DSM-IV criteria for [panic disorder](#), with or without [agoraphobia](#). Patients were given fixed doses of either [venlafaxine](#) (75 or 150 mg/day in one study and 75 or 225 mg/day in the other study) or placebo. Efficacy was evaluated using the outcomes of 3 variables: the percentage of patients free of full-symptom panic attacks on the Panic and Anticipatory Anxiety Scale (PAAS); the mean change from baseline to endpoint on the [Panic Disorder](#) Severity Scale (PDSS) total score; and the percentage of patients who were much or very much improved (rated as responders) on the Clinical Global Impressions (CGI) Improvement scale. Efficacy was significantly greater with [venlafaxine](#) than with placebo. A dose-response relationship was not established in these fixed-dose studies. A longer-term study designed to study [relapse](#), responders from the 12-week open-phase study with [venlafaxine](#) extended-release capsules (75 to 225 mg/day) were randomly assigned to continue on [venlafaxine](#) (75, 150, or 225 mg/day) or switched to placebo. [Relapse](#) was defined as having 2 or more full-symptom panic attacks per week for 2 consecutive weeks or discontinuation due to loss of efficacy. Prior to being randomized, patients were in response status on average for 34 days. Results from the randomized phase indicated that patients who continued to receive [venlafaxine](#) took a significantly longer time to [relapse](#) [5].

4.5.1.A.4] Social phobia

FDA Labeled Indication

a) Overview

FDA Approval: Adult, yes (extended-release capsule and tablet only); **Pediatric, no**

Efficacy: Adult, Effective; Pediatric, Evidence favors efficacy

Recommendation: Adult, Class IIa; **Pediatric, Class IIb**

Strength of Evidence: Adult, Category B; Pediatric, Category B

See Drug Consult reference: **RECOMMENDATION AND EVIDENCE RATINGS**

b) Summary:

Venlafaxine extended-release capsules and tablets are approved for treating adults with **social anxiety disorder**, also known as **social phobia**, as defined in DSM-IV [5][6].

Low-dose (75 mg/day) and high-dose (150 to 225 mg/day) **venlafaxine** extended-release were both effective for the treatment of generalized **social anxiety disorder** during a 6-month, randomized, placebo-controlled trial (n=395) [22].

Results of a randomized, placebo-controlled trial (n=293) demonstrated the efficacy and safety of **venlafaxine** extended-release in the treatment of pediatric **social anxiety disorder** [23].

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

c) Adult:

1) Venlafaxine extended-release (XR) was safe and effective for the treatment of generalized **social anxiety disorder** (GSAD) in adults. During a double-blind, parallel-group study, adult outpatients (n=395; mean age, approximately 37 years) diagnosed with GSAD as defined by DSM-IV were randomized to a fixed dose of **venlafaxine** XR 75 mg per day (n=128), a flexible higher dose of **venlafaxine** XR 150 to 225 mg per day (n=129), or placebo (n=129) for 28 weeks. The primary efficacy measure was the change on the Liebowitz Social Anxiety Scale (LSAS). Some secondary efficacy measures included the proportion of responders (ie, Clinical Global Impressions (CGI) Global Improvement Item score of 1 or 2) and the proportion of remitters (ie, LSAS score of 30 or less). The proportion of patients who withdrew from the study for any reason was 66% in the placebo group and 48% and 56% in the fixed- and flexible-dose **venlafaxine** XR groups, respectively (p less than 0.05 for both). The final intent to treat population was 364, and the mean daily dose of **venlafaxine** XR at week 28 was 72.2 mg for the fixed-dose group and 213.7 mg for the flexible-dose group. The adjusted mean change from baseline in the LSAS total score at week 28 was -38.1 for the fixed-dose group, -37.6 for the higher, flexible-dose group, -37.8 for the combined **venlafaxine** XR groups, and -23.5 for the placebo group (p less than 0.001 for all comparisons). At the last observation carried forward study endpoint, 33% and 58% of placebo and **venlafaxine** XR-treated patients (combined and at low- and high-dose), respectively, were responders (p less than 0.001 compared with placebo) and 16% and 31% of placebo and **venlafaxine** XR-treated patients (combined and at low- and high-dose), respectively, were remitters (p less than 0.01 compared with placebo). Although not powered for comparison of **venlafaxine** groups, the study did not find significant differences in response or remission rates between the low and higher dosages of **venlafaxine** XR. The most common treatment-emergent adverse events associated with **venlafaxine** XR at a higher rate than placebo included abnormal ejaculation (12 to 18% vs 1%) anorexia (19 to 22% vs 3%), asthenia (19 to 25% vs 11%), dizziness (19 to 24% vs 12%), dry mouth (19 to 23% vs 6%), nausea (34 to 37% vs 10%), and somnolence (24 to 29% vs 14%). One patient in the high-dose **venlafaxine** XR group with a history of 2 other suicide attempts committed suicide on day 86 of the study. There were 3 other reports of **suicidal ideation** or attempts during the study: two patients receiving **venlafaxine** XR 75 mg/day and one patient receiving placebo [22].

d) Pediatric:

1j) Results of a randomized, placebo-controlled trial (n=293) demonstrated the efficacy and safety of [venlafaxine](#) extended-release (XR) in the treatment of [social anxiety disorder](#) (SAD) in children and adolescents. Pediatric outpatients (aged 8 to 17 years) diagnosed with SAD were randomized to [venlafaxine](#) XR or placebo for 16 weeks. The initial dose of [venlafaxine](#) XR was 37.5 mg orally daily and was titrated based on patient weight to a maximum dose of 225 mg daily. The primary efficacy measures included the child or adolescent version of the Social Anxiety Scale (SAS-CA) and the Clinical Global Impression Improvement (CGI-I) score which identified response rates. A positive response was defined as a CGI-I score of 1 (very much improved) or 2 (much improved) at week 16. Of the 293 patients randomized, 285 were included in the intent-to-treat population (ITT) for analysis. Treatment was discontinued in 35% of patients receiving [venlafaxine](#) XR and in 27% of patients receiving placebo. The most common reason for discontinuation was lack of efficacy. The mean daily dose of [venlafaxine](#) XR ranged from 2.6 to 3 mg/kg. The mean SAS-CA scores improved from a baseline of 64.8 +/- 10.1 to 40.6 +/- 1.25 at week 16 for the [venlafaxine](#) XR group and from 66.2 +/- 10.6 to 47.7 +/- 1.25 for the placebo group. The ITT random regression analyses indicated a statistically significant improvement associated with [venlafaxine](#) XR compared with placebo (p=0.001) on the SAS-CA. Rates of response adjusted for baseline SAS-CA score were 56% (95% confidence interval (CI), 47% to 64%) for patients receiving [venlafaxine](#) XR and 37% (95% CI, 29% to 45%) for patients receiving placebo. The effect of baseline SAS-CA score was not significant (p=0.172), whereas effect of treatment was (p=0.001) when both were entered in the logistic regression model. The effect size (Hedge's g=0.46) and number needed to treat (n=5; 95% CI, 3 to 13) indicate a moderately clinically meaningful benefit. Common treatment-emergent adverse effects reported with [venlafaxine](#) XR that were more common than with placebo included asthenia (20% vs 9%; p=0.012), anorexia (22% vs 3%; p less than 0.001), and nausea (23% vs 11%; p=0.012). Adverse effects were generally mild to moderate and most often resolved with continued therapy. Discontinuation of treatment due to adverse events occurred in 4% and 6% of [venlafaxine](#) XR and placebo patients, respectively. There were 3 cases of [suicidal ideation](#) in patients receiving [venlafaxine](#) (two during treatment and one during tapering) compared with no cases reported with placebo. There were no suicides or suicide attempts reported during the study period [23].

4.5.2] Non FDA Uses

4.5.2.A] [Venlafaxine](#) Hydrochloride

4.5.2.A.1] [Antineoplastic adverse reaction - Neurotoxicity](#)

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:

Venlafaxine extended-release completely resolved paclitaxel-disabling neurosensory toxicity in a 69-year-old woman [50].

See Drug Consult reference: Chemotherapy-Induced [Peripheral Neuropathy](#)- Guidelines

c) Adult:

1) In a single case report, [venlafaxine](#) hydrochloride extended-release (XR) completely resolved paclitaxel-disabling neurosensory toxicity in a 69-year-old woman receiving [paclitaxel](#) 175 mg/m² and [carboplatin](#) for ovarian [cancer](#). After failure of [clonazepam](#) 1.5 mg, [venlafaxine](#) XR 37.5 mg administered orally twice daily quickly (within 2 days) and completely resolved pin pricks and paresthesias in both her hands and wrists [50].

4.5.2.A.2] Attention deficit hyperactivity disorder

a) Overview

FDA Approval: Adult, no; [Pediatric, no](#)

Efficacy: Pediatric, Evidence favors efficacy

Recommendation: [Pediatric, Class IIb](#)

Strength of Evidence: Pediatric, Category B

See Drug Consult reference: [RECOMMENDATION AND EVIDENCE RATINGS](#)

b) Summary:

[Venlafaxine](#) was similar to [methylphenidate](#) for the treatment ADHD in pediatric patients in a randomized, double-blind, comparison trial (n=38) [31].

Results of a prospective, 6-week, open-label trial (n=13) demonstrate that [venlafaxine](#) therapy improved symptoms of [attention deficit hyperactivity disorder](#) in pediatric patients [32].

c) Pediatric:

1) [Venlafaxine](#) was similar to [methylphenidate](#) for the treatment ADHD in pediatric patients in a randomized, double-blind, comparison trial (n=38). Eligible outpatients had confirmed ADHD (DSM-IV-text revision criteria and Kiddie Schedule for Affective Disorders and Schizophrenia-Present and Lifetime diagnostic interview) and at least 1.5 standard deviations above normal for patient age and gender on the ADHD Rating Scale-IV (ADHD-RS-IV) School Version total and/or subscale scores. Patients were equally randomized to receive [venlafaxine](#) (n=19; mean age, 9.42 +/- 2.19 years; 74% male) or [methylphenidate](#) (n=19; mean age, 9.57 +/- 1.86 years; 68% male) for 6 weeks. The study regimens were based on weight: [venlafaxine](#) 50 mg orally daily (weight less than 30 kg) to 75 mg daily (weight greater than 30 kg) and [methylphenidate](#) 20 mg/day or 30 mg/day, respectively. Both treatments were titrated up during the first 2 to 3 weeks ([venlafaxine](#), week 1: 25 mg once a day; week 2: 25 mg in the morning and midday; and if needed for week 3: 25 mg in the morning, 25 mg midday, and 25 mg at 4 PM; [methylphenidate](#), week 1: 5 mg in the morning and 5 mg at midday; week 2: 10 mg in the morning and 10 mg at midday; and if needed for week 3: 10 mg in the morning, 10 mg at midday, and 10 mg at 4 PM). All patients were Persian and had newly diagnosed combined subtype ADHD. While both treatment arms demonstrated statistically significant within-group improvement in Parent and Teacher ADHD-RS-IV from baseline to 6 weeks (p less than 0.001), there was no significant difference between [venlafaxine](#) and [methylphenidate](#) in the change in mean Parent and Teacher ADHD-RS-IV

from baseline to 6 weeks (primary outcome; intent-to-treat). At 6 weeks, change in the mean Parent ADHD-RS-IV scores from baseline was -14.15 +/- 7.01 for [venlafaxine](#) and -16.63 +/- 8.59 for [methylphenidate](#) (difference, $p=0.33$). Similarly at 6 weeks, change in the mean Teacher ADHD-RS-IV from baseline was -13.05 +/- 4.77 for [venlafaxine](#) and -15.31 +/- 8.13 for [methylphenidate](#) (difference, $p=0.3$). Adverse events were tolerable and mild to moderate in severity and were not significantly different except for insomnia (10.52% vs 52.63%) and headaches (15.78% vs 57.89%) in the [venlafaxine](#) and [methylphenidate](#) arms, respectively. The most commonly reported events were abdominal pain, somnolence, and restlessness [31].

2) Symptoms of [attention deficit hyperactivity disorder](#) (ADHD) improved following [venlafaxine](#) treatment in pediatric patients. In a prospective, open-label study, children and adolescents ($n=13$) 6 to 15 years of age (mean age, 9.9 years) with ADHD and without comorbid depression received [venlafaxine](#) (initial, 18.75 mg/day, titrated up to 56.25 mg/day as tolerated; mean dose, 40.38 mg/day) for 6 weeks. No other psychotropic medications were allowed during the study. Response was defined as a rating of "very much improved" or "much improved" on the Clinical Global Impression (CGI)-Improvement scale. The total mean score of the Connor Parent Index was significantly improved from baseline to endpoint (20 vs 14.46; p less than 0.002), including significant improvement in individual index items such as "short attention span", "easily distracted", "easily frustrated", and "mood changes quickly" (p less than 0.05, all values). The CGI-Severity rating was also significantly improved from baseline to endpoint (p less than 0.05) and there was a 61.5% response rate as assessed by the CGI-I scale. Three of the five patients who did not respond to [venlafaxine](#) treatment had comorbid conditions, including tic disorder or [oppositional defiant disorder](#). The authors suggest that comorbid conditions with ADHD may be complicated by [venlafaxine](#) therapy. Transient adverse effects included stomachache ($n=2$), somnolence ($n=2$), and headache ($n=1$). Three cases of sedation were observed at higher doses (56.25 mg/day) and one patient, with a comorbid tic disorder, experienced behavioral activation and worsening of ADHD symptoms. Larger, controlled studies are needed to further establish the safety and efficacy of [venlafaxine](#) in the treatment of ADHD in pediatric patients [32].

4.5.2.A.3] [Binging - Eating disorder](#)

a) Overview

FDA Approval: Adult, no; [Pediatric, no](#)

Efficacy: Adult, Evidence favors efficacy

Recommendation: Adult, Class IIb

Strength of Evidence: Adult, Category B

See Drug Consult reference: [RECOMMENDATION AND EVIDENCE RATINGS](#)

b) Summary:

Results of a retrospective study ($n=35$) indicate [venlafaxine](#) may be an effective treatment for [binge-eating disorder](#) associated with [obesity](#) [34].

c) Adult:

1) The results of a small, retrospective study indicate that [venlafaxine](#) may be an effective treatment for [binge-eating disorder](#) associated with [obesity](#). Overweight or obese patients with [binge-eating disorder](#) ($n=35$) received [venlafaxine](#) alone ($n=29$) or as an adjunctive therapy

(n=6) at a mean dose of 222 mg/day (dosage range, 75 to 300 mg/day) for a median of 120 days (range, 28 to 300 days). Some patients also received behavioral dietary counseling (91%), formal psychotherapy (3%) or both (3%). In the combination therapies, [venlafaxine](#) was added to [amitriptyline](#), [bupropion](#), [paroxetine](#), or [sertraline](#). Patients on single or combination [venlafaxine](#) therapy with active or inactive [binge-eating disorder](#), showed significant reductions in weekly binge frequency, Clinical Global Impressions-Severity of Illness (CGI-S) scale scores for binge eating and [depressive disorder](#), body mass index, weight, and waist circumference (all values, p less than 0.0001). Fifteen (43%) patients lost at least 5% of their baseline weight and 7 (20%) patients lost at least 10% of their baseline weight. The most common adverse events were dry mouth (23%), sexual dysfunction (14%), insomnia (14%), nausea (11%), and blood pressure changes (46%). A small increase in pulse was also observed over time [34].

4.5.2.A.4] [Bipolar disorder](#), depressed phase

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:

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](#) in a randomized, double-blind, comparative trial (n=174) [28].

[Venlafaxine](#) monotherapy was more effective than [lithium](#) for the initial treatment of bipolar II [major depressive episode](#) with similar occurrence of hypomanic switch in a prospective, randomized, open-label, clinical trial (n=83) [29].

[Venlafaxine](#) and [paroxetine](#) were both significantly effective adjunctive treatments for breakthrough [depression in bipolar](#) disorder, but a slightly higher risk of hypomanic or manic switch was observed with [venlafaxine](#) in a single-blind, randomized, comparative trial (n=60) [30].

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 [28]. Therefore, effective treatment of acute bipolar [depressive episode](#) is critical for reduction of morbidity and mortality in patients with [bipolar affective disorder](#). However, practice guidelines are essentially empirical and inconsistent rendering them somewhat inadequate. The American Psychiatric Association recommends that initial treatment of bipolar II [major depressive episode](#) begin with mood stabilizer monotherapy or with combination mood stabilizer

and the lowest-effective dose, short-term antidepressant therapy [29]. Conversely, the Expert Consensus Panel for [Bipolar Disorder](#) suggests that antidepressant monotherapy may be considered in bipolar II [major depressive episode](#) in patients with a minimal history of [hypomania](#). Other practice guidelines or expert panels propose mood stabilizer monotherapy for mild to moderate bipolar II depression and combination mood stabilizer-antidepressant therapy for more severe depression or avoidance of antidepressant treatment completely [29]. Historical studies have provided evidence that antidepressants, particularly medications with combined noradrenergic-serotonergic activity (eg, [venlafaxine](#), tricyclic antidepressants) may increase the risk of switch into a hypomanic or [manic episode](#) [30]. 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](#); however, the risk of (hypo)mania switch was significantly higher with [venlafaxine](#) compared with [bupropion](#) and [sertraline](#) [28]. Similarly, a randomized, comparative trial revealed adjunctive antidepressant treatment with [venlafaxine](#) or [paroxetine](#) were both significantly effective for the treatment of breakthrough depression in patients with [bipolar disorder](#), but a slightly higher risk of hypomanic or manic switch was observed with [venlafaxine](#) [30]. In contrast, [venlafaxine](#) monotherapy was found to be an effective alternative to [lithium](#) for the initial treatment of bipolar II [major depressive episode](#) with low occurrence of hypomanic switch in a prospective, randomized trial [29]. Additional studies incorporating larger patient population sizes, distinguishing between inclusions of bipolar I or bipolar II patients, a clear definition of switch, determination of duration of antidepressant treatment and replication of study findings would be beneficial for consistent and effective control of [major depressive episode](#) and minimization of (hypo)manic switch in [bipolar affective disorder](#) [28][29][30].

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, double-blind, double-dummy, comparative 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 statistically significant between groups and controlling for [lithium](#) use did not alter the results. However, the risk of switching to mania or [hypomania](#) was higher 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 ($p=0.002$), and controlling for [lithium](#) demonstrated similar results (p less than 0.01). 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](#) ($p=0.01$, adjusted for [lithium](#)) and between [venlafaxine](#) and [bupropion](#) (p less than 0.01, adjusted for [lithium](#)), while there was no significant difference between [sertraline](#) and [bupropion](#) ($p=0.9$). 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 in the [bupropion](#), [sertraline](#) and [venlafaxine](#) groups, respectively ($p=0.052$), 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 lower with [bupropion](#) when compared with [venlafaxine](#) (p less than 0.01) 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 [28].

b) Venlafaxine monotherapy was more effective than [lithium](#) for the initial treatment of bipolar II [major depressive episode](#) with similar occurrence of hypomanic switch in a prospective, randomized, open-label, clinical trial ($n=83$). DSM-IV bipolar II adult patients with an ongoing acute (less than 2 years) or chronic (2 years and over) [major depressive episode](#) (MDE) were included in the trial. All patients had a baseline, 17-item Hamilton Depression Rating Scale (HAM-D 17) score of 18 or higher. Patients were excluded if they had a history of mania or [psychosis](#) in the preceding 3 months or if they were nonresponsive to [venlafaxine](#) or [lithium](#) during the current [major depressive episode](#). Concomitant antidepressants, mood stabilizers, neuroleptics, tranquilizers or over-the-counter antidepressant agents were not allowed. Any previously established psychotropic regimens were discontinued prior to randomization. Concomitant [zolpidem](#), [zaleplon](#) or [trazodone](#) was allowed for severe insomnia. Eligible patients aged 37.2 ± 13.4 years (43% male) were randomized to either [venlafaxine](#) ($n=43$) or [lithium](#) ($n=40$) for 12 weeks. [Venlafaxine](#) was initiated at 37.5 mg/day, increased to 75 mg/day during week 1, and titrated in 37.5-mg or 75-mg increments to a maximum dose of 375 mg/day by week 4. The highest tolerated dose was maintained for an additional 8 weeks. [Lithium](#) was initiated at 600 mg/day for 1 week, and titrated to 900 mg/day to reach a minimum required serum [lithium](#) level of 0.5 millimoles (mmol)/L during week 2. [Lithium](#) dose was optimized to a therapeutic steady-state [lithium](#) level between 0.5 and 1.5 mmol/L by week 4, and maintained for an additional 8 weeks. At baseline, study subjects had a history of bipolar II for 18.5 ± 12 years, and MDE for 15 ± 19.3

months. Patients experienced their first MDE at age 18.7 +/- 8.7 years and first hypomanic episode at age 20.7 +/- 8.2. The mean baseline HAM-D 28 score for the [venlafaxine](#) group was 28.9 +/- 7.5 compared with 28.58 +/- 7.5 for the [lithium](#) group. At the end of the study, 79.1% of patients in the [venlafaxine](#) group and 37.5% of patients in the [lithium](#) group completed the study. Based on the modified intent-to-treat analysis, there was a greater reduction in HAM-D 28 (primary endpoint) with [venlafaxine](#) monotherapy compared with [lithium](#) monotherapy, with an estimated difference in overall change of -6.57 points (95% CI, -11.97 to -1.18; p=0.017). [Venlafaxine](#) monotherapy yielded a greater number of responders (at least 50% reduction in HAM-D 28) compared with [lithium](#) monotherapy (60.4% vs 20%; p less than 0.0005). The proportion of remitters (final HAM-D 28 score of 8 or less) was also significantly greater with [venlafaxine](#) compared with [lithium](#) (44.2% vs 7.5%; p less than 0.0005). There was no significant difference between treatment groups in the mean Young Mania Rating Scale (YMRS) scores at any week. One patient in the [venlafaxine](#) and [lithium](#) arm each, experienced subsyndromal hypomanic and hypomanic symptoms (2.4% vs 2.6%; p=0.99). One patient in the [venlafaxine](#) group discontinued due to induction of [hypomania](#) and 1 patient in the [lithium](#) group discontinued due to increasing [suicidal ideation](#). Other common adverse effects included headaches (34.9% vs 32.5%), nausea/vomiting (25.6% vs 47.5%), dry mouth (32.6% vs 10%), somnolence (30.2% vs 22.5%) and difficulty thinking (16.3% vs 32.5%) in the [venlafaxine](#) and [lithium](#) groups, respectively. The authors noted study limitations of lack of a placebo/control group, short treatment duration and small sample population size [29].

c) [Venlafaxine](#) and [paroxetine](#) were both significantly effective adjunctive treatments for breakthrough depression in patients with [bipolar disorder](#), but a slightly higher risk of hypomanic or manic switch was observed with [venlafaxine](#) in a single(rater)-blind, randomized, comparative trial (n=60). Study subjects had a DSM-IV diagnosis of [bipolar disorder](#) and a [major depressive episode](#) indicated by a score of greater than 17 on the 17-item Hamilton Rating Scale for Depression (HAM-D 17). All patients were on at least 1 mood stabilizer ([lithium](#), [valproate](#), [carbamazepine](#), other) for at least 6 months prior to the current [depressive episode](#), and required to maintain the same mood stabilizer therapy at optimal therapeutic blood level ranges throughout the study period. Recent treatment with antidepressant or antipsychotics during the previous 3 months was not permitted. Patients were excluded if they were at risk for suicide attempt, currently abusing alcohol or other psychotropics, using concomitant anxiolytics, had previously used [venlafaxine](#) or [paroxetine](#), or scored 8 or higher on the Young Mania Rating Scale (YMRS). Eligible patients were randomly assigned to either [venlafaxine](#) (n=30; age 45.5 years (yr) +/- 13.7 yr; 70% female) or [paroxetine](#) (n=30; age 47.1 yr +/- 15.2 yr; 63% female) for 6 weeks. Based on response and tolerability, the [venlafaxine](#) group received 37.5 mg twice daily, titrated by 75-mg/day increments. The mean [venlafaxine](#) dose at the end of the trial was 179.2 +/- 91 mg/day. The [paroxetine](#) group received 20 mg/day titrated by 10-mg/day increments, and the final mean [paroxetine](#) dose was 32.3 +/- 11.2 mg/day. Based on the modified intent-to-treat population, defined as all patients who took at least 1 dose of study medication and had at least 1 study assessment, both [venlafaxine](#) and [paroxetine](#) provided significant improvement in HAM-D 28 scores from baseline to endpoint (primary endpoint). The change in HAM-D 28 score was from 21.2 +/- 3.2 to 12.2 +/- 6.1 for [venlafaxine](#) and 20.7 +/- 3 to 13.8 +/- 6.7 for [paroxetine](#) (both p less than 0.0001). [Venlafaxine](#) was numerically superior to [paroxetine](#) in efficacy and in

switch rates but not statistically different. The response rate, defined as a reduction in HAM-D 28 score by 50% or more from baseline, was 48% in the [venlafaxine](#) group compared with 43% in the [paroxetine](#) group. The remission rate, defined as a HAM-D score of less than 10 and a Clinical Global Impressions (CGI) severity score of 1 was 33% in the [venlafaxine](#) group compared with 32% in the [paroxetine](#) group. Switch to [hypomania](#) occurred in 4 patients (13%) in the [venlafaxine](#) group: 2 switched to [hypomania](#) (YMRS score=12 and 14) and 2 switched to full mania (YMRS score=23 and 31) compared with 1 patient (3%) in the [paroxetine](#) group who switched to [hypomania](#) (YMRS score=17) (p not significant). The (hypo)mania episodes resolved but were more than 1 week in duration despite prompt treatment and antidepressant discontinuation. One [manic episode](#) required hospitalization. Common adverse events included nausea (17% vs 23%), dry mouth (13% vs 3%), dizziness (10% vs 7%), headache (3% vs 10%) and insomnia (10% vs 0%) in the [venlafaxine](#) and [paroxetine](#) groups, respectively. The authors note study limitations of lack of a placebo group, single-blind study design, small sample population size and short follow-up period [30].

4.5.2.A.5] [Cancer pain](#)

See Drug Consult reference: Management of Cancer-Related Pain in Adult Patients

4.5.2.A.6] [Cerebrovascular accident - Depression](#)

a) Overview

FDA Approval: Adult, no; [Pediatric, no](#)

Efficacy: Adult, Evidence favors efficacy

Recommendation: Adult, Class IIb

Strength of Evidence: Adult, Category B

See Drug Consult reference: [RECOMMENDATION AND EVIDENCE RATINGS](#)

b) Summary:

During an open study, 12 post-stroke patients benefited from [venlafaxine](#) treatment administered within 2 weeks post-stroke [35].

c) Adult:

1) Twelve patients who received [venlafaxine](#) within 2 weeks of a [stroke](#) showed a decrease in depressive symptoms without significant side effects. [Venlafaxine](#) was initiated at 75 mg daily with an increase to 150 mg daily after 2 days. Response was evaluated with the Hamilton Depression Rating Scale (HAM-D) and the Montgomery Asberg Depression Rating Scale (MADRS). After 5 weeks of treatment, the HAM-D score decreased from 24.3 to 7.25, and the MADRS decreased from 26.7 to 7.6. None of the patients stopped treatment due to side effects. The dose was decreased in 1 patient due to agitation; 3 patients had nausea during initiation of treatment. Based on results of this open study, a controlled clinical trial may be warranted in patients with depression secondary to [stroke](#) [35].

4.5.2.A.7] [Depression - Perimenopausal disorder](#)

a) Overview

FDA Approval: Adult, no; **Pediatric, no**

Efficacy: Adult, Evidence favors efficacy

Recommendation: Adult, Class IIb

Strength of Evidence: Adult, Category B

See Drug Consult reference: [RECOMMENDATION AND EVIDENCE RATINGS](#)

b) Summary:

In a small, open-label trial, extended-release [venlafaxine](#) therapy reduced depressive symptoms and baseline vasomotor symptoms in depressed perimenopausal women [33].

c) Adult:

1) In a small, 8-week, open-label trial, treatment with extended-release [venlafaxine](#) reduced depressive and vasomotor symptoms in depressed perimenopausal women. Women were deemed perimenopausal if they reported one or more climacteric symptoms (hot flushes, sweating, vaginal dryness, [menstrual irregularity](#)) and were between 42 to 51 years old. Additional study inclusion criteria comprised of presence of current [depressive disorder](#) confirmed by the DSM-IV Axis I disorders, no psychotropic [therapy or estrogen replacement](#) therapy (ERT) for 1 month, and use of a non-hormonal method of contraception. The study was initiated on day 10, 11, or 12 of the menstrual cycle. Participants (n=16) were given 37.5 mg extended-release [venlafaxine](#) orally once daily during week 1 and 75 mg daily during week 2. Data collection instruments included the Hamilton depression (Ham-D) rating scale, Hamilton anxiety (Ham-A) rating scale, clinical global impression severity (CGI-S), and a standard measure of 4 subscales: psychiatric, somatic, vasomotor, and sexual dysfunction. Follow-up visits were conducted after weeks 2, 4, and 8. When clinically necessary, dosage was increased in 75-mg increments after the week 2 and week 4 visit. In the 14 participants that completed the study, psychotropic effects of [venlafaxine](#) were observed by week 2 and were sustained through week 8. Antidepressant response (greater than 50% Ham-D reduction) was observed in 13 subjects (81.3%) and remission (Ham-D less than or equal to 7) was achieved in 12 subjects (75%) after 8 weeks of [venlafaxine](#) therapy (75 to 225 mg/day). At week 8, GCS total scores were reduced by 60%, depression subscores reduced by 71%, and anxiety subscores reduced by 63%. Vasomotor and sexual dysfunction subscores were not significantly affected from baseline scores; although, for 10 participants with baseline vasomotor subscores greater than 0, a 37.5% decline was observed at week 8 (p less than 0.05). However, the investigators contend that a placebo effect cannot be ruled out for the decreased vasomotor symptoms observed in women who had baseline vasomotor symptoms and that further studies are required to address the usefulness of [venlafaxine](#) in treating perimenopausal depression [33].

4.5.2.A.8] [Diabetic neuropathy](#)**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:

Dose-related, clinically significant reductions in pain were demonstrated with [venlafaxine](#) extended-release therapy during a randomized, double-blind placebo-controlled study (n=244) [36].

One case report demonstrated the effectiveness of [venlafaxine](#) depot combined with [gabapentin](#) for the relief of severe pain of [peripheral diabetic neuropathy](#) [37].

[Venlafaxine](#) relieved the unremitting pain of [diabetic peripheral neuropathy](#) in 8 patients who found no relief from a variety of other treatments [38].

In a series of 11 patients, [venlafaxine](#) relieved the pain associated with [diabetic peripheral neuropathy](#) [39].

c) Adult:

1j) The efficacy of [venlafaxine](#) extended-release (XR) for the treatment of [painful diabetic neuropathy](#) was demonstrated during a double-blind, randomized, controlled trial involving 244 adult outpatients with metabolically stable type 1 or 2 [diabetes](#) and bilateral distal [peripheral neuropathy](#) of at least moderate severity for 3 months or longer. Patients were randomized to [venlafaxine](#) XR at a dose of 75 mg or 150 to 225 mg daily or placebo orally for 6 weeks. Primary efficacy measures included scores on the daily 100 mm Visual Analog Pain Intensity (VAS-PI) and Pain Relief (VAS-PR) scales. Of the 244 patients randomized, 242 made up the intent-to-treat (ITT) population and 202 completed the study. Pain intensity scores at baseline were 69.9 mm in the [venlafaxine](#) XR 75 mg group, 67.3 mm in the [venlafaxine](#) XR 150 to 225 mg group, and 68.8 in the placebo group. At week 6 using last observation carried forward (LOCF) analysis, the reductions in mean adjusted pain intensity scores were 32%, 50%, and 27% for [venlafaxine](#) XR 75 mg, [venlafaxine](#) XR 150 to 225 mg, and placebo, respectively. Higher-dose [venlafaxine](#) XR was significantly more effective than placebo (p less than 0.001) and [venlafaxine](#) XR 75 mg (p =0.006) at week 6, while [venlafaxine](#) XR 75 mg was not superior to placebo. With regard to pain relief, [venlafaxine](#) 150 to 225 mg was significantly more effective than placebo by week 6 (59.9 mm versus 43.6 mm, respectively; p less than 0.001), and [venlafaxine](#) XR 75 mg was not superior to placebo (51 mm versus 43.6 mm). The percentages of patients who were considered responders (at least 50% reduction from baseline on the VAS-PI score) in the [venlafaxine](#) 150 to 225 mg and placebo groups at week 6 (LOCF) were 56% and 34%, respectively (p less than 0.01). The number needed to treat (NNT) for 50% reduction in pain intensity with [venlafaxine](#) XR 150 to 225 mg was 4.5 at week 6. The most common treatment-emergent adverse events associated with both [venlafaxine](#) XR groups were nausea and somnolence. [Electrocardiogram](#) (ECG) rhythm changes occurred in 6%, 5%, and 1% of the [venlafaxine](#) XR 75 mg, [venlafaxine](#) XR 150 to 225 mg, and placebo groups, respectively. A total of 7 patients on [venlafaxine](#) XR had clinically important ECG changes during treatment. Adverse events leading to study withdrawal did not significantly differ between the 3 treatment groups [36].

2j) The combination of [venlafaxine](#) depot (75 mg three times daily) and [gabapentin](#) relieved the severe pain of [peripheral diabetic neuropathy](#) in a 26-year-old woman with a 13-year history of [type 1 diabetes](#). The patient developed burning pain and tenderness of the arms and legs and distal edema of the legs in association with [bulimia](#) and [high blood glucose](#) levels. Her pain was not relieved despite the following treatments: [paracetamol](#) and dextropropoxyphene for 7 months; [amitriptyline](#), [clonazepam](#), [gabapentin](#), and [diclofenac](#) for 4 months; and

tramadol and buprenorphine for 3 months; then eight different analgesics. Placing her legs in buckets of cold water for long periods of time provided the only relief, and she was bedridden otherwise. She developed orthostatism, preproliferative retinopathy and moderate signs of distal sensory, autonomic, and motor neuropathy. She was started on venlafaxine depot (75 mg/day, later increased to 75 mg three times daily), and after 7 months was greatly improved with controllable distal pains. Analgesics were reduced, but the reduction of gabapentin caused pain to return [37].

3) Venlafaxine relieved the unremitting pain of diabetic peripheral neuropathy in 8 patients who found no relief from a variety of other treatments. Nonsteroidal anti-inflammatory drugs, acetaminophen, carbamazepine, capsaicin, and amitriptyline were not successful, either due to lack of efficacy or to intolerable side effects. Within 2 to 8 days of beginning treatment, all 8 patients responded to venlafaxine 37.5 mg twice daily with dramatic relief in symptoms associated with painful peripheral neuropathy. Two patients experienced nausea, which resolved rapidly without interruption of treatment. No serious side effects were observed [38].

4) Eleven patients with type 2 diabetes mellitus and painful diabetic neuropathy had a 75% to 100% reduction in pain within a few days after beginning venlafaxine [39]. All patients had been treated unsuccessfully with other medications known to alleviate the pain associated with diabetic peripheral neuropathy. Within 3 to 14 days after starting venlafaxine 37.5 to 75 mg/day, all patients noted a 75% to 100% reduction in pain. No adverse effects were reported. Two patients who were pain-free stopped taking venlafaxine and had a recurrence of pain 2 to 3 days later. When venlafaxine was restarted, the pain was relieved promptly. This series suggests that venlafaxine may be useful for treating diabetic neuropathy.

4.5.2.A.9] 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:

During 9-week, open study, venlafaxine was effective for treating dysthymic disorder in 14 patients [40].

c) Adult:

1) In a 9-week, open study, 10 and 4 patients showed a complete and modest response, respectively, to venlafaxine for the treatment of dysthymic disorder [40]. After determination of baseline Hamilton Rating Scale for Depression (HAM-D-17) and Beck Depression Inventory (BDI) scores, patients were treated with venlafaxine 37.5 mg daily which was titrated to a maximum dose of 225 mg daily. Seven patients improved with venlafaxine 75 mg daily; whereas, 7 required the maximum dose. Six patients had a HAM-D-17 of less than 4 at 9 weeks, and met proposed criteria for remission of dysthymic disorder. This study suggests that

venlafaxine is useful for treating [dysthymic disorder](#); however, long-term, placebo-controlled studies are needed.

4.5.2.A.10] Hot sweats, Breast cancer-related

a)] Overview

FDA Approval: Adult, no; [Pediatric, no](#)

Efficacy: Adult, Evidence favors efficacy

Recommendation: Adult, Class IIb

Strength of Evidence: Adult, Category B

See Drug Consult reference: [RECOMMENDATION AND EVIDENCE RATINGS](#)

b)] Summary:

In two randomized, double-blind, crossover trials, treatment with oral extended-release [venlafaxine](#) 37.5 mg or 75 mg per day yielded modest but statistically significantly greater reductions in hot flash frequency, severity, and bother compared to placebo in [breast cancer](#) survivors [41].

In a randomized, double-blind German study (n=80), treatment with oral [venlafaxine](#) was significantly more effective than [clonidine](#) in decreasing the frequency of hot flashes among adult women with primary [breast cancer](#) [42].

c)] Adult:

1)] General Information

a)] Practice guidelines and limited clinical trials support short-term efficacy of oral [venlafaxine](#) in [breast cancer](#) patients with moderate to severe hot flashes [43][41][42][44]. In two, 14-week, randomized, double-blind, placebo-controlled, crossover trials assessing 6 weeks of treatment with extended-release (ER) [venlafaxine](#), primarily in Caucasian [breast cancer](#) survivors, both doses administered demonstrated modest reductions in primary outcomes of hot flash frequency (both self-reported and physiologically-assessed), severity, and bother compared to placebo [41]. Furthermore, a strong placebo effect with subjective (self-reported) hot flash measures was evident in this study. In another 4-week, randomized, double-blind, controlled study in adult women with primary [breast cancer](#) (n=80), treatment with oral [venlafaxine](#) decreased hot flash frequency to a greater extent compared to [clonidine](#) [42]. Treatment-emergent adverse events included dry mouth, severe constipation, and sleep difficulties in these studies [41][42].

2)] Clinical Trials

a)] Treatment with oral extended-release (ER) [venlafaxine](#) 37.5 mg (low-dose) or 75 mg (high-dose) per day yielded modest but statistically significantly greater reductions in hot flash frequency, severity, and bother compared to placebo in [breast cancer](#) survivors in two randomized, double-blind, crossover trials. Nondepressed adult women with a history of [breast cancer](#) (the use of [tamoxifen](#) and/or aromatase inhibitors were not allowed), experiencing 1 or more daily hot flashes without current treatment, and with no other [cancer](#) were enrolled in the two, 14-week crossover

trials. In the low-dose trial (n=52; mean age, 50.5 years; 91% Caucasian), patients were randomized to receive either oral [venlafaxine](#) ER 37.5 mg (n=26) or placebo (n=26) once daily for 6 weeks; subsequently, without a washout period, patients from each arm were crossed over to the other arm to continue study drug for another 6 weeks. The high-dose trial (n=18; mean age, 53 years; 90% Caucasian) had a similar design except [venlafaxine](#) ER (n=9) was dosed at 37.5 mg orally once daily during weeks 1 and 6 and at 75 mg once daily during weeks 2 to 5. Hot flash frequency was evaluated using both a weekly, 24-hour (hr), ambulatory sternal skin conductance monitor (physiological) as well as using patient-maintained electronic event markers and written diaries that were completed during one 24-hr period each week (self-reported). Additional assessments included hot flash severity and bother (both rated using separate 10-point numeric scales; range; 0=not at all and 10=extremely severe or bothersome) and hot flash interference (assessed using the validated Hot Flash-Related Daily Interference Scale). Data for the 2 crossover trials were analyzed separately using mixed linear models and adjusted means. For the low- and high-dose groups, study populations at week 14 (n=45 and n=15, respectively) provided 86% and 43% power, respectively (using a two-sided paired t-test), to detect a medium effect size (equal to 0.5 standard deviation), and 80% power to detect a large effect size (equal to 0.78 standard deviation) in the high-dose group. At baseline, mean physiological hot flash frequency and self-reported hot flash frequency per 24 hr among study patients (pooled data from both studies) was 7.46 and 6.02, respectively. After 6 weeks of therapy, the physiological hot flash frequency per 24 hr decreased from baseline by 22% (adjusted mean reduction, -1.7) in the low-dose [venlafaxine](#) group compared to no change in the placebo group (p less than 0.001), yielding an effect size of 0.16 (95% confidence interval (CI), 0.09 to 0.23). In the high-dose trial, [venlafaxine](#)-treated patients experienced a 14% (adjusted mean reduction, -1.03) decrease from baseline in physiological hot flash frequency per 24 hr compared to a 13% (adjusted mean increase, +0.98) increase in the placebo group (p=0.013) (effect size, 0.22; 95% CI, 0.05 to 0.39). Self-reported hot flash frequency decreased from baseline by 42% and 18% (p less than 0.001) in the [venlafaxine](#) ER and placebo groups, respectively, in the low-dose trial (effect size, 0.22; 95% CI, 0.16 to 0.29), and by -25% and -4% (p=0.001), respectively, in the high-dose trial (effect size, 0.24; 95% CI, 0.1 to 0.38). Additionally, both [venlafaxine](#) doses reduced hot flash severity (low-dose, -7% vs +6%; high-dose, -27% vs -5%; p less than 0.001 for both) and bother (low-dose, -4% vs 10%; high-dose, -19% vs +6%; p less than 0.001 for both) to a greater extent compared to placebo. However, significantly greater improvements from baseline in hot flash interference occurred only in the high-dose [venlafaxine](#) group (placebo, -36% vs 75 mg/day, -47%; p=0.003). Overall, there were no significant differences between the [venlafaxine](#) and placebo groups for secondary outcomes, which included negative affect, fatigue, sleep quality, and quality of life. While the frequency of adverse events was similar among [venlafaxine](#)- and placebo-treated patients, severe constipation and dry mouth occurred more frequently in the low- and high-dose [venlafaxine](#) groups compared to placebo. This study was limited by the placebo effect that was evident for self-reported hot flashes at both [venlafaxine](#) doses; additionally, blinding was inadequate as almost three-quarters of study patients were able to correctly identify receipt of placebo by study end [41].

b) Treatment with oral [venlafaxine](#) was significantly more effective than [clonidine](#) in decreasing the frequency of hot flashes among adult women with primary [breast cancer](#) in a randomized, double-blind German study (n=80). Enrollees, who were

required to have bothersome hot flashes at least 14 times/week and for at 4 weeks prior to study entry, were randomized to receive either [venlafaxine](#) 37.5 mg (n=40) or [clonidine](#) 0.075 mg (n=40) orally twice daily for 4 weeks. Concurrent therapy with [tamoxifen](#), aromatase inhibitors, or gonadotropin-releasing agonists was allowed provided patients were on it for at least a month and it was continued throughout the study. Patients with [metastatic disease](#) were excluded from the study. The primary efficacy measure was the patient-recorded hot flash frequency at end of therapy. The hot flash severity score was adapted from the North Central Cancer Treatment Group, as a secondary efficacy endpoint. At baseline 61% of patients in each group were over 50 years of age, with 90% and 82% receiving concurrent antihormone therapy in the [venlafaxine](#) and [clonidine](#) groups, respectively. At baseline, the median daily hot flash frequency was 11 (range, 3 to 23) and 9.7 (range, 2.4 to 20.9) in the [venlafaxine](#) and [clonidine](#) groups, respectively, the median daily hot flash severity was 1.7 (range, 1 to 3) and 1.8 (range, 1 to 3.1), respectively, and the median daily hot flash scores were 18.1 (range, 3 to 47.14) and 17.6 (range, 3 to 65.5), respectively. Among the evaluable population (n=63), the median hot flash frequency decreased from baseline by 7.6 hot flashes/day in the [venlafaxine](#) group compared to 4.85 hot flashes/day in the [clonidine](#) group at week 4 (p=0.025). Additionally, more patients in the [venlafaxine](#) group had a 75% reduction in baseline daily hot flash frequency (29% vs 12%), and a complete reduction of hot flashes occurred only in the [venlafaxine](#) group (n=6). The median daily hot flash score decreased by 39% (standard deviation (SD), 5.4) and 57% (SD, 6.2) in the [venlafaxine](#) and [clonidine](#) groups, respectively (p=0.043). Ten patients discontinued treatment due to adverse events ([venlafaxine](#), n=6; [clonidine](#), n=4). Among the [venlafaxine](#) and [clonidine](#) groups, dry mouth (35.5% vs 51.1%), tiredness (35.5% vs 42.4%), and restless sleep (35.5% vs 51.5%) were the most commonly reported events, respectively; however, between-group differences were not statistically significant [42].

4.5.2.A.11] Menopausal flushing

a) Overview

FDA Approval: Adult, no; [Pediatric, no](#)

Efficacy: Adult, Evidence favors efficacy

Recommendation: Adult, Class IIb

Strength of Evidence: Adult, Category B

See Drug Consult reference: [RECOMMENDATION AND EVIDENCE RATINGS](#)

b) Summary:

In a randomized, double-blind study (n=80), treatment with oral, extended-release [venlafaxine](#) 75 mg per day for 12 weeks significantly reduced patient-perceived effects of postmenopausal hot flashes as well as improved mental health and vitality outcomes compared to placebo [45].

Extended-release [venlafaxine](#) was effective for treating hot flashes in women with a history of [breast cancer](#) (BC) as well as in patients with reluctance to hormonal treatment due to fear of BC during a 4-week, double-blind, randomized, placebo-controlled trial (n=229) [46]; efficacy was maintained during an 8-week, open-label phase of this trial [47].

During a 4-week, open, pilot study (n=21), [venlafaxine](#) was effective in decreasing the incidence of hot flashes in men receiving androgen deprivation therapy for [prostate cancer](#) [48].

Low-dose [venlafaxine](#) was effective in reducing the incidence and severity of hot flashes in women with a history of [breast cancer](#) (n=23) and in men who had received androgen deprivation therapy (n=5) [49].

c) Adult:

1) Treatment with oral, extended-release (ER) [venlafaxine](#) 75 mg per day for 12 weeks significantly reduced patient-perceived effects of postmenopausal hot flashes as well as improved mental health and vitality outcomes compared to placebo in a randomized, double-blind study (n=80). Women who were in natural or [surgical menopause](#) and were experiencing more than 14 hot flashes per week were included. Women concurrently on antidepressants or chemotherapy were excluded. Study patients were randomized to receive either [venlafaxine](#) ER 75 mg (n=40; mean age, 52.7 years) or placebo (n=40; mean age, 51.6 years) for 12 weeks, and followed at 4, 8 and 12 weeks after initiation of therapy. [Venlafaxine](#) was initiated at a dose of 37.5 mg for 1 week and then increased to 75 mg/day for the remainder of the study. The patient-perceived hot flash score, assessing interference of hot flashes with daily living, was calculated at monthly visits using a 5-point Likert scale. Additionally, patients completed a daily hot flash diary, noting the frequency and severity of hot flashes (score range, 1=mild to 4=very severe). At baseline, the majority of patients (approximately 80%) were in natural menopause, the mean patient-perceived hot flash score was higher in the [venlafaxine](#) group (72.4 vs 61.5; p=0.07), and alcohol use was more common in the [venlafaxine](#) group (67.6% vs 36.8%; p=0.008). At the 3-month follow-up, the average between-group difference in the mean patient-perceived hot flash score from baseline was 21 points (95% confidence interval (CI), 11 to 32; p less than 0.001). Although reductions in the score were evident at month 1 in both groups, between-group differences emerged at the month 2 visit, with a mean score of 35.3 in the [venlafaxine](#) group at month 3 compared with a rebound in the placebo group. Accounting for the heterogeneity in the treatment effect during the follow-up visits (p=0.01), the estimated treatment effect of [venlafaxine](#) remained significant compared to placebo (28 points; 95% CI, 16 to 39; p less than 0.001), with a 51% reduction in the mean score compared to a 15% reduction in the placebo group. Based on diary data, hot flash severity and frequency scores were reduced in both groups with no statistically significant between-group differences. [Venlafaxine](#) was associated with a mean reduction of 2.6 points (95% CI, -2.3 to 7.5; p=0.25 vs placebo) in severity score and 1.4 episodes (95% CI, -0.7 to 3.6) from baseline. Quality of life measures, assessed monthly using a modified Short Form-36 Health Survey mood scale, showed statistically significant improvements from baseline for the mental health (between-group difference, 8.7; 95% CI, 2.8 to 14.6) and vitality (between-group difference, 8.5; 95% CI, 2.8 to 14.2) domains compared to placebo (p=0.004 for both). Treatment-emergent adverse events occurring commonly and more frequently than placebo included dry mouth (81% vs 44%), sleeplessness (88% vs 47%), and decreased appetite (81% vs 53%). Among 19 patients who withdrew from the study ([venlafaxine](#), n=11; placebo, n=8), difficulty sleeping, decreased libido, nausea, and anxiety accounted for the main reasons for withdrawal in the [venlafaxine](#) group. Notably, 93% of the venlafaxine-treated study participants chose to continue [venlafaxine](#) treatment following study completion [45].

2) Extended-release [venlafaxine](#) was effective for the treatment of hot flashes in [breast cancer](#) (BC) survivors as well as in patients with reluctance to hormonal treatment due to fear of BC in a four-week, double-blind, randomized, placebo-controlled trial. Eligible patients (n=229) were required to have troublesome hot flashes at a frequency of at least 14 times/

week and present for at least 1 month prior to study entry, and a performance status of 0 to 1 on the Eastern Cooperative Oncology Group scale. Patients were assigned to one of the following four treatment groups: 1) 4 weeks treatment with placebo (n=56), 2) 4 weeks treatment with 37.5 mg [venlafaxine](#) daily (n=56), 3) 1 week of 37.5 mg daily followed by 75 mg daily for 3 weeks (n=55), and 4) 1 week of 37.5 mg daily, 1 week of 75 mg daily, and 2 weeks of 150 mg daily (n=54). Use of antiestrogens ([tamoxifen](#) and [raloxifene](#)) and aromatase inhibitors was permitted provided they were initiated 4 weeks prior to study entry and continued during the entire study duration. The primary endpoint was the mean daily hot flash activity, which included the number of hot flashes, and a combined score of frequency and severity (range, 1=mild to 4=very severe). At baseline, study patients had a mean hot flash frequency and average scores of 8 and 13.3, respectively. Based on the modified intent-to-treat analysis of 191 evaluable patients at the end of the study, patients receiving [venlafaxine](#) of any strength showed significant improvement in the median daily hot flash activity scores at week 4 from baseline (37%, 61%, and 61% reduction in the [venlafaxine](#) 37.5 mg, 75 mg, and 150 mg groups, respectively) compared with 27% in the placebo group (all p less than 0.001 vs placebo). A reduction of more than 50% in hot flash activity occurred in 45%, 63%, and 55% of patients in the [venlafaxine](#) 37.5 mg, 75 mg, and 150 mg groups, respectively, versus 20% in the placebo group. No difference in efficacy was noted between the 75 mg and the 150 mg groups; however, treatment was better tolerated in the 75 mg group. Treatment-emergent adverse events included dry mouth, nausea, decreased appetite, and constipation, which occurred more frequently in the [venlafaxine](#) 75- and 150-mg dose groups than placebo [46].

a) An 8-week, open-label, longitudinal extension of this trial demonstrated that efficacy of [venlafaxine](#) in reducing hot flash activity was maintained. Of the 157 patients from the 4-week, randomized, placebo-controlled trial that entered the open-label continuation phase, 102 patients were evaluated for efficacy. [Venlafaxine](#) dose was titrated to the optimal dose, ranging from 37.5 to 150 mg/day. At 8 weeks, the [venlafaxine](#) doses used were 37.5 mg (n=26), 75 mg (n=35), 112.5 mg (n=6), and 150 mg (n=34). Overall, a mean 60% to 68% reduction from baseline (week 1 of placebo-controlled phase) in hot flash frequency was reported at study end. While patients who received the 37.5 mg dose in the placebo-controlled phase experienced an additional mean 26% reduction in hot flash scores, the approximate 60% reduction in scores seen patients in the 75- and 150-mg dose groups during the placebo-controlled phase was maintained during the open-label extension. Common adverse events in the continuation phase included decreased appetite (10%), constipation (30%), and dry mouth (41%) [47].

3) Low-dose [venlafaxine](#) decreased hot flash activity by 81% in men receiving androgen deprivation therapy for [prostate cancer](#). In this open, pilot study, 21 men were treated with [venlafaxine](#) 12.5 mg twice daily for 4 weeks. Using a diary, patients recorded the number and severity of daily hot flashes. Of the 21 enrolled, 16 were evaluable for efficacy. The average number of daily hot flashes decreased from 10 at baseline to 6 after 4 weeks of treatment. This was accompanied by a decrease in severe and very severe hot flashes from 2.3 to 0.6 daily at 4 weeks. At 4 weeks, 52% of patients wished to continue [venlafaxine](#) treatment. Nausea was the primary adverse effect and required withdrawal of treatment in 3 patients [48].

4) Low-dose [venlafaxine](#) was effective in reducing the incidence and severity of hot flashes in women with a history of [breast cancer](#) (n=23) and in men who had received androgen

deprivation therapy (n=5). Patients received [venlafaxine](#) 25 mg daily for 5 weeks. The average number of hot flashes per day decreased from 6.6 to 4.3 by the end of the treatment period. Fifteen (54%) patients reported a 50% or greater decrease in the incidence of hot flashes (P less than 0.0002). Two patients discontinued treatment due to adverse effects of [venlafaxine](#). Results of this study were consistent with previous studies [49].

4.5.2.A.12] Migraine; Prophylaxis

See Drug Consult reference: Migraine -- Recommendations for Prophylaxis in Adults

4.5.2.A.13] [Obsessive-compulsive disorder](#)

a) Overview

FDA Approval: Adult, no; [Pediatric, no](#)

Efficacy: Adult, Evidence favors efficacy

Recommendation: Adult, Class IIa

Strength of Evidence: Adult, Category B

See Drug Consult reference: [RECOMMENDATION AND EVIDENCE RATINGS](#)

b) Summary:

[Venlafaxine](#) extended-release (XR) was as effective as [paroxetine](#) in the primary treatment of patients with [obsessive compulsive disorder](#) during a randomized, double-blind study (n=150) [51].

During a double-blind study (n=150), [venlafaxine](#) was effective as a crossover therapy in patients with [obsessive compulsive disorder](#) who did not respond to initial SSRI treatment [52].

[Venlafaxine](#) was effective for the treatment of [obsessive compulsive disorder](#) in two separate case studies involving patients who failed to respond to other treatments [53][54].

c) Adult:

1) Primary Therapy

a) [Venlafaxine](#) extended-release (XR) was as effective as [paroxetine](#) in the treatment of patients with [obsessive compulsive disorder](#) (OCD). In a randomized, double-blind, comparative study, patients (n=150) with OCD and a score of at least 18 (or at least 12, if only obsessions or only compulsions were present) on the Yale-Brown Obsessive Compulsive Scale (Y-BOCS) received either [venlafaxine](#) XR (initial, 75 mg/day, titrated to 300 mg/day by week 7) or [paroxetine](#) (initial, 15 mg/day, titrated to 60 mg/day by week 7) for 12 weeks. Both [paroxetine](#) and [venlafaxine](#) XR treatments were effective, producing mean reductions of 7.8 and 7.2 points, respectively, in the Y-BOCS score from baseline to endpoint. A significant decrease in the total Y-BOCS score from baseline was seen at week 3 for [venlafaxine](#) XR-treated patients (p=0.008) and at week 5 for patients in the [paroxetine](#) group (p=0.018). There were no significant differences in responder rates between treatment groups. In the [venlafaxine](#) XR group, 37% and 25% of patients were partial responders and full responders, respectively. Similarly, in the [paroxetine](#) group, 44% and 22% of patients were partial responders and full responders, respectively. Additionally, no significant differences were observed between the two treatments with regard to reduction of

anxious or depressive symptoms (as measured by the Hamilton Anxiety Scale and the Hamilton Rating Scale for Depression, respectively). For both treatments, most adverse effects were of mild or moderate severity and included somnolence, sweating, insomnia, and nausea [51].

2) Crossover Therapy

a) Patients with **obsessive-compulsive disorder** (OCD) refractory to initial treatment with a selective serotonin reuptake inhibitor (SSRI) responded to crossover therapy with another SSRI. In a double-blind switch study, patients (n=150) with primary OCD received **venlafaxine** (titrated to 300 mg/day) or **paroxetine** (titrated to 60 mg/day) for 12 weeks and then non-responders (n=43) were switched to the opposite therapy (**venlafaxine**, n=16; **paroxetine**, n=27) for an additional 12 weeks following a 4-week washout period between phases. Non-response was defined as a reduction in the Yale-Brown Obsessive-Compulsive Scale (Y-BOCS) below 25%. Following crossover, the Y-BOCS total score decreased in both groups from baseline (week 16) to endpoint, however the score was significantly reduced in paroxetine-treated patients (p less than 0.000), but not in venlafaxine-treated patients (p=ns). **Paroxetine** was statistically superior as compared with **venlafaxine** (p=0.017). The response rate during phase II of the study was 42% (18/43) overall, with a 16% (3/16) response rate in the **venlafaxine** group and a 56% (15/27) response rate in the **paroxetine** group (p=0.01). At the end of both phases 73% (109/150) of patients had responded to treatment. Adverse effects were similar between treatment groups including somnolence, sweating, headache, constipation, insomnia, nausea, change in mood, loss of libido, and dry mouth [52].

b) **Venlafaxine** was effective in the treatment of **obsessive-compulsive disorder** in a 28-year-old man [53]. He refused to take **clomipramine** after one 50-mg dose resulted in sedation, nausea, and dry mouth. A 3-week course of **paroxetine** 20 mg/day was discontinued after a lack of therapeutic response and the development of depersonalization, anxiety, and agitation. **Venlafaxine** 25 mg 3 times daily was initiated and titrated up to 75 mg 3 times daily; five weeks later his Yale-Brown Obsessive Compulsive Scale score had fallen from 24 to 7. Ten months later the patient was still responding well.

c) **Venlafaxine** may be useful in the treatment of **obsessive-compulsive disorder**. In one case report, a 66-year-old female with intermittent **major depression** and chronic **obsessive-compulsive disorder** refractory to **amitriptyline**, **fluoxetine**, and **clomipramine** was treated with **venlafaxine** at an initial dose of 25 mg/day, increased to 300 mg/day over 4 weeks. Her baseline NIMH Global Obsessive-Compulsive Scale score was 12. At 4 weeks, there was significant improvement in obsessive-compulsive symptoms but not in depressive symptoms. The dose of **venlafaxine** was increased to 375 mg/day over the next week; continued improvement in obsessive-compulsive symptoms, but not depressive symptoms, occurred over the next 8 weeks (NIMH score=4). At that time, the patient requested discontinuation of **venlafaxine** due to persisting depressive symptoms. She was tapered off **venlafaxine**, and within 7 days, her NIMH score went back to 12 [54].

4.5.2.A.14] **Posttraumatic stress disorder**

a) Overview

FDA Approval: Adult, no; **Pediatric, no**

Efficacy: Adult, Evidence favors efficacy

Recommendation: Adult, Class IIb

Strength of Evidence: Adult, Category B

See Drug Consult reference: **RECOMMENDATION AND EVIDENCE RATINGS**

b) Summary:

Venlafaxine extended-release was somewhat effective and well tolerated for the treatment of **posttraumatic stress disorder** in adult patients during both a 12-week double-blind, randomized controlled trial (n=538) [25] and a 6-month, double-blind, randomized controlled trial (n=329) [26].

c) Adult:

1) The efficacy and safety of **venlafaxine** extended-release (XR) were demonstrated in a 6-month, double-blind, randomized, controlled trial involving adult outpatients (n=329) with a primary diagnosis of **posttraumatic stress disorder** (PTSD). Patients were included in the study if they had a score of at least 60 on the Clinician-administered PTSD Scale (CAPS-SX-17) and had symptoms of PTSD for at least the previous 6 months. Following a washout period of at least 1 week, patients were randomized to flexible dose-venlafaxine XR (37.5 to 300 mg/day) (n=161; mean age, 42.2 years) or placebo (n=168; mean age, 40.5 years) for 24 weeks. The primary outcome measure was the change from baseline to week 24 in the CAPS-SX-17 score. Secondary measures included the frequency of remission (defined as 20 or less on the CAPS-SX-17), time to remission, and changes in symptom cluster scores. Of the 329 patients randomized, 224 (68%) completed the study. The mean maximum daily dose of **venlafaxine** XR was 221.5 mg/day. In the intention-to-treat group the CAPS-SX-17 total score decreased from 81 at baseline to 29.2 at week 24 in the venlafaxine-XR group compared with a decrease from 82.9 to 38.1 in the placebo group (p=0.006 for pairwise comparisons). The mean change scores from baseline to week 24 in completers were -59.2 and -54, for **venlafaxine** XR and placebo, respectively, and were not statistically significant (p=0.06). **Venlafaxine** XR demonstrated significantly greater improvement from week 4 onward (last observation carried forward (LOCF)). Mean LOCF change scores from baseline at week 12 were -47.5 for **venlafaxine** XR and -37.6 for placebo (p less than 0.001). Efficacy measures related to symptom cluster scores are outlined in the table [26]:

Outcome Measure	Venlafaxine XR Baseline	Venlafaxine XR Week 24	Placebo Baseline	Placebo Week 24
CAPS-SX-17 cluster B (reexperiencing) score	24.6	8	24.9	10.6
CAPS-SX-17 cluster C (avoidance/numbing) score	31.8	11.5	32.9	15.2
CAPS-SX-17 cluster D (hyperarousal) score	24.6	9.8	25.1	12.2

LOCF remission rates for **venlafaxine** XR and placebo were 50.9% and 37.5% (p=0.01), respectively, at week 24. Among completers, remission rates at week 24 for

venlafaxine XR and placebo were 44.7% and 33.3%, respectively (p=0.04). The most commonly reported adverse effects associated with venlafaxine XR were headache (28.6%), nausea (21.7%), and dizziness (18%). A weight change of at least 7% occurred more frequently in venlafaxine-treated patients (12%) than placebo-treated patients (7%) [26].

2j) The efficacy and safety of venlafaxine extended-release (XR) were demonstrated in a 12-week, double-blind, randomized, controlled trial involving adult outpatients (n=538) with a primary diagnosis of posttraumatic stress disorder (PTSD). Patients were included in the study if they had a score of at least 60 on the 17-item Clinician-administered PTSD Scale (CAPS-SX-17) and had symptoms of PTSD for at least the previous 6 months. Following a washout period of at least 1 week, patients were randomized to flexible-dose venlafaxine XR (75 to 300 mg/day) (n=179), flexible-dose sertraline (50 to 200 mg/day) (n=173), or placebo (n=179) for 12 weeks. The primary outcome measure was the last observation carried forward (LOCF) change from baseline in the CAPS-SX-17 score week 12. Secondary efficacy measures included changes in CAPS-SX-17 symptom cluster scores from baseline to endpoint and frequency of remission (defined as a CAPS-SX-17 score of 20 or less). Of the 538 patients randomized, 531 received treatment and 350 (66%) completed the study. The mean maximum daily prescribed dose of venlafaxine XR was 224.6 mg compared with 151.4 mg for sertraline. Change scores for the primary outcome measure and for the changes in CAPS-SX-17 symptom cluster scores at endpoint (LOCF) for venlafaxine and placebo are summarized in the table below. The magnitude of the differences in improvement between the venlafaxine XR and sertraline treatment groups with regard to both primary and secondary efficacy values was minimal and clinically insignificant [25]:

	Mean Change From Baseline (95% Confidence Interval)	Effect Size	p Value	
CAPS-SX-17 Outcome Measure	Venlafaxine XR	Placebo	Venlafaxine XR versus Placebo	Ven
Total Score	-41.51	-34.17	0.266	0.01
Reexperiencing Cluster Score	-12.54	-11.23	0.141	0.19
Avoidance Cluster Score	-16.99	-13.87	0.252	0.02
Hyperarousal Cluster Score	-11.57	-9.38	0.245	0.02

Remission rates at week 12 were 30.2% for venlafaxine XR and 19.6% for placebo (p less than 0.05). Venlafaxine XR treatment was well tolerated overall, with the most commonly reported adverse effects being headache (29%), nausea (24%), and dry mouth (18%) [25].

4.5.2.A.15] Premenstrual dysphoric disorder

a) Overview

FDA Approval: Adult, no; Pediatric, no

Efficacy: Adult, Evidence favors efficacy

Recommendation: Adult, Class IIb

Strength of Evidence: Adult, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:

Venlafaxine was superior to placebo for alleviation of [premenstrual dysphoric disorder](#) symptoms during a randomized controlled trial (n=143) [55].

c) Adult:

1) Venlafaxine was superior to placebo for alleviation of symptoms associated with [premenstrual dysphoric disorder](#) (PMDD). Women who met DSM-III-R diagnostic criteria for luteal phase dysphoric disorder (renamed PMDD in DSM-IV) after 3 levels of screening were randomly assigned to receive immediate-release [venlafaxine](#) or placebo continuously throughout 4 menstrual cycles. The initial dose of [venlafaxine](#) was 25 mg twice daily. In the absence of response, the dose could be increased by 50 mg daily at the beginning of each cycle, to a maximum of 200 mg daily. Data from 143 women were used in the efficacy analysis. The mean doses of [venlafaxine](#) were 84 mg/day in cycle 2, 115 mg/day in cycle 3, and 140 mg/day in cycle 4. In the first cycle, [venlafaxine](#) was associated with a 42% decrease in symptoms, as assessed by the Daily Symptom Report (DSR); the comparable decrease with placebo was 14% (p less than 0.001). In the second cycle and thereafter, decrease from baseline was 57% for [venlafaxine](#) and 31% for placebo. Improvement with [venlafaxine](#) was apparent in emotion, function, pain, and physical symptoms. There was no difference between [venlafaxine](#) and placebo in effect on appetite. The rate of response (greater than 50% improvement from baseline values) was 60% in the [venlafaxine](#) group and 35% in the placebo group (p=0.003). There were no serious adverse effects. The most common adverse effects associated with [venlafaxine](#) were nausea, which decreased from 36% in the first cycle to 15% in the second cycle; insomnia; dizziness; and decreased libido [55].

4.5.2.A.16] Tension-type headache; Prophylaxis

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:

Treatment with [venlafaxine](#) extended-release resulted in less days with [tension-type headache](#) when compared with placebo during a randomized, double-blind, controlled trial (n=60) [27].

c) Adult:

1) Results of a prospective, double-blind, randomized controlled trial demonstrated the efficacy and safety of [venlafaxine](#) extended-release (XR) for the prophylaxis of [tension-type headache](#) (TTH) in outpatients (n=60) without a current diagnosis of depression or anxiety disorders or a history of migraine attacks. Patients were randomized to [venlafaxine](#) XR (n=34) or placebo (n=26) orally daily for 12 weeks. The dose of [venlafaxine](#) XR was 75 mg daily for 1 week and then was increased to 150 mg daily for the remainder of the study period. The primary efficacy variable was the number of days with headache as assessed using patients' diaries. Diary completion rates upon study completion were 73.5% (25/34) for the group receiving [venlafaxine](#) XR and 57.7% (15/25) for the group receiving placebo.

The difference between [venlafaxine](#) XR and placebo in terms of days with headache when compared to baseline became statistically significant during period two (days 29 to 56) of the study and remained significant to study endpoint. The median days with headache at baseline for patients receiving [venlafaxine](#) XR and placebo were 13.5 and 11, respectively. The median days with headache for patients receiving [venlafaxine](#) XR and placebo during period two were 7.5 and 10.5, respectively ($p=0.05$) and 7 and 12.5, respectively ($p=0.033$) during period three (days 57 to 84). The differences between treatment groups with regard to hours with headache and total headache intensity index (HII) were not statistically significant at during any period. The median percentage change from baseline in headache frequency was a 44.8% decrease for [venlafaxine](#) XR and a 15.7% increase for placebo ($p=0.023$). The number of responders (defined as a reduction of at least 50% in days with headache, total hours, or HII score) at final evaluation was significantly different for the days with headache (44% and 15% for [venlafaxine](#) XR and placebo, respectively; p less than 0.05) but not for hours with headache or HII. The most common adverse events reported with [venlafaxine](#) XR use were vomiting (14.7%), nausea (8.8%), stomach ache (8.8%) and dizziness (8.8%) [27].

4.6] Comparative Efficacy / Evaluation With Other Therapies

4.6.A] [Bupropion](#)

4.6.A.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 [28].

4.6.B] [Buspirone](#)

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

a) One small study suggests that [venlafaxine](#) could be an alternative to [busPIRone](#) in patients with [generalized anxiety disorder](#) (GAD). As part of a larger study, patients with clinically significant signs of GAD received [venlafaxine](#) XR 75 milligrams (mg)/day ($n=4$), [venlafaxine](#) XR 150 mg/day ($n=4$), [busPIRone](#) 30 mg/day ($n=4$), or placebo ($n=2$) for 8 weeks. Improvement was defined as a greater than 50% decline on the Hamilton Anxiety Scale. Improvement was seen in 2 [venlafaxine](#) 75 mg patients, 2 [venlafaxine](#) 150 mg patients, and in 1 [busPIRone](#) patient. With this study's small sample size, no specific conclusions could be made [470].

b) [Venlafaxine](#) XR was useful for treating [generalized anxiety disorder](#) (GAD); for many efficacy measures, it appeared to be better than [busPIRone](#) [471]. Patients ($n=405$) with GAD diagnosed by DSM-IV criteria were randomly assigned to blinded treatment with placebo, [busPIRone](#) 30 milligrams(mg)/day, or [venlafaxine](#) XR 75 or 150 mg/day for 8 weeks; dosage for active treatment was titrated over 1 week. At study conclusion, the Hamilton Rating Scale for Anxiety (HAM-A) score was NOT statistically significant for any active treatment compared to placebo; however, the HAM-A psychic anxiety, HAM-A [anxious mood](#), and HAM-A tension scores were significantly lower for [venlafaxine](#) XR at selected weeks compared to placebo. [Venlafaxine](#) XR was superior to placebo and [busPIRone](#) for selected weeks on the Clinical Global Impressions-Severity of Illness scale (CGI-S) and CGI Improvement scale. Active treatments were generally well tolerated although 10%, 22%, 28%, and 15% of patients treated with placebo, [venlafaxine](#) XR 75 mg, [venlafaxine](#) XR 150 mg, and [busPIRone](#), respectively, stopped treatment due to adverse effects.

4.6.C] [Carbamazepine](#)

4.6.C.1] [Diabetic peripheral neuropathy](#)

a) In a randomized trial in adults with metabolically stable type 1 or 2 [diabetes](#) and [painful diabetic neuropathy](#) ($N=257$; mean baseline visual analogue scale (VAS) pain intensity score, 77 mm), 4 weeks of [carbamazepine](#) 200 mg/day, pregabalin 150 mg/day, or [venlafaxine](#) 150 mg/day resulted in significant improvement in pain scores for all 3 groups; however, pregabalin significantly improved VAS score compared with [carbamazepine](#) and [venlafaxine](#) (33.4 vs 39.6 and 46.6), with no difference between [carbamazepine](#) and [venlafaxine](#). A significantly greater proportion of patients achieved a 50% or greater reduction in mean pain score with pregabalin (76.7% vs 41.2% and 41.9%), as well as reduction in mean sleep and work interference scores. Pregabalin and [venlafaxine](#) significantly improved mean score for pain related to mood interference at day 35 compared with [carbamazepine](#). There was a significantly greater incidence of adverse events with pregabalin (73.2%) compared with [carbamazepine](#) (12.9%) and [venlafaxine](#) (63.9%), including dizziness (73.2% vs 11.8% and 41.9%) and somnolence (53.3% vs 3.5% and 23.3%) [473].

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) [475].

4.6.E] Clomipramine

4.6.E.1] Depression

a) Venlafaxine 105 milligrams/day (average dose) tended to be more effective than clomiPRAMINE 105 milligrams/day (average dose) for the treatment of depression in a 6-week study with 102 patients; however, the difference was not statistically significant [467]. Patients were assessed using the Hamilton Depression Rating Scale, Montgomery-Asberg Depression Rating Scale, and the Clinical Global Impressions scale. Venlafaxine was associated with fewer anticholinergic side effects and a greater incidence of headache/nausea than clomiPRAMINE.

4.6.F] Clonazepam

4.6.F.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%) [474].

4.6.G] Clonidine Hydrochloride

4.6.G.1] Breast cancer, History - Menopausal flushing

a) Clonidine and venlafaxine each demonstrated efficacy for the treatment of hot flashes compared with placebo, in a randomized, double-blind, trial in women with a history of breast cancer (n=102). Women (median age, 49 years; range, 28 to 71 years) who experienced at least 2 hot flashes daily were randomized (2:2:1) to receive clonidine hydrochloride 0.1 mg (n=41), venlafaxine 75 mg (n=41), or placebo (n=20) daily. At week 12, median daily hot flash scores were reduced by approximately 45% in the combined clonidine and venlafaxine treatment groups compared with placebo (p=0.03), without a between-group difference (p=0.58). When individual agents were compared with placebo, week 12 median daily hot flash scores encompassing both severity and frequency (primary endpoint) were significantly lower for clonidine (p=0.03), but not for venlafaxine (p=0.07):

Median Daily Hot Flash Scores			
Time Interval	Placebo (n=17)	Clonidine (n=28)	Venlafaxine (n=35)

Baseline	14.4(IQR, 10.3 to 21.8)	14.3 (IQR, 9.1 to 22.8) (p=0.71)	13.3 (IQR, 9 to 23)
Weeks 1 to 4	12.1(IQR, 7.1 to 16.5)	10.3 (IQR, 4.6 to 15) (p=0.26)	6.6 (IQR, 3.2 to 10) (p=0.01)
Weeks 5 to 8	12.4(IQR, 6.1 to 17)	8 (IQR, 2.2 to 13.1) (p=0.04)	7.1 (IQR, 3.3 to 10) (p=0.04)
Weeks 9 to 12	12(IQR, 6.2 to 17)	7.4 (IQR, 1.9 to 10.3) (p=0.02)	8.1 (IQR, 3.5 to 11) (p=0.08)
Week 12*	10.9(IQR, 7.4 to 15.8)	7.5 (IQR, 2 to 10.8) (p=0.03)	7.6 (IQR, 4 to 11.4) (p=0.07)

* = primary endpoint; IQR
= interquartile range; p
values vs placebo

b) Anxiety, adjusted for baseline scores and measured on the Hospital Anxiety and Depression Scale, was significantly higher in patients treated with [clonidine](#) (p=0.04) at week 12, while depression scores were higher in the [venlafaxine](#) group (p=0.03). There were no differences in measures of sexual function, sleep quality, blood pressure, and heart rate during treatment when [clonidine](#) was compared with [venlafaxine](#). Adverse effects that occurred more frequently in patients treated with [venlafaxine](#) compared with placebo included nausea (p=0.02) and constipation (p=0.04). The study results may be limited by the small population size (80% of the sample size for which the study was powered) and self reporting of the primary endpoint [472].

4.6.H] [Duloxetine Hydrochloride](#)

4.6.H.1] [Major depressive disorder](#)

a) In a systematic review and metaanalysis in 15 randomized trials of patients aged 60 years or older with [major depressive disorder](#), treatment with [duloxetine](#) (62%), [paroxetine](#) (48%), or [sertraline](#) (28%) was associated with a significantly greater likelihood of achieving a partial response (defined as 50% or greater reduction from baseline in depression score based on the Hamilton Depression Rating Scale, which is preferred, or the Montgomery-Asberg Depression Rating Scale) compared with placebo. [Venlafaxine](#) and escitalopram each had a nonsignificant 20% likelihood of a partial response, while [fluoxetine](#) (8%) and [citalopram](#) (7%) had the lowest benefit. As for dizziness, [duloxetine](#) had a significant 194% increased risk compared with placebo, while a nonsignificant risk was seen with [sertraline](#) (10% increase in risk) and [paroxetine](#) (47% increase risk) [475].

b) A meta-analysis of published, peer-reviewed, randomized, placebo-controlled, double-blind trials found that [duloxetine](#) and [venlafaxine](#) extended-release (XR) are significantly superior compared to placebo in remission and response rates for [major depressive disorder](#) and although there was a trend in favor of [venlafaxine](#) XR the differences did not reach statistical significance when compared to [duloxetine](#). A systematic literature search of Cochrane, EMBASE, and MEDLINE (1996 to January 2005) was performed by two independent reviewers. Data was obtained from 8 trials to evaluate efficacy (n=1754) and discontinuation/safety (n=1791). Patients had a one week placebo lead-in period followed by either [duloxetine](#) 40 to 120 milligrams (mg) per day or [venlafaxine](#) XR 75 to 225 mg per day for a minimum of 8 weeks. The primary outcomes were remission and response rates. Remission was defined as an improvement in the Hamilton Rating Scale for Depression (HAM-D) score to less than or equal to 7 or to a Montgomery-Asberg Depression Rating Scale (MADRS) score of less than or equal to 10. Response was defined as an improvement of 50% from baseline in either the HAM-D or MADRS scores. The secondary outcomes evaluated were dropout rates and rates of adverse effects. Both remission and response rates improved for [duloxetine](#) and [venlafaxine](#) XR and were statistically significant compared to placebo (both p less than 0.001). No significant difference was found for remission and response rates when [duloxetine](#) and [venlafaxine](#) XR were compared. Patients receiving placebo had a higher dropout rate due to lack of efficacy compared to those patients receiving [duloxetine](#) or [venlafaxine](#) XR (both p less than 0.001).

More patients in the active drug treatment groups dropped out due to adverse effects compared to placebo (**duloxetine** $p=0.008$; **venlafaxine XR** p less than 0.001). Again, when **duloxetine** and **venlafaxine XR** were compared, no statistically significant differences were found for dropout rates due to lack of efficacy or adverse drug reactions. The reported adverse events were comparable between drugs. A sensitivity analysis was also performed and included 2 additional studies, one study for **venlafaxine XR** dealing with patients with comorbid anxiety and one study for **duloxetine** dealing with patients with comorbid pain. Adding the 2 studies demonstrated similar results with both drugs having a statistically significant difference from placebo for remission and response rates [478].

Outcome	Active Drug	Active Drug vs Placebo Difference(a)	95% CI	p Value
Remission	duloxetine	0.142	0.089 to 0.195	<0.001
	venlafaxine XR	0.178	0.09 to 0.265	<0.001
Response	duloxetine	0.186	0.13 to 0.242	<0.001
	venlafaxine XR	0.244	0.15 to 0.337	<0.001
Dropout rate due to ADRs	duloxetine	0.057	0.015 to 0.1	0.008
	venlafaxine XR	0.061	0.025 to 0.097	<0.001
Dropout rate due to lack of efficacy	duloxetine	-0.111 (c)	-0.159 to -0.63	<0.001
	venlafaxine XR	-0.107	-0.151 to -0.064	<0.001

ADRs = adverse drug reactions; XR
= extended release; CI = confidence
interval

(a) The rate when meta-analytic rate
of placebo is subtracted from the
active drug rate.

(b) Corresponding p value of the
difference rate calculated with a Z-
test.

(c) Negative difference rates indicate
a larger effect for placebo.

4.6.I] Escitalopram Oxalate

4.6.I.1] Major depressive disorder

a) In a systematic review and metaanalysis in 15 randomized trials of patients aged 60 years or older with **major depressive disorder**, treatment with **duloxetine** (62%), **paroxetine** (48%), or **sertraline** (28%) was associated with a significantly greater likelihood of achieving a partial response (defined as 50% or greater reduction from baseline in depression score based on the Hamilton Depression Rating Scale, which is preferred, or the Montgomery-Asberg Depression Rating Scale) compared with placebo. **Venlafaxine** and **escitalopram** each had a nonsignificant 20% likelihood of a partial response, while **fluoxetine** (8%) and **citalopram** (7%) had the lowest benefit. As for dizziness, **duloxetine** had a significant 194% increased risk compared with placebo, while a nonsignificant risk was seen with **sertraline** (10% increase in risk) and **paroxetine** (47% increase risk) [475].

4.6.J] Estradiol

4.6.J.1] Abnormal vasomotor function - Menopause symptoms present

a) In the MsFLASH trial (N=339, midlife women), low-dose oral **estradiol** or low-dose **venlafaxine** decreased the mean frequency of vasomotor symptoms (VMS) associated with menopause at week 8 by 53% and 48%, respectively, a difference that was statistically significant compared with placebo (29%). Patients were randomized in a 2:2:3 ratio to 17-beta-estradiol 0.5-mg/day orally, **venlafaxine XR** 75 mg/

day orally (titrated from 37.5 mg/day up to 75 mg/day over 1 week), or placebo for 8 weeks. The mean VMS frequency at baseline was 8.1/day [459].

4.6.K] Fluoxetine Hydrochloride

4.6.K.1] Depression

a) Analysis of pooled data from 8 randomized, double-blind studies (n=2045) showed a remission rate of depression of 45% with [venlafaxine](#) treatment, 35% with serotonin reuptake inhibitors (SSRIs), and 25% with placebo. Remission was defined as a total score of 7 or less on the 17-item Hamilton Rating Scale for Depression. [Venlafaxine](#) was significantly (p less than 0.001) more effective than SSRIs from 2 weeks onward and from placebo from 3 weeks onward. The end-of-therapy remission rate with SSRIs was significantly better than that with placebo (p=0.001). The odds ratio for remission was 1.5, in favor of [venlafaxine](#) over SSRIs [482].

b) [Venlafaxine](#) and [fluoxetine](#) had similar efficacy in the treatment of [major depression](#) in an 8 week, double-blind study. Patients were randomized to receive [venlafaxine](#) 37.5 mg twice daily (n=196) or [fluoxetine](#) 20 mg once daily (n=186). If patients did not demonstrate an adequate response to therapy, [venlafaxine](#) was increased to 75 mg twice daily and [fluoxetine](#) to 20 mg twice daily. Primary outcome measures were scores on the Hamilton Rating Scale for Depression (HAM-D), the Montgomery-Asberg Depression Rating Scale (MADRS), the Clinical Global Impressions Severity of Illness Score (CGI-S), and the Clinical Global Impressions Improvement Score (CGI-I). In both treatment groups, HAM-D and MADRS scores improved significantly after 8 weeks of therapy. CGI-I scores were also improved, 80.6% of patients scored 1 (very much improved) or 2 (much improved) with [venlafaxine](#) and 83.9% with [fluoxetine](#). Remission rates were equivalent in both groups, 60.2%, as determined by scores of 8 or less on the HAM-D scale. The only significant difference between treatment groups was the number of patients that required a dosage increase, [fluoxetine](#) (n=54) and [venlafaxine](#) (n=43). After treatment with higher doses, the number of patients scoring 1 on the CGI-I were significantly greater in the [venlafaxine](#) group than the [fluoxetine](#) group. The frequency of adverse events associated with both medications were comparable. Overall, there were very few differences in efficacy and tolerability between [venlafaxine](#) and [fluoxetine](#) (Cost e Silva, 1998).

c) [Venlafaxine](#) was effective in the treatment of [major depression](#) in an 8-week, open-label, comparative trial with [fluoxetine](#). At the initiation of the study, 55 patients received [venlafaxine](#) 37.5 mg twice daily; 55 received [fluoxetine](#) 20 mg daily. If after 15 days of treatment response was inadequate, doses were increased to [venlafaxine](#) 75 mg twice daily and [fluoxetine](#) 40 mg daily. Both medications were significantly effective in treating [major depression](#), as determined by improvements in patient scores on the Hamilton Depression Rating Scale (HAM-D), Montgomery-Asberg Depression Rating Scale (MADRS), and the Clinical Global Impressions Scale (CGI). There were no significant differences between the 2 medications. A trend towards greater improvement existed in patients requiring higher doses of [venlafaxine](#) than [fluoxetine](#). Patients treated with [venlafaxine](#) were significantly more likely to experience constipation, dizziness, dry mouth, and vomiting [483].

d) Efficacy of [venlafaxine](#) 200 mg/day was similar to [fluoxetine](#) 40 mg/day in a 6-week inpatient study of adults with [major depression](#) (n=68). Patients were assessed using the Hamilton Depression Rating Scale, Montgomery-Asberg Depression Rating Scale, and the Clinical Global Impressions scale. The incidence of adverse effects was similar for both groups [484].

4.6.K.2] 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) [475].

4.6.K.3] Mixed anxiety and depressive disorder

a) Extended-release (XR) venlafaxine was more effective than placebo for improving the symptoms of depression and anxiety in patients with major depressive disorder and comorbid generalized anxiety disorder (GAD). However, time to response was greater in patients with comorbidity than in patients with major depressive disorder only. Fluoxetine, on the other hand, was not significantly better than placebo in patients with comorbidity. From the data of all the patients meeting DSM-IV criteria for major depressive disorder in a double-blind, randomized trial (n=368), results from the subset of patients who had comorbid GAD (n=92) were analyzed separately and compared to results of the noncomorbid patients. Patients took once-daily doses of venlafaxine XR 75 mg (titration to maximum 225 mg/day), fluoxetine 20 mg (titration to maximum 60 mg/day), or placebo for 12 weeks. According to the criteria of more than 50% reduction (from baseline) in the Hamilton-Depression (HAM-D) and Hamilton- Anxiety (HAM-A) scores, improvement with venlafaxine was significantly greater (p less than 0.05) than with placebo by 12 weeks of treatment. There was a similar trend with fluoxetine, but at no time was fluoxetine statistically superior to placebo. About one-third of patients with comorbidity showed response at 4 weeks; however, overall, there was no evident trend for a placebo:drug difference until after the eighth week of treatment. Among patients without comorbidity, the placebo:venlafaxine difference was evident as early as week 2. By week 12, response rate was 66% on HAM-D and 59% on HAM-A for those taking venlafaxine, 52% and 45% for those taking fluoxetine, and 36% and 24% for those taking placebo [481].

4.6.K.4] Adverse Effects

a) A post-hoc analysis of the randomized, placebo-controlled, double-blind PREVENT study revealed similar incidences of treatment-emergent sexual dysfunction during long-term use of venlafaxine extended-release (ER) or fluoxetine in outpatient adults with recurrent major depressive disorder. Patients (mean age, 40 years; 61% to 65% female) received flexible-dose venlafaxine ER 75 to 300 mg/day (n=820) or fluoxetine 20 to 60 mg/day (n=275) during the 10-week acute phase, and the highest tolerated dose was then given during the 6-month continuation phase. The mean doses used during the acute and continuation phases were venlafaxine ER 161.3 mg and 206.2 mg and fluoxetine 40.8 mg and 49.2 mg, respectively. Assessment of sexual function utilized 8 instruments in the PREVENT trial, and this analysis focused on results from the 17-item Hamilton Rating Scale for Depression (HAM-D; specifically item 14) and the Inventory of Depressive Symptomatology-Self Report (IDS-SR; specifically item 22). Baseline rates of sexual dysfunction based on the HAM-D and IDS-SR were 57.9% and 48.8%, respectively. New-onset sexual dysfunction occurring during either phase and on either of the 2 measurement instruments was reported in 63.9% of venlafaxine ER patients and 68% of fluoxetine patients. Reporting of new-onset sexual dysfunction peaked for venlafaxine ER at week 2 for both measures and for fluoxetine at week 4 (IDS-SR) and 6 (HAM-D). New-onset sexual dysfunction resolved in approximately 80% or more patients during continued therapy (depending on instrument used). Spontaneously reported treatment-emergent adverse events related to sexual dysfunction during both phases in the venlafaxine ER and fluoxetine groups included abnormal ejaculation/orgasm (8% vs 8%), anorgasmia (7% vs 7%), impotence (4% vs 1%; p less than 0.05), decreased libido (10% vs 11%), and abnormal sexual function (1% vs less than 1%). Comparing responders, nonresponders, and remitters, the mean rates of sexual dysfunction across all visits were: 10.5% vs 27.6% vs 4.6% (acute phase, HAM-D item 14); 8.8% vs 15.3% vs 5.4% (acute phase, IDS-SR item 22); 11.9% vs 31.8% vs

4.7% (continuation phase, HAM-D item 14); and 11.9% vs 27.4% vs 4.7% (continuation phase, IDS-SR item 22) [479].

b) During a randomized, double-blind trial of elderly patients with **major depression**, the rate of study discontinuation as a result of adverse events was significantly greater for patients receiving **venlafaxine** (27%) compared with patients receiving placebo (9%; $p=0.0017$) but there were no significant differences when the **fluoxetine** group (19%) was compared with the placebo group ($p=0.0666$) or when **fluoxetine** was compared to **venlafaxine** ($p=0.1838$). Elderly patients (mean age, 71 years) with **major depression** were randomized to **venlafaxine** immediate-release ($n=104$), **fluoxetine** ($n=100$), or placebo ($n=96$) for 8 weeks. The dose of **venlafaxine** was titrated from 37.5 to 225 mg/day, and **fluoxetine** doses were titrated from 20 to 60 mg/day over a 29-day period. The most frequently reported adverse events in the **venlafaxine** and **fluoxetine** groups were nausea (45% and 23%) and headache (26% and 18%). The adverse events most frequently reported in the placebo group were headache (22%) and dry mouth (15%) [480].

4.6.L] **Imipramine**

4.6.L.1] **Depression**

a) **Venlafaxine** and **imipramine** resulted in similar improvement in depression with **melancholia** in hospitalized patients at 6 weeks; however, **venlafaxine** produced an earlier response than **imipramine** on 1 test [461]. Over 5 days, the dose of **venlafaxine** was rapidly increased from 75 to 375 milligrams(mg)/day; this dose was continued until day 14 and was then decreased to 150 mg/day. The dose of **imipramine** was increased from 50 to 200 mg/day over 5 days and was continued at this dose for the remainder of the study. The time to a 50% response rate was similar for the Montgomery-Asberg Depression Rating Scale (MADRS), but for the 21-item Hamilton Rating Scale for Depression (HAM-D), the time to response was 1 week earlier with **venlafaxine** than **imipramine** ($p=0.036$). Adverse effects were reported in 69% and 76% of patients treated with **venlafaxine** and **imipramine**, respectively. Statistically significant differences in dry mouth and tremor were reported for **imipramine** (p less than 0.05) and nausea for **venlafaxine** ($p=0.011$). While this study enrolled 167 patients, this was lower than planned, and only 115 patients completed the 6-week study. Additional studies are needed to provide conclusive evidence for a more rapid onset of effect with **venlafaxine**.

b) **Venlafaxine** was found to have antidepressant efficacy comparable to **imipramine** in outpatients with moderate to marked depression. **Venlafaxine** was compared to **imipramine** in a 6 week, double-blind placebo controlled study in 224 outpatients with depression of moderate to marked severity. Baseline and weekly efficacy measurements were obtained utilizing the 21 item Hamilton Rating Scale for Depression (HAM-D), the Montgomery-Asberg Depression Rating Scale (MADRS), the Clinical Global Impression severity and improvement scales (CGI). The mean maximal total daily dose of **venlafaxine** was 182 mg +/- 48 milligrams and the mean maximal total daily dose of **imipramine** was 176 milligrams and +/- 56 mg. All study medications were administered in a three times a day schedule after meals. **Venlafaxine** showed a significant clinical advantage over **imipramine** at the week 6 endpoint on the Ham-D total score. It was noted that this effect was probably due to the higher attrition rate for **imipramine** as compared to **venlafaxine**. Attrition rates due to adverse effects were 25% and 16% for **imipramine** and **venlafaxine** respectively. Nausea, sedation, dry mouth, and dizziness were the most prominently reported adverse effects for **venlafaxine** [462].

4.6.M] **Medroxyprogesterone Acetate**

4.6.M.1] **Hot sweats**

a) Single dose [medroxyPROGESTERone](#) acetate ([MPA](#)) significantly reduces hot flashes compared to [venlafaxine](#). In an open-label controlled trial (n=227), subjects were stratified by age (18 to 49 years old versus those older than 50), current [tamoxifen](#) and [raloxifene](#) use, duration of hot flash symptoms (less than 9 months versus greater than or equal to 9 months) and reported frequency of hot flashes per day (two to three versus four to nine or more). Patients were then randomized to receive either [venlafaxine](#) 37.5 milligrams (mg) per day for 1 week and then daily 75 mg continuously, [MPA](#) 400 mg intramuscularly (IM) for one dose or [MPA](#) 500 mg IM at 2 week intervals for three total doses. The multidose [MPA](#) arm was discontinued after nine patients were randomly assigned to this arm due to unexpectedly slow accrual rate. The completed study analysis refers mainly to the two major study arms. Patients completed a daily hot flash diary questionnaire to measure frequency and severity at 1 week of baseline and throughout the 6 week treatment period. After 6 weeks, if patients were satisfied with their treatment, they continued the treatment (or no treatment if randomized to [MPA](#)). Nurses contacted patients monthly for the next 5 months and then every other month for the next 6 months. If the patients were still experiencing hot flashes, they were asked about the average number of mild, moderate, or severe hot flashes they were experiencing per day. At the end of the 6 week treatment period, 86% (n=94) reported a greater than 50% reduction from baseline with [MPA](#) compared with 53% (n=94) in the [venlafaxine](#) group (p<0.0001). No hot flashes were reported in 23% of the [MPA](#) arm compared to 1% in the [venlafaxine](#) arm during the sixth treatment week (p=<0.0001). During the first treatment week, [venlafaxine](#) group had significantly more nausea (p=.0001), appetite loss (p<.0001), dizziness (p=0.007), constipation (p=.001), mouth dryness (p=.01) and sleepiness (p=.02) in comparison to the [MPA](#) group. As measured by patient diaries and quality of life tools (treatment week 6 score minus baseline score), other potential symptom differences between the two study groups include constipation, hot flash distress and abnormal sweating [469].

4.6.N] [Methylphenidate Hydrochloride](#)

4.6.N.1] [Attention deficit hyperactivity disorder](#)

a) [Venlafaxine](#) was similar to [methylphenidate](#) for the treatment ADHD in pediatric patients in a randomized, double-blind, comparison trial (n=38). Eligible outpatients had confirmed ADHD (DSM-IV-text revision criteria and Kiddie Schedule for Affective Disorders and Schizophrenia-Present and Lifetime diagnostic interview) and at least 1.5 standard deviations above normal for patient age and gender on the ADHD Rating Scale-IV (ADHD-RS-IV) School Version total and/or subscale scores. Patients were equally randomized to receive [venlafaxine](#) (n=19; mean age, 9.42 +/- 2.19 years; 74% male) or [methylphenidate](#) (n=19; mean age, 9.57 +/- 1.86 years; 68% male) for 6 weeks. The study regimens were based on weight: [venlafaxine](#) 50 mg orally daily (weight less than 30 kg) to 75 mg daily (weight greater than 30 kg) and [methylphenidate](#) 20 mg/day or 30 mg/day, respectively. Both treatments were titrated up during the first 2 to 3 weeks ([venlafaxine](#), week 1: 25 mg once a day; week 2: 25 mg in the morning and midday; and if needed for week 3: 25 mg in the morning, 25 mg midday, and 25 mg at 4 PM; [methylphenidate](#), week 1: 5 mg in the morning and 5 mg at midday; week 2: 10 mg in the morning and 10 mg at midday; and if needed for week 3: 10 mg in the morning, 10 mg at midday, and 10 mg at 4 PM). All patients were Persian and had newly diagnosed combined subtype ADHD. While both treatment arms demonstrated statistically significant within-group improvement in Parent and Teacher ADHD-RS-IV from baseline to 6 weeks (p less than 0.001), there was no significant difference between [venlafaxine](#) and [methylphenidate](#) in the change in mean Parent and Teacher ADHD-RS-IV from baseline to 6 weeks (primary outcome; intent-to-treat). At 6 weeks, change in the mean Parent ADHD-RS-IV scores from baseline was -14.15 +/- 7.01 for [venlafaxine](#) and -16.63 +/- 8.59 for [methylphenidate](#) (difference, p=0.33). Similarly at 6 weeks, change in the mean Teacher ADHD-RS-IV from baseline was -13.05 +/- 4.77 for [venlafaxine](#) and -15.31 +/- 8.13 for [methylphenidate](#) (difference, p=0.3). Adverse events were tolerable and mild to moderate in severity and were not significantly different except for insomnia (10.52% vs 52.63%) and headaches (15.78% vs

57.89%) in the [venlafaxine](#) and [methylphenidate](#) arms, respectively. The most commonly reported events were abdominal pain, somnolence, and restlessness [31].

4.6.O] [Mirtazapine](#)

4.6.O.1] [Major depression, melancholic type](#)

a) [Mirtazapine](#) and [venlafaxine](#) both were effective in alleviating symptoms of depression in hospitalized patients diagnosed with DSM-IV severe depression with [melancholia](#). [Mirtazapine](#) tended to be superior with respect to both efficacy and dropout rate due to adverse reactions. In a randomized, double-blind comparison, 157 patients were given either [mirtazapine](#), starting at 15 milligrams (mg)/day and increasing rapidly to as high as 60 mg/day, or [venlafaxine](#), starting at 75 mg/day and increasing rapidly to 225 mg/day, for 8 weeks. Group means on the Montgomery-Asberg Depression Rating Scale (MADRS) and the Hamilton Rating Scale for Depression (HAM-D-17) improved for both groups. At all time points, scores of both scales indicated greater improvement with [mirtazapine](#), although differences were not statistically significant. Sleep disturbances improved more with [mirtazapine](#) than with [venlafaxine](#) (p less than 0.001 for weeks 2 to 8). More mirtazapine-treated patients (74.4%) than venlafaxine-treated patients (65.8%) reported at least one adverse reaction. However, significantly more patients from the [venlafaxine](#) group dropped out of the study because of adverse events (15.3% vs 5.1%, p=0.037). The most common adverse events in the [mirtazapine](#) group were weight increase (10.3% of patients), dry mouth (9%), headache (7.7%), sleepiness (7.7%), and nausea (6.4%). In the [venlafaxine](#) group, most common were increased sweating (19%), constipation (15.2%), headache (11.4%), nausea (10.1%), orthostatic hypotension (6.3%), and decreased salivation (6.3%) [466].

4.6.P] [Paroxetine](#)

4.6.P.1] [Bipolar disorder, depressed phase](#)

a) [Paroxetine](#) and [venlafaxine](#) had similar efficacy in the treatment of [depression in bipolar](#) patients taking concomitant mood stabilizers. This randomized, single-blind (rater blind), comparative, 6-week study demonstrated that [paroxetine](#) and [venlafaxine](#) produced responses in 43% and 48% of the patients, respectively. At the end of the 6-week trial, both treatment groups showed significant improvement in the Hamilton Rating Scale for Depression (HAM-D) and the Clinical Global Impressions (CGI) for severity rating scores, with a mean HAM-D change of -6.9 for the [paroxetine](#) group and -9.0 for the [venlafaxine](#) group. These responses were significantly different compared to baseline, but not among treatment groups. At baseline, patients (n=60) were assessed using CGI ratings, the HAM-D, the Structured Clinical Interview for Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV), Axis I Disorders (SCID-I), and the Young Mania Rating Scale (YMRS). All patients were being treated with 1 or more mood stabilizers for at least 6 months prior to onset of the current [major depressive episode](#), and had not taken antidepressant or antipsychotic medication for at least 3 months prior to the start of the study. During the study, doses were adjusted for efficacy and tolerability. The starting dose of [venlafaxine](#) was 37.5 milligrams (mg) twice a day, which could be increased in increments of 75 mg per day (mg/d) every week. The starting dose of [paroxetine](#) was 20 mg/d, which could be adjusted in increments of 10 mg/d every week. The mean doses of [venlafaxine](#) and [paroxetine](#) were 179 mg/d and 32 mg/d, respectively. There were no significant differences in reported adverse events (43% for [paroxetine](#), 50% for [venlafaxine](#)); the most common adverse events were nausea (20% of all patients), and dizziness (8.3% of all patients). One patient (3%) in the [paroxetine](#) group had a switch to [hypomania](#) during treatment, 4 patients (13%) in the [venlafaxine](#) group switched to either [hypomania](#) (2 patients) or full mania (2 patients). Limitations of the study include concomitant use of several different mood stabilizing drugs, no placebo group, a single-blind study design, and a short follow up period [30].

4.6.P.2] Obsessive-compulsive disorder

a) Venlafaxine extended-release (XR) was as effective as paroxetine in the treatment of patients with obsessive compulsive disorder (OCD). In a randomized, double-blind, comparative study, patients (n=150) with OCD and a score of at least 18 (or at least 12, if only obsessions or only compulsions were present) on the Yale-Brown Obsessive Compulsive Scale (Y-BOCS) received either venlafaxine XR (initial, 75 milligrams (mg)/day, titrated to 300 mg/day by week 7) or paroxetine (initial, 15 milligrams (mg)/day, titrated to 60 mg/day by week 7) for 12 weeks. Both paroxetine and venlafaxine XR treatments were effective, producing mean reductions of 7.8 and 7.2 points, respectively, in the Y-BOCS score from baseline to endpoint. A significant decrease in the total Y-BOCS score from baseline was seen at week 3 for venlafaxine XR- treated patients (p=0.008) and at week 5 for patients in the paroxetine group (p=0.018). There were no significant differences in responder rates between treatment groups. In the venlafaxine XR group, 37% and 25% of patients were partial responders and full responders, respectively. Similarly, in the paroxetine group, 44% and 22% of patients were partial responders and full responders, respectively. Additionally, no significant differences were observed between the two treatments with regard to reduction of anxious or depressive symptoms (as measured by the Hamilton Anxiety Scale and the Hamilton Rating Scale for Depression, respectively). For both treatments, most adverse effects were of mild or moderate severity and included somnolence, sweating, insomnia, and nausea [468].

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) [475].

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) [475].

4.6.S] Pregabalin

4.6.S.1] Diabetic peripheral neuropathy

a) In a randomized trial in adults with metabolically stable type 1 or 2 diabetes and painful diabetic neuropathy (N=257; mean baseline visual analogue scale (VAS) pain intensity score, 77 mm), 4 weeks of carbamazepine 200 mg/day, pregabalin 150 mg/day, or venlafaxine 150 mg/day resulted in significant improvement in pain scores for all 3 groups; however, pregabalin significantly improved VAS score compared with carbamazepine and venlafaxine (33.4 vs 39.6 and 46.6), with no difference between carbamazepine and venlafaxine. A significantly greater proportion of patients achieved a 50% or greater reduction in mean pain score with pregabalin (76.7% vs 41.2% and 41.9%), as well as reduction in mean sleep and work interference scores. Pregabalin and venlafaxine significantly improved mean score for pain related to mood interference at day 35 compared with carbamazepine. There was a significantly greater incidence of adverse events with pregabalin (73.2%) compared with carbamazepine (12.9%) and venlafaxine (63.9%), including dizziness (73.2% vs 11.8% and 41.9%) and somnolence (53.3% vs 3.5% and 23.3%) [473].

4.6.S.2] Generalized anxiety disorder

a) In a multicenter, randomized, double-blind, placebo-controlled, parallel-group study (n=374), treatment with pregabalin but not venlafaxine-XR significantly improved anxiety symptom scores compared with placebo in patients with generalized anxiety disorder (GAD). Patients who were 18 to 65 years of age with a primary diagnosis of GAD and a total Hamilton Anxiety Rating Scale (HAM-A) score of 20 or greater (with a HAM-A psychic and somatic anxiety factors score of 10 or greater) were eligible for enrollment. Following a one-week, open-labeled, lead-in period, patients were randomized to receive 8 weeks of oral pregabalin (150 milligrams (mg) twice daily for the first week then titrated to a dose range of 300 to 600 mg/day given twice daily) (n=121), venlafaxine-XR (75 mg/day for the first week then titrated to a dose range of 75 to 225 mg/day administered in the morning with matching placebo given in the evening) (n=125), or placebo (n=128). Patients in the pregabalin arm but not the venlafaxine-XR arm had a significant improvement in least squares (LS) mean change HAM-A total scores compared with placebo (primary endpoint). Additionally, treatment with pregabalin significantly improved some secondary investigator-rated efficacy measures including the HAM-A psychic anxiety factor score, the Clinical Global Impression (CGI) severity scale, and the Hamilton Depression Rating Scale (HAM-D) compared to placebo while treatment with venlafaxine-XR did not (see Table 1). On treatment day 4, patients who received pregabalin had significantly improved LS mean change HAM-A total scores compared with venlafaxine-XR (p=0.008) or placebo (p=0.001). Severe adverse events were reported less often in pregabalin-treated patients (9.1%) compared with venlafaxine-XR-treated patients (20%) [476].

Table 1

	Pregabalin (n=121)	Venlafaxine-XR (n=125)	Placebo (n=128)		
LS mean +/- SE	p-value	LS mean +/- SE	p-value	LS mean +/- SE	
HAM-A total score (primary endpoint)					
Baseline	27.6 +/- 0.4	0.028	27.4 +/- 0.4	0.97	26.8 +/- 0.4
Endpoint change	-14.5 +/- 0.9	-12 +/- 0.9	-11.7 +/- 0.9		
HAM-A psychic anxiety factor score					
Baseline	14.4 +/- 0.3	0.017	14 +/- 0.3	0.9	13.8 +/- 0.3
Endpoint change	-7.3 +/- 0.5	-5.9 +/- 0.5	-5.6 +/- 0.5		
HAM-A somatic anxiety factor score					
Baseline	13.3 +/- 0.3	0.11	13.4 +/- 0.3	0.996	12.9 +/- 0.3
Endpoint change	-7.3 +/- 0.4	-6.1 +/- 0.5	-6.2 +/- 0.5		
CGI severity score					
Baseline	4.7 +/- 0.1	0.14	4.6 +/- 0.1	0.55	4.5 +/- 0.1

Endpoint change	-2 +/- 0.2	-1.7 +/- 0.2	-1.5 +/- 0.2		
CGI improvement score					
Endpoint change	2.3 +/- 0.1	0.05	2.5 +/- 0.1	0.53	2.7 +/- 0.1
HAM-D score					
Baseline	11.5 +/- 0.2	0.018	11.5 +/- 0.2	0.36	11.3 +/- 0.2
Endpoint change	-4.4 +/- 0.5	-3.6 +/- 0.5	-2.8 +/- 0.5		
LS mean, least squares mean change; SE, standard error; HAM-A, Hamilton Anxiety Rating Scale; CGI, Clinical Global Impression; HAM-D, Hamilton Depression Rating Scale					

b) Treatment with oral pregabalin at daily doses of 400 or 600 milligrams (mg) per day was comparable to [venlafaxine](#) 75 mg per day, and both agents were more effective than placebo in reducing anxiety symptoms in adults with moderate to severe [generalized anxiety disorder](#) (GAD) in a randomized, double-blind, 4-arm, parallel-group, fixed-dose study. Outpatients (mean age, 44.1 +/- 12.3 years) meeting the DSM-IV criteria for primary GAD and who had total scores of 20 or greater on the Hamilton Rating Scale for Anxiety (HAM-A; mean range, 26 to 27.4), 9 or greater on the Covi Anxiety Scale, and 7 or lower on the Raskin Depression Scale were included. Patients were randomized to receive either pregabalin 400 mg/day (n=97), pregabalin 600 mg/day (n=110), [venlafaxine](#) 75 mg/day (n=113), or placebo (n=101) orally (given in divided doses twice daily) for 6 weeks, followed by a 1-week double-blind taper phase. Pregabalin was initiated at 100 or 150 mg/day (400 or 600 mg/day groups, respectively) and titrated up to target doses over 1 week. Based on the modified intention-to-treat analysis (all randomized patients who received at least 1 dose of study drug), the change in mean HAM-A total scores at endpoint from baseline (primary endpoint) was -14.7 +/- 0.8, -14.1 +/- 0.8, and -14.1 +/- 0.8 in the pregabalin 400 mg/day (n=94), pregabalin 600 mg/day (n=104), and [venlafaxine](#) (n=110) arms, respectively, compared with -11.6 +/- 0.8 in the placebo (n=100) arm (all p less than or equal to 0.03 vs placebo). Statistically significant improvement in HAM-A total scores occurred in both pregabalin arms compared with placebo during week 1 of treatment but not in the [venlafaxine](#) arm. Compared with placebo (45%) at endpoint, significantly more patients in the pregabalin 400 mg/day (61%; p=0.02) and [venlafaxine](#) 75 mg/day (62%; p=0.01) arms responded to treatment (ie, had a 50% or greater reduction in baseline HAM-A score); the difference in response in the pregabalin 600 mg/day (58%; p=0.06) was not significant. Among other secondary endpoints, all 3 treatment groups had comparable and significant improvement over placebo in HAM-A subscale scores of anxiety, tension, and insomnia, except a statistical insignificance on the insomnia subscale between [venlafaxine](#) and placebo. The proportion of patients rated as much improved or very much improved on the Clinical Global Impression-Improvement (CGI-I) scale was higher in the pregabalin 400 mg/day (56.4%), pregabalin 600 mg/day (58.7%), and [venlafaxine](#) (60.9%) arms compared with placebo (42%; all p less than or equal to 0.04). Treatment was well tolerated across all 3 arms, with dizziness, somnolence, and nausea being the most commonly reported adverse events in the pregabalin arms and nausea, dizziness, and asthenia being the most common in the [venlafaxine](#) arm. However, discontinuation rates due to adverse events were lower in the pregabalin 400 mg/day group (6.2%) compared with [venlafaxine](#) (20.4%; p less than 0.01) and pregabalin 600 mg/day (13.6%) [477].

4.6.T] [Sertraline](#)

4.6.T.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 [28].

4.6.T.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 [463]:

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](#) [464].

4.6.T.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 [465].

4.6.U] Sertraline Hydrochloride

4.6.U.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) [475].

4.6.U.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%) [474].

4.6.V] [Trazodone](#)

4.6.V.1] Depression

a) [Venlafaxine](#) produced antidepressant efficacy comparable to [trazodone](#) in a double-blind, placebo controlled trial. In this outpatient study, 225 patients were randomized to [venlafaxine](#) (75 to 200 milligrams (mg) per day, [trazodone](#) (mean = 300 mg/day) or placebo. Response rates were 72%, 60% and 55% respectively. [Venlafaxine](#) appeared to be more effective than [trazodone](#) in treating the cognitive disturbance and retardation factor as evidenced on the Hamilton Rating Scale for Depression (HAM-D). It was noted that this effect may have been due to the sedating nature of [trazodone](#). Nausea was more common in the [venlafaxine](#) group compared to dizziness and somnolence in the [trazodone](#) group [460].

4.6.W] [Vortioxetine Hydrobromide](#)

4.6.W.1] Recurrent [major depression](#)

a) Vortioxetine 10 mg/day was not inferior to [venlafaxine](#) XR 150 mg/day in adults (aged 65 years or younger) with [recurrent major depressive disorder](#) evaluated using the change from baseline to week 8 on the Mont-gomery-Asberg Depression Rating Scale (MADRS) total score in a randomized trial (N=443). There were similar improvements between groups in MADRS response and remission rates, Hamilton Anxiety Rating Scale, Clinical Global Impression scale, and the health-related quality of life assessment. Discontinuation of treatment was significantly higher with [venlafaxine](#) XR (27.4% vs 18%) with the most frequent reason for withdrawal of adverse events (14.2% vs 6.6%) [485].

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