

DRUGDEX-EV 0573

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TRAZODONE

[Overview](#)
[Dosing Information](#)
[Pharmacokinetics](#)
[Cautions](#)
[Clinical Applications](#)
[References](#)

0.0] Overview

1) Class

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

Antidepressant

2) Dosing Information

a) [Trazodone](#) Hydrochloride

1) Adult

a) Withdrawal symptoms may occur, dose should be gradually reduced prior to complete discontinuation of therapy [4][1].

1) Insomnia

a) 50 to 100 mg orally 1 hour prior to bedtime (off-label dosage) [14][15][16]

2) Major depressive disorder

a) (Immediate-release tablets) Initial, 150 mg orally daily in divided doses after a light meal or snack; titration, increase gradually on basis of tolerance and clinical response, may increase dosage by 50 mg/day every 3 to 4 days; maintenance, dosage may gradually be reduced to lowest effective dose once therapeutic response has been achieved; MAX, 400 mg/day for outpatients and 600 mg/day for inpatients [4]

b) (Extended-release tablets) Initial, 150 mg/day orally in the evening, preferably at bedtime on an empty stomach; titration, may increase by 75 mg/day every 3 days; maintenance, dosage may gradually be reduced to lowest

effective dose once therapeutic response has been achieved; MAX, 375 mg/day [1]

2)) Pediatric

- a))** Safety and effectiveness in pediatric patients have not been established [4][1].

3)) Contraindications

a)) Trazodone Hydrochloride

- 1))** Coadministration with an MAOI, including [linezolid](#) or IV methylene blue, or use within 14 days of discontinuing an MAOI; increased risk of [serotonin syndrome](#) [1]
- 2))** Concomitant use with [saquinavir/ritonavir](#) [21]
- 3))** Hypersensitivity to [trazodone](#) hydrochloride [22]

4)) Serious Adverse Effects

a)) Trazodone Hydrochloride

- 1))** [Cardiac dysrhythmia](#)
- 2))** [Hypersensitivity reaction](#)
- 3))** Hypotension
- 4))** [Priapism](#)
- 5))** Prolonged QT interval
- 6))** Seizure
- 7))** [Serotonin syndrome](#)
- 8))** Suicidal thoughts
- 9))** Suicide
- 10))** [Torsades de pointes](#)

5)) Clinical Applications

a)) Trazodone Hydrochloride

- 1))** FDA Approved Indications
 - a))** [Major depressive disorder](#)
- 2))** Non-FDA Approved Indications

a) Insomnia

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

[Trazodone](#)

[Trazodone HCl](#)

[Trazodone Hydrochloride](#)

C) Physicochemical Properties

1) Molecular Weight

a) Hydrochloride: 408.32 [22][19]

2) Solubility

a) [Trazodone](#) is freely soluble in water [22][19].

3) [Trazodone](#) is not chemically related to tricyclic, tetracyclic, or other known antidepressants [22].

1.2] Storage and Stability

A) [Trazodone](#) Hydrochloride

1) Preparation

a) Oral route

1) Administration (Immediate Release Tablets)

a) Swallow tablets whole; tablets may be broken in half at the score line [4].

b) Take shortly after a meal or light snack [4].

c) If drowsiness occurs, may reduce the dose or administer a major portion of the daily dose at bedtime to minimize symptoms [4].

2) Administration (Extended Release Tablets)

a) Do not chew or crush; tablets may be broken in half at the score line [1].

b) Take at the same time every day in the late evening, preferably at bedtime and on an empty stomach [19].

B) Trazodone Hydrochloride

1) Oral route

a) Tablet

1) Store at controlled room temperature, 20 to 25 degrees C (68 to 77 degrees F), with excursions permitted between 15 and 30 degrees C (59 and 86 degrees F) [22].

b) Tablet, Extended Release

1) Store at room temperature between 15 and 30 degrees C (59 and 86 degrees F) [337].

1.3] Adult Dosage

1.3.1] Normal Dosage

1.3.1.A] Important Note

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

2) Do not initiate trazodone in a patient receiving linezolid or IV methylene blue. If a patient is already receiving trazodone and treatment with linezolid or IV methylene blue is unavoidable, and the potential benefit of therapy outweighs the risk for serotonin syndrome, discontinue trazodone promptly. Monitor for symptoms of serotonin syndrome for 2 weeks or for 24 hours after the last dose of linezolid or IV methylene blue, whichever comes first. Resume trazodone therapy 24 hours after the last dose of linezolid or IV methylene blue [1].

1.3.1.B] Trazodone

1.3.1.B.1] Electroconvulsive therapy

See Drug Consult reference: Drugs for Seizure Prolongation in ECT

1.3.1.C] Trazodone Hydrochloride

1.3.1.C.1] Oral route

1.3.1.C.1.a] Insomnia

1) Off-label Dosage

a) Dosage: 50 to 100 mg orally 1 hour prior to bedtime [14][15][16]

1.3.1.C.1.b] Major depressive disorder

1)) Immediate-release

a)) Initial dosage: 150 mg orally daily in divided doses shortly after a light meal or snack [4]

b)) Dosage titration: Increase gradually on basis of tolerance and clinical response, may increase dosage by 50 mg/day every 3 to 4 days [4].

c)) Maintenance dosage: May gradually reduce to lowest effective dose once therapeutic response has been achieved [4].

d)) Maximum dosage: Do not exceed 400 mg/day in outpatients or 600 mg/day in inpatients [4].

2)) Extended-release

a)) Initial dosage: 150 mg/day orally in the evening, preferably at bedtime, on an empty stomach [1]

b)) Dosage titration: May increase by 75 mg once daily every 3 days [1]

c)) Maintenance dosage: May gradually reduce to lowest effective dose once therapeutic response has been achieved [4].

d)) Maximum dosage: Do not exceed 375 mg/day [4]

1.3.1.C.1.c)) General Dosage Information

1)) Withdrawal symptoms may occur, dose should be gradually reduced prior to complete discontinuation of therapy [4][1].

1.3.2] Dosage in Renal Failure**A)) Trazodone Hydrochloride**

1)) Dosage adjustments are not required in renal insufficiency [17].

1.3.4] Dosage in Geriatric Patients**A)) Trazodone Hydrochloride**

1)) Geriatric patients may not tolerate a single oral daily dose, divided-dosing should be considered [18].

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 initiation of trazodone. Allow at least 14 days to elapse between discontinuation of trazodone and initiation of MAOIs intended to treat psychiatric disorders [1].

J) Do not initiate trazodone in a patient receiving linezolid or IV methylene blue. If a patient is already receiving trazodone and treatment with linezolid or IV methylene blue is unavoidable, and the potential benefit of therapy outweighs the risk for serotonin syndrome, discontinue trazodone promptly. Monitor for symptoms of serotonin syndrome for 2 weeks or for 24 hours after the last

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

1.4.1.B| Trazodone Hydrochloride

1) Safety and effectiveness in pediatric patients have not been established [4][1].

2.0| Pharmacokinetics

Onset and Duration

Drug Concentration Levels

ADME

2.1| Onset and Duration

A) Onset

1) Trazodone Hydrochloride

a) Initial Response

1) Depression, oral: 1 week [22].

a) Symptomatic relief may be seen during the first week, with optimal antidepressant effects typically evident within 2 weeks. Among patients who responded to trazodone, 33% and 50% of inpatients and outpatients, respectively, had a significant therapeutic response by the end of the first week, while 75% of all responders demonstrated a significant therapeutic effect by the end of the second week. Twenty-five percent of responders required 2 to 4 weeks for a significant response [22].

b) Peak Response

1) Depression, oral: 2 to 4 weeks [22]

a) Optimal antidepressant effects are typically evident within 2 weeks; however, 25% of patients that responded to trazodone required more than 2 weeks (up to 4 weeks) of drug administration [22].

2.2| Drug Concentration Levels

A) Trazodone Hydrochloride

1) Peak Concentration

a) Oral, immediate-release, multiple-dose: 3.118 mcg/mL (100 mg three times a day) [19]

1j) The mean steady-state C_{max} following oral administration of immediate-release trazodone hydrochloride 100 mg three times a day for 1-week was 3.118 +/- 0.758 mcg x hr/mL [19].

bj) Oral, extended-release, multiple-dose: 1.812 mcg/mL (300 mg once daily); single-dose: 1.188 +/- 0.362 mcg/mL (300 mg) [19].

1j) The mean steady-state C_{max} following oral administration of extended-release trazodone hydrochloride 300 mg once daily for 1-week was 1.812 +/- 0.621 mcg/mL. The C_{max} following single-dose oral administration of extended-release trazodone hydrochloride 300 mg under fasting conditions was 1.188 +/- 0.362 mcg/mL [19].

2j) Time to Peak Concentration

aj) Oral, immediate-release: fasting, 1 hr; with food, 2 hr [22]; extended-release: 9 hr [19]

1j) Peak plasma levels occur approximately 1 hr postdose when trazodone hydrochloride is taken on an empty stomach, or 2 hr postdose when taken with food [22].

2j) Following single-dose oral administration of extended-release trazodone hydrochloride, the mean peak trazodone plasma concentration occurred at a median of 9 hr postdose [19].

3j) Area Under the Curve

aj) Oral, immediate-release, multiple-dose: 33.058 mcg x hr/mL (100 mg three times a day) [19]

1j) The mean steady-state AUC following oral administration of immediate-release trazodone hydrochloride 100 mg three times a day for 1-week was 33.058 +/- 8.006 mcg x hr/mL [19].

bj) Oral, extended-release, multiple-dose: 29.131 mcg x hr/mL (300 mg once daily) [19].

1j) The mean steady-state AUC following oral administration of extended-release trazodone hydrochloride 300 mg once daily for 1-week was 29.131 +/- 9.931 mcg x hr/mL [19].

2.3j ADME

2.3.1j Absorption

Aj) Trazodone Hydrochloride

1j) Bioavailability

aj) Oral: 65% [322].

1j) The bioavailability was 65 +/- 6% and 63 +/- 4% after administration of immediate-release trazodone hydrochloride 100 mg with and without food, respectively (n=8) [322].

2j) Effects of Food

a) Immediate-release

1j) increased absorption, decreased C_{max}, T_{max} delayed [22]

a) Taking immediate-release trazodone hydrochloride shortly after ingestion of food may increase the amount of drug absorbed, decrease the C_{max} and cause a delay in T_{max}. Peak plasma levels occur approximately 1 hr after dosing when taken on an empty stomach and 2 hr after dosing when taken with food. Immediate-release trazodone hydrochloride should be taken shortly after a meal or light snack [22].

b) In a 3-way crossover pharmacokinetic study of immediate-release trazodone in healthy subjects (n=8) absorption was irregular in fasting subjects and improved after food intake. Subjects were administered trazodone hydrochloride 100 mg orally with and without food, and by infusion. Administration of trazodone with food significantly decreased C_{max} (1.88 to 1.47 mcg/mL) and increased T_{max} (1.3 to 2 hr). The bioavailability was 65% +/- 6% and 63% +/- 4%, when taken with or without food, respectively [322].

b) Extended-release

1j) C_{max} increased by about 86% [19]

a) When trazodone hydrochloride extended-release tablets are taken shortly after ingestion of a high-fat meal, the C_{max} increases by about 86% compared to taking it under fasting conditions. The AUC (0 to infinity) and T_{max} are not significantly affected by food. The manufacturer recommends taking extended-release trazodone hydrochloride on an empty stomach [19].

2.3.2] Distribution

A) Distribution Sites

1j) Trazodone Hydrochloride

a) Protein Binding

1j) 89% to 95% [19]

a) Trazodone hydrochloride is 89% to 95% protein bound [19].

b) Tissues and Fluids

1) Trazodone does not appear to selectively localize in any one tissue type but may accumulate in the plasma [22].

B) Distribution Kinetics

1) Trazodone Hydrochloride

a) Volume of Distribution

1) 0.47 to 0.84 L/kg [323][322]

a) The volume of distribution following a single 100-mg oral trazodone dose is 0.84 +/- 0.16 L/kg; following multiple oral trazodone doses, the Vd ranges from 0.47 +/- 0.10 to 0.52 +/- 0.16 L/kg [323][322].

2.3.3] Metabolism

A) Metabolism Sites and Kinetics

1) Trazodone Hydrochloride

a) Liver, extensive [19][324][325]

1) Trazodone is extensively metabolized in the liver by oxidation and hydroxylation [324][325]. Only 0.13% of a dose is recovered in the urine as unchanged trazodone [326].

B) Metabolites

1) Trazodone Hydrochloride

a) meta-chlorophenylpiperazine (mCCP), active [19][22][327].

1) Trazodone is metabolized (via oxidative cleavage) to an active metabolite m-chlorophenylpiperazine (mCCP) by CYP3A4 [19]. It appears that CYP2D6 is also involved in its metabolism [327].

2.3.4] Excretion

A) Kidney

1) Trazodone Hydrochloride

a) Renal Clearance (rate)

1)) 3 to 5.3 L/hr [322][323].

a)) Renal clearance of trazodone hydrochloride is 3 to 5.3 L/hr [322][323].

b)) Renal Excretion (%)

1)) 70% to 75% [19][328][326]

a)) Elimination is primarily renal with 70% to 75% of an oral dose being recovered in the urine within the first 72 hr of ingestion [19]. Only 0.13% of a dose is recovered in the urine as unchanged trazodone [326]

B)) Feces

1)) Trazodone Hydrochloride

a)) 21% [329]

1)) Trazodone is 21% fecally eliminated [329].

C)) Total Body Clearance

1)) Trazodone Hydrochloride

a)) 5.3 L/hr [322]

1)) The total body clearance for trazodone was estimated as 5.3 L/hr in a pharmacokinetic study in normal volunteers (n=8) [322].

2.3.5] Elimination Half-life

A)) Parent Compound

1)) Trazodone Hydrochloride

a)) Immediate-release

1)) 7 hr [322][323].

a)) The elimination half-life of trazodone calculated at steady-state in psychiatric patients was 7 +/- 1.2 hr (n=7) [323]. The elimination half-life following single-dose oral and intravenous administration of trazodone hydrochloride 100 mg was 7.3 +/- 0.8 hr in a pharmacokinetic crossover trial in healthy subjects (n=8) [322]

b)) Extended-release

1j) 10 hr [19]

a) A mean apparent terminal half-life of 10 hr was reported following single-dose oral administration of extended-release trazodone hydrochloride 300 mg [19].

3.0] Cautions

[Contraindications](#)

[Precautions](#)

[Adverse Reactions](#)

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

[Drug Interactions](#)

3.0.A] Black Box WARNING**Trazodone Hydrochloride**

Oral (Tablet, Extended Release; Tablet)

Suicidality and Antidepressant Drugs

Antidepressants increased the risk compared to placebo of suicidal thinking and behavior (suicidality) in children, adolescents, and young adults in short-term studies of major depressive disorder (MDD) and other psychiatric disorders. Anyone considering the use of trazodone hydrochloride tablets 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. Trazodone hydrochloride tablets are not approved for use in pediatric patients [20][1].

3.1] Contraindications**A) [Trazodone](#) Hydrochloride**

1j) Coadministration with an MAOI, including [linezolid](#) or IV methylene blue, or use within 14 days of discontinuing an MAOI; increased risk of [serotonin syndrome](#) [1]

2j) Concomitant use with [saquinavir/ritonavir](#) [21]

3j) Hypersensitivity to [trazodone](#) hydrochloride [22]

3.2] Precautions

A) Trazodone Hydrochloride

- 1) Black box warning: Increased risk of suicidal thinking and behavior, particularly in children, adolescents, and young adults taking antidepressants, and especially during first few months of therapy or following changes in dosage; monitoring recommended [1][22][23]
- 2) Cardiovascular: Use is not recommended during acute recovery period of recent [myocardial infarction](#) [1][22].
- 3) Cardiovascular: A prolonged QT/QTc interval may occur, resulting in [torsade de pointes](#) and sudden death; increased risk with concomitant use of CYP3A4 inhibitors or other drugs known to prolong the QTc interval and in patients with congenital [long QT syndrome](#), hypokalemia, or hypomagnesemia [1].
- 4) Cardiovascular: Use with caution in patients with preexisting cardiac disease; monitoring recommended [22][1].
- 5) Cardiovascular: Hypotension, including orthostatic hypotension and syncope, has been reported; dose adjustments of concomitant antihypertensives may be required [22][1].
- 6) Endocrine and metabolic: Preexisting hypokalemia or hypomagnesemia increases the risk of [torsades de pointes](#) and sudden death [1].
- 7) Endocrine and metabolic: [Hyponatremia](#), usually the result of SIADH, has occurred, especially in volume-depleted and elderly patients or with concurrent diuretic therapy; discontinue if symptoms develop [1].
- 8) Hematologic: Abnormal bleeding, including life-threatening hemorrhages, may occur; increased risk with concomitant NSAIDs, [aspirin](#), [warfarin](#), or other anticoagulants [1].
- 9) Neurologic: Somnolence or sedation resulting in cognitive and motor impairment may occur [1].
- 10) Ophthalmic: Pupillary dilation, resulting in an angle closure attack, may occur in patients with anatomically narrow angles and without a patent [iridectomy](#) [1].
- 11) Psychiatric: [Bipolar disorder](#) increases the risk of precipitation of a mixed episode; rule out disorder prior to initiating therapy [22][1].
- 12) Reproductive: [Priapism](#) may occur, especially in those with predisposing conditions, including [sickle cell anemia](#), [multiple myeloma](#), [leukemia](#), or anatomical deformation of the penis; immediate discontinuation required for an erection lasting longer than 6 hours [22][1].
- 13) [Serotonin syndrome](#): Has been reported, often with concurrent use of other serotonergic drugs (eg, triptans, tricyclic antidepressants, [fentanyl](#), [lithium](#), [tramadol](#), [buspirone](#), tryptophan, St John's wort), MAOIs (including methylene blue IV and [linezolid](#)), and drugs that impair serotonin metabolism; monitoring recommended and discontinue if suspected [1]
- 14) Surgery: Patients undergoing elective surgery should discontinue use for as long as clinically feasible prior to surgery [22].
- 15) Withdrawal: Abrupt discontinuation may result in severe withdrawal symptoms [22][1].

3.3] Adverse Reactions

3.3.1] Cardiovascular Effects

3.3.1.A] Trazodone Hydrochloride

3.3.1.A.1] Bradyarrhythmia

a) Bradycardia has been reported with trazodone use during postmarketing surveillance [22][19].

3.3.1.A.2] Cardiac dysrhythmia

a) Summary

1) Clinical studies in patients with preexisting cardiac disease, indicate that trazodone may be arrhythmogenic in some patients in that population. Arrhythmias identified include isolated premature ventricular contractions, ventricular couplets, and in two patients, short episodes (3 to 4 beats) of ventricular tachycardia. There have also been several post-marketing reports of arrhythmias in trazodone- treated patients who had preexisting cardiac disease. Until the results of prospective studies are available, patients with pre existing cardiac disease should be closely monitored, particularly for cardiac arrhythmias. Trazodone should not be used during the initial recovery phase of myocardial infarction [19][25][26][27][28][29].

b) Trazodone administration has been associated with aggravation of ventricular arrhythmias in 2 patients with preexisting cardiac disease [25][26]. One patient had a mitral valve prolapse and the other had hypertension, stable angina pectoris and atherosclerosis. Administration of trazodone 50 to 300 milligrams daily resulted in an increase in the frequency of ventricular arrhythmias within 1 to 2 weeks. The authors suggest that patients with cardiac arrhythmias and/or mitral valve prolapse should be carefully monitored during trazodone administration.

c) Trazodone was associated with the occurrence of premature ventricular contractions and angina in a 45-year-old male when the dose of the drug was increased to 250 milligrams (mg) daily, following an approximate one month course of 50 to 150 mg daily [27]. After withdrawal from trazodone, the chest pain and arrhythmias resolved. The patient had no previous history of cardiovascular disease.

d) In a hospitalized patient who developed ventricular fibrillation following surgery, administration of trazodone 75 milligrams for three days was associated with sinus tachycardia alternating with bradycardia and sinus arrest, hypotension, and premature ventricular contractions [28].

e) In three patients, aged 26, 61 and 41 years with preexisting cardiac disease, therapeutic use of trazodone appears to have exacerbated premature ventricular contractions in two cases and ventricular tachycardia in one case [25][29].

3.3.1.A.3] Edema

a) Incidence: at least 1% [19]

b) Edema has been reported in at least 1% of trazodone extended-release (mean daily dose of 310 mg over 6 weeks) recipients (n=202) in clinical studies of adults, ages 18 to 80 years old over a total duration of 8 weeks [19].

c) Edema has been reported with trazodone use during postmarketing surveillance [22].

d) Peripheral edema was described in 10 of 100 patients administered trazodone in doses of 50 to 600 mg daily for depression [30]. The mean age of the patients was 56 years, with 9 being women. The mean dose of the drug that induced edema was 370 mg daily and was associated with a weight gain of 4.5 kg (mean) (range 2 to 6.8 kg). The authors failed to provide information on the time of onset of edema during trazodone therapy. Withdrawal of the drug or reduction in dose resulted in edema resolution

in all patients. Peripheral edema, with an onset within 24 hours of initiation of [trazodone](#) therapy, was attributed to an allergic response in one case, but no immunologic evidence was presented [31].

3.3.1.A.4] Heart block

a) Conduction block has been reported with [trazodone](#) use during postmarketing surveillance [22][19]. [Trazodone](#) may be arrhythmogenic in patients with cardiac disease [19]

b) [Trazodone](#) has been reported to produce minimal to no effects on cardiac conduction and has not produced the [cardiotoxicity](#) observed with tricyclic antidepressants [18][32]. However, other data have described [ventricular arrhythmias](#) and [heart block](#) with [trazodone](#) in heart patients [25][33], suggesting caution in patients with preexisting cardiac disease [33].

c) [Complete heart block](#) occurred in 77-year-old alcoholic with depression 40 minutes following a single dose of [trazodone](#) (50 milligrams). The patient had a history of [atherosclerotic cardiovascular disease](#), [hypertension](#) and [mitral regurgitation](#); a history of [transient ischemic attacks](#) was also present [33]. These data suggest that even one dose of [trazodone](#) may produce cardiac conduction defects in patients at risk for conduction delay.

3.3.1.A.5] Hypertension

a) Incidence: 1.3% to 2.1% [22]

b) [Hypertension](#) has been reported in 1.3% to 2.1% of [trazodone](#) recipients (n=299) compared with less than 1% to 1.1% of placebo recipients (n=253) in clinical trials [22].

3.3.1.A.6] Hypotension

a) Incidence: 3.8% to 7% [22]

b) Hypotension has been reported in 3.8% to 7% of [trazodone](#) recipients (n=299) compared with 0% to 1.1% of placebo recipients (n=253) in clinical trials [22].

c) Hypotension has been reported in patients receiving [trazodone](#) [19].

3.3.1.A.7] Orthostatic hypotension

a) Orthostatic hypotension has been reported with [trazodone](#) use during postmarketing surveillance [22][19].

b) The most frequent cardiovascular side effect during therapy is postural hypotension, which may be accompanied by syncope, especially in patients taking concomitant [antihypertensive therapy](#) (Rakel, 1984)[34]. The mild hypotension that has been reported during [trazodone](#) therapy is usually transient and not requiring discontinuation [35][36][37][38].

3.3.1.A.8] Prolonged QT interval

a) [Trazodone](#) is known to prolong the QT interval and has been reported during postmarketing experience. [Trazodone](#) may be arrhythmogenic in patients with cardiac disease [19].

b) [Trazodone](#) 150 milligrams, administered in a single dose to eight healthy volunteers, was found to significantly prolong the QTc interval and decrease T wave height at 30 minutes after ingestion [41].

3.3.1.A.9] Syncope

a) Incidence: 2.8% to 4.5% [22]

b) Syncope has been reported in 2.8% to 4.5% of [trazodone](#) recipients (n=299) compared with 1.3% to 2.1% of placebo recipients (n=253) in clinical trials [22].

3.3.1.A.10] Tachycardia

a) Summary

- 1) Trazodone may be associated with the exacerbation of ventricular tachycardia [39][40][29].
- b) Tachycardia/palpitations have been reported in 0% to 7% of trazodone recipients (n=299) compared with 0% to 7% of placebo recipients (n=253) in clinical trials [22]. Trazodone may be arrhythmogenic in patients with cardiac disease [19].
- c) Exercise-induced nonsustained ventricular tachycardia was described in a 79-year-old woman with no underlying heart disease receiving trazodone 50 milligrams twice daily. The relationship to trazodone was confirmed by treadmill testing initially, following discontinuation, and after rechallenge with trazodone [39].
- d) Trazodone does not appear to produce tachycardia, even in patients with hypotension, and consistently lowers baseline heart rate in therapeutic doses [40].
- e) Exacerbation of ventricular tachycardia was associated with administration of trazodone to a 41-year-old female patient. The patient had a history of complex ventricular ectopy and was symptomatic only with palpitations. On one occasion, while not receiving antiarrhythmics, she was started on trazodone 50 milligrams daily for depression. Two weeks after the start of therapy, the patient experienced dizzy spells and a Holter recording demonstrated ventricular tachycardia at a rate of 160 beats per minute. Trazodone was discontinued and within 24 hours the ectopy returned to baseline. Due to potential hazards, the patient was not rechallenged [29]. Administration of trazodone to patients with ventricular ectopy should be accompanied by cardiac monitoring.

3.3.1.A.11] Torsades de pointes

- a) Torsades de Pointes has been reported with immediate-release trazodone at doses of 100 mg/day or less in postmarketing experience [19].

3.3.2] Dermatologic Effects

3.3.2.A] Trazodone Hydrochloride

3.3.2.A.1] Acne

- a) Incidence: less than 1% [19]
- b) Acne has been reported in less than 1% of trazodone extended-release (mean daily dose of 310 mg over 6 weeks) recipients (n=202) in clinical studies of adults, ages 18 to 80 years old over a total duration of 8 weeks [19].

3.3.2.A.2] Erythema multiforme

- a) Erythema multiforme was described in a 63-year-old woman with depression following four days of oral trazodone 300 mg to 400 mg. The patient presented with a disseminated macular papular eruption and erythematous scaly plaques on both the hands and soles of the feet. Lithium carbonate had also been prescribed and both drugs were discontinued prior to initiation of symptomatic treatment with betamethasone ointment. The patient developed bullae on the right heel and erosions on the tongue and buccal mucosa two days after admission and Domeboro(R) foot soaks and Chloraseptic(R) mouthwash were begun. The patient gradually recovered without sequelae. Lithium has not been associated with erythema multiforme and was taken by this patient for two weeks without incident. The first symptoms of a rash began four days after trazodone was begun; this led the authors to suggest that trazodone was the offending agent [66].

3.3.2.A.3] Flushing

- a) Incidence: less than 1% [19]
- b) Flushing has been reported in less than 1% of [trazodone](#) extended-release (mean daily dose of 310 mg over 6 weeks) recipients (n=202) in clinical studies of adults, ages 18 to 80 years old over a total duration of 8 weeks [19].

3.3.2.A.4] Night sweats

- a) Incidence: less than 1% [19]
- b) Hyperhidrosis has been reported in less than 1% of [trazodone](#) extended-release (mean daily dose of 310 mg over 6 weeks) recipients (n=202) in clinical studies of adults, ages 18 to 80 years old over a total duration of 8 weeks [19].
- c) Sweating/clamminess has been reported in 0% to 1.4% of [trazodone](#) recipients (n=299) compared with less than 1% to 1.1% of placebo recipients (n=253) in clinical trials [22].

1) Incidence: at least 1% [19]

2) Night sweats have been reported in at least 1% of [trazodone](#) extended-release (mean daily dose of 310 mg over 6 weeks) recipients (n=202) in clinical studies of adults, ages 18 to 80 years old over a total duration of 8 weeks [19].

3.3.2.A.5] Photosensitivity

- a) Incidence: less than 1% [19]
- b) [Photosensitivity reaction](#) has been reported in less than 1% of [trazodone](#) extended-release (mean daily dose of 310 mg over 6 weeks) recipients (n=202) in clinical studies of adults, ages 18 to 80 years old over a total duration of 8 weeks [19].

3.3.2.A.6] Rash

- a) Skin rashes, which respond to drug withdrawal and/or antihistamine therapy, have occurred during [trazodone](#) therapy [67]; (Al- Yassiri & Bridges, 1980).

3.3.3] Endocrine/Metabolic Effects**3.3.3.A] [Trazodone](#) Hydrochloride****3.3.3.A.1] [Isolated prolactin deficiency](#)**

- a) Several studies have demonstrated no change [53] or slightly decreased serum prolactin levels [54] [55] during [trazodone](#) therapy. No reports of breast tenderness were found in the literature [56], but the manufacturer received 8 incident reports, although none had substantiated prolactin levels (Pers Comm, 1985).

3.3.3.A.2] Weight gain

- a) Incidence: 1.4% to 4.5% [22]
- b) Weight gain has been reported in 1.4% to 4.5% of [trazodone](#) recipients (n=299) compared with 0% to 1.9% of placebo recipients (n=253) in clinical trials [22].

3.3.3.A.3] Weight loss

- a) Incidence: up to 5.7% [22]
- b) Weight loss has been reported in up to 5.7% of [trazodone](#) recipients (n=299) compared with 2.5% to 3.2% of placebo recipients (n=253) in clinical trials [22].

3.3.4] Gastrointestinal Effects

3.3.4.A] [Trazodone](#) Hydrochloride

3.3.4.A.1] Abdominal pain

- a) Incidence: at least 1% [19]
- b) Abdominal pain has been reported in at least 1% of [trazodone](#) extended-release (mean daily dose of 310 mg over 6 weeks) recipients (n=202) in clinical studies of adults, ages 18 to 80 years old over a total duration of 8 weeks [19].

3.3.4.A.2] Constipation

- a) Incidence: 7% to 8% [22][19]
- b) Constipation has been reported in 8% of [trazodone](#) extended-release (mean daily dose of 310 mg over 6 weeks) recipients (n=202) compared with 2% of placebo recipients (n=204) in clinical studies of adults, ages 18 to 80 years old over a total duration of 8 weeks [19].
- c) Constipation has been reported in 7% to 7.6% of [trazodone](#) recipients (n=299) compared with 4.2% to 5.7% of placebo recipients (n=253) in clinical trials [22].
- d) Constipation has been reported as an adverse effect of [trazodone](#) therapy. In a comparative study with [imipramine](#), the incidence of constipation was less in [trazodone](#) patients (8%) than [imipramine](#) treated patients (20%) [58].

3.3.4.A.3] Diarrhea

- a) Incidence: up to 9% [19]
- b) Diarrhea has been reported in 9% of [trazodone](#) extended-release (mean daily dose of 310 mg over 6 weeks) recipients (n=202) compared with 11% of placebo recipients (n=204) in clinical studies of adults, ages 18 to 80 years old over a total duration of 8 weeks [19].
- c) Diarrhea has been reported in up to 4.5% of [trazodone](#) recipients (n=299) compared with 1.1% to 1.9% of placebo recipients (n=253) in clinical trials [22].

3.3.4.A.4] [Gastro-esophageal reflux disease with esophagitis](#)

- a) Incidence: less than 1% [19]
- b) [Reflux esophagitis](#) has been reported in less than 1% of [trazodone](#) extended-release (mean daily dose of 310 mg over 6 weeks) recipients (n=202) in clinical studies of adults, ages 18 to 80 years old over a total duration of 8 weeks [19].

3.3.4.A.5] Loss of appetite

- a) Incidence: up to 3.5% [22]
- b) Decreased appetite has been reported in 0% to 3.5% of [trazodone](#) recipients (n=299) compared with up to 5.3% of placebo recipients (n=253) in clinical trials [22].
- c) Anorexia and [hypomania](#) have been reported in a patient given 100 mg [trazodone](#) and 500 mg of tryptophan three times a week. Appetite returned when [trazodone](#) was discontinued [57].

3.3.4.A.6] Nausea

a) Incidence: 21% [19]

b) Nausea has been reported in 21% of [trazodone](#) extended-release (mean daily dose of 310 mg over 6 weeks) recipients (n=202) compared with 13% of placebo recipients (n=204) in clinical studies of adults, ages 18 to 80 years old over a total duration of 8 weeks [19].

3.3.4.A.7] Nausea and vomiting

a) Nausea/vomiting has been reported in 9.9% to 12.7% of [trazodone](#) recipients (n=299) compared with 1.1% to 9.5% of placebo recipients (n=253) in clinical trials [22].

3.3.4.A.8] Taste sense altered

a) Incidence: up to 1.4% [22][19]

b) Dysgeusia has been reported in at least 1% of [trazodone](#) extended-release (mean daily dose of 310 mg over 6 weeks) recipients (n=202) in clinical studies of adults, ages 18 to 80 years old over a total duration of 8 weeks [19].

c) Bad taste in mouth has been reported in 0% to 1.4% of [trazodone](#) recipients (n=299) compared with 0% of placebo recipients (n=253) in clinical trials [22].

3.3.4.A.9] Vomiting

a) Incidence: at least 1% [19]

b) Vomiting has been reported in at least 1% of [trazodone](#) extended-release (mean daily dose of 310 mg over 6 weeks) recipients (n=202) in clinical studies of adults, ages 18 to 80 years old over a total duration of 8 weeks [19].

3.3.4.A.10] Xerostomia

a) Incidence: 14% to 33.8% [22][19]

b) Dry mouth has been reported in 25% of [trazodone](#) extended-release (mean daily dose of 310 mg over 6 weeks) recipients (n=202) compared with 13% of placebo recipients (n=204) in clinical studies of adults, ages 18 to 80 years old over a total duration of 8 weeks [19].

c) Dry mouth has been reported in 14.8% to 33.8% of [trazodone](#) recipients (n=299) compared with 8.4% to 20.3% of placebo recipients (n=253) in clinical trials [22].

d) [Xerostomia](#) has been reported with [trazodone](#) therapy, but the incidence is lower (15%) than in imipramine-treated patients (45%) [58].

3.3.5] Hematologic Effects

3.3.5.A] [Trazodone Hydrochloride](#)

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

a) A 40-year-old male had been using [trazodone](#) for one month prior to admission, with no history of any other concurrent drug or chemical use. He was admitted for perianal [furuncles](#). Hematology laboratory values were normal with the exception of an elevated [erythrocyte sedimentation rate](#) (ESR) and decreased [leukocyte](#) count of 3.7×10^9 (normal range of $4.0 - 10.0 \times 10^9$). Differential cell count was reported to be 74% [lymphocytes](#), 25% monocytes, and 1% eosinophils (absolute neutrophil count 0). Pus from his [furuncles](#) yielded staphylococcus aureus. Treatment was begun with flucloxacillin. [Trazodone](#) therapy was discontinued. Four days later, his [leukocyte](#) count had increased and ESR had decreased. Eleven days after admission, laboratory values had returned to normal [24].

3.3.5.A.2] Hemolytic anemia

a)] Hemolytic anemia has been reported with trazodone use during postmarketing surveillance [22][19].

3.3.5.A.3] Leukocytosis

a)] Leukocytosis has been reported with trazodone use during postmarketing surveillance [22][19].

3.3.5.A.4] Methemoglobinemia

a)] Methemoglobinemia has been reported with trazodone use during postmarketing surveillance [22][19].

3.3.6] Hepatic Effects

3.3.6.A] Trazodone Hydrochloride

3.3.6.A.1] Cholestasis

a)] Summary

1)] Cholestasis has resulted from the use of trazodone [59][60].

b)] A 46-year-old Hispanic man developed acute hepatitis and cholestasis 4 days after receiving trazodone as part of standard protocol for cocaine withdrawal. The man was HIV positive, hepatitis Ab positive, and hepatitis C virus positive. The detoxification treatment consisted of methadone 50 milligrams (mg) per day, clonidine 0.1 mg twice daily, and trazodone 200 mg/day. The patient's symptoms of depression, listlessness, fatigue, and poor sleep over the next 3 days were attributed to cocaine withdrawal. However, laboratory tests on day 5 showed a 100-fold increase in ALT (alanine amino transferase) and a 50-fold increase in AST (aspartate amino transferase). Clonidine and trazodone were discontinued. Ten days later, hepatotoxicity was greatly reduced. Six months later, laboratory results were completely normal and the patient was asymptomatic. Since trazodone has been previously associated with hepatotoxicity (and clonidine has not), and since the timing and extent of response were not characteristic of an exacerbation of hepatitis, it was presumed that trazodone was responsible for the hepatotoxicity [59].

c)] Intrahepatic cholestasis was reported in a 71-year-old woman who had received trazodone 50 milligrams daily for two weeks. The patient presented with increased bilirubin, aspartate transaminase (AST), and alkaline phosphatase levels (ALP). Tests for viral hepatitis were negative. Upon discontinuation of trazodone, bilirubin levels continued to increase; however AST and ALP levels both decreased. Eight weeks after trazodone was withdrawn, liver enzymes and bilirubin returned to normal [60]. It is suggested that monitoring of hepatic enzymes and bilirubin be undertaken during the first four weeks of treatment in trazodone- treated patients.

3.3.6.A.2] Hepatitis

a)] Summary

1)] Hepatitis has resulted from use of trazodone [59][63].

b)] A 46-year-old Hispanic man developed acute hepatitis and cholestasis 4 days after receiving trazodone as part of standard protocol for cocaine withdrawal. The man was HIV positive, hepatitis Ab positive, and hepatitis C virus positive. The detoxification treatment consisted of methadone 50 milligrams (mg) per day, clonidine 0.1 mg twice daily, and trazodone 200 mg/day. The patient's

symptoms of depression, listlessness, fatigue, and poor sleep over the next 3 days were attributed to cocaine withdrawal. However, laboratory tests on day 5 showed a 100-fold increase in ALT (alanine amino transferase) and a 50-fold increase in AST (aspartate amino transferase). Clonidine and trazodone were discontinued. Ten days later, hepatotoxicity was greatly reduced. Six months later, laboratory results were completely normal and the patient was asymptomatic. Since trazodone has been previously associated with hepatotoxicity (and clonidine has not), and since the timing and extent of response were not characteristic of an exacerbation of hepatitis, it was presumed that trazodone was responsible for the hepatotoxicity [59].

c) A 75-year-old Asian woman, who had experienced chronic nausea and anorexia since starting trazodone, presented with dark urine, pale stools, and jaundice following approximately eight months of trazodone treatment, 150 milligrams/day, for depression. Laboratory tests showed elevated prothrombin time (PT), partial thromboplastin time (PTT), bilirubin, and liver enzymes. Negative immunostains on liver biopsy and serologic tests for hepatitis B were consistent with remote past exposure to hepatitis B but not of ongoing viral infection. One week after discontinuing trazodone, the nausea and anorexia resolved. Aminotransferase enzyme levels, PT, and PPT normalized within 2 weeks, while bilirubin and gamma glutamyltransferase levels gradually returned to normal in 6 months [63].

3.3.6.A.3] Increased liver enzymes

a) Summary

1) Trazodone has been reported to cause elevated liver enzymes. The enzyme levels seem to normalize after discontinuing the drug [61][62].

b) Jaundice and elevated liver function tests occurred in a 38-year-old woman after she had been taking trazodone for 18 months and while she was also using low-dose steroids for rheumatoid arthritis. She presented with itching, nausea, and an episode of vomiting. All medications were withdrawn, and her liver tests started to improve. Approximately a week later, the patient on her own took trazodone for two days. Her bilirubin, aspartate aminotransferase, and alanine transaminase levels promptly rose. Normalization occurred with a second withdrawal of trazodone [61].

c) Hepatotoxicity was reported in a 63-year-old male treated for a chronic major depressive disorder with trazodone, following three weeks of therapy (doses up to 500 milligrams daily). At that time, liver function tests were mildly elevated. Eight days later, liver enzymes were markedly elevated and biopsy revealed mild portal expansion with moderate numbers of eosinophils, several mononuclear and polymorphonuclear leukocytes, scattered foci of Kupffer cells and acidophil bodies. Hepatic enzymes returned to normal four weeks after withdrawal of trazodone [62]. A cause and effect relationship is difficult to establish in this case since liver enzymes did not peak until eight days after discontinuing the drug.

3.3.7] Immunologic Effects

3.3.7.A] Trazodone Hydrochloride

3.3.7.A.1] Hypersensitivity reaction

a) Incidence: less than 1% [19]

b) Hypersensitivity has been reported in less than 1% of trazodone extended-release (mean daily dose of 310 mg over 6 weeks) recipients (n=202) in clinical studies of adults, ages 18 to 80 years old over a total duration of 8 weeks [19].

3.3.8] Musculoskeletal Effects

3.3.8.A] Trazodone Hydrochloride**3.3.8.A.1] Backache**

- a) Incidence: 5% [19]
- b) Back pain has been reported in 5% of **trazodone** extended-release (mean daily dose of 310 mg over 6 weeks) recipients (n=202) compared with 3% of placebo recipients (n=204) in clinical studies of adults, ages 18 to 80 years old over a total duration of 8 weeks [19].

3.3.8.A.2] Musculoskeletal symptom

- a) Incidence: at least 1% [19]
- b) Musculoskeletal complaints have been reported in at least 1% of **trazodone** extended-release (mean daily dose of 310 mg over 6 weeks) recipients (n=202) in clinical studies of adults, ages 18 to 80 years old over a total duration of 8 weeks [19].

3.3.8.A.3] Myalgia

- a) Incidence: up to 5.6% [22][19]
- b) Myalgia has been reported in at least 1% of **trazodone** extended-release (mean daily dose of 310 mg over 6 weeks) recipients (n=202) in clinical studies of adults, ages 18 to 80 years old over a total duration of 8 weeks [19].
- c) Muscle aches/pains have been reported in 5.1% to 5.6% of **trazodone** recipients (n=299) compared with 2.5% to 3.2% of placebo recipients (n=253) in clinical trials [22].

3.3.8.A.4] Spasmodic movement

- a) Incidence: less than 1% [19]
- b) Muscle twitching has been reported in less than 1% of **trazodone** extended-release (mean daily dose of 310 mg over 6 weeks) recipients (n=202) in clinical studies of adults, ages 18 to 80 years old over a total duration of 8 weeks [19].

3.3.9] Neurologic Effects**3.3.9.A] Trazodone Hydrochloride****3.3.9.A.1] Abnormal gait**

- a) Incidence: less than 1% [19]
- b) Gait disturbance has been reported in less than 1% of **trazodone** extended-release (mean daily dose of 310 mg over 6 weeks) recipients (n=202) in clinical studies of adults, ages 18 to 80 years old over a total duration of 8 weeks [19].

3.3.9.A.2] Amnesia

- a) Incidence: less than 1% [19]
- b) Amnesia has been reported in less than 1% of **trazodone** extended-release (mean daily dose of 310 mg over 6 weeks) recipients (n=202) in clinical studies of adults, ages 18 to 80 years old over a total duration of 8 weeks [19].

3.3.9.A.3] Aphasia

- a) Incidence: less than 1% [19]

b) **Aphasia** has been reported in less than 1% of **trazodone** extended-release (mean daily dose of 310 mg over 6 weeks) recipients (n=202) in clinical studies of adults, ages 18 to 80 years old over a total duration of 8 weeks [19].

3.3.9.A.4] Confusion

a) Incidence: up to 5.7% [22][19]

b) Confusion has been reported in at least 1% of **trazodone** extended-release (mean daily dose of 310 mg over 6 weeks) recipients (n=202) in clinical studies of adults, ages 18 to 80 years old over a total duration of 8 weeks [19].

c) Confusion has been reported in 4.9% to 5.7% of **trazodone** recipients (n=299) compared with 0% to 7.6% of placebo recipients (n=253) in clinical trials [22].

3.3.9.A.5] Coordination problem

a) Incidence: up to 4.9% [22][19]

b) Abnormal coordination has been reported in at least 1% of **trazodone** extended-release (mean daily dose of 310 mg over 6 weeks) recipients (n=202) in clinical studies of adults, ages 18 to 80 years old over a total duration of 8 weeks [19].

c) Incoordination has been reported in 1.9% to 4.9% of **trazodone** recipients (n=299) compared with 0% of placebo recipients (n=253) in clinical trials [22].

3.3.9.A.6] Disorientated

a) Incidence: up to 2.1% [22][19]

b) Disorientation has been reported in at least 1% of **trazodone** 310 mg (mean daily dose over 6 weeks) recipients (n=202) in clinical studies of adults, ages 18 to 80 years old over a total duration of 8 weeks [19].

c) Disorientation has been reported in up to 2.1% of **trazodone** recipients (n=299) compared with 0% of placebo recipients (n=253) in clinical trials [22].

3.3.9.A.7] Dizziness

a) Incidence: 25% [19]

b) Dizziness has been reported in 25% of **trazodone** extended-release (mean daily dose of 310 mg over 6 weeks) recipients (n=202) compared with 12% of placebo recipients (n=204) in clinical studies of adults, ages 18 to 80 years old over a total duration of 8 weeks [19].

c) Dizziness/lightheadedness has been reported in 19.7% to 28% of **trazodone** recipients (n=299) compared with 5.3% to 15.2% of placebo recipients (n=253) in clinical trials [22].

3.3.9.A.8] Dystonia

a) Summary

1) Dystonic reactions have been reported only in case reports. A possible mechanism for this effect is impairment of nigrostriatal **dopamine** activity by serotonin [43][44].

b) In one case report, a 14-year-old boy was initially treated with **fluvoxamine** 50 milligrams (mg)/day (given in the morning) with gradual increases to 150 mg/day by day 28. **Trazodone** 50 mg/day (given at night) was added to the regimen on day seven. By day 34 (of **fluvoxamine** treatment), the boy developed acute **DYSTONIA**, manifested as jaw **trismus** and neck rigidity, which was controlled with three intramuscular doses of 2 mg **benztropine** within 24 hours. **Trazodone** was discontinued and the symptoms did not recur [43].

c) In a case report, [dystonia](#) was reported in a 24-year-old man treated for [posttraumatic stress disorder](#). The patient started on [trazodone](#) 25 milligrams (mg) at bedtime for two weeks, and then this dose was increased to 50 mg. Three days after starting the higher dosages, he presented to the emergency department with his mouth immobile in an open position, complaining of jaw stiffness and feeling as if his face was "frozen." The symptoms were relieved by administration of a single 50 mg dose of intravenous [diphenhydramine](#). Because the same adverse effect was noted over a year later in the patient's treatment after he began treatment with [sertraline](#), the authors hypothesized that the mechanism causing the [dystonia](#) was common to both drugs, possibly associated with enhancement of serotonergic neurotransmission that impairs nigrostriatal [dopamine](#) activity [44].

3.3.9.A.9] Excitement

a) Excitement has been reported in 1.4% to 5.1% of [trazodone](#) recipients (n=299) compared with 1.1% to 5.7% of placebo recipients (n=253) in clinical trials [22].

3.3.9.A.10] Headache

a) Incidence: 9.9% to 33% [22][19]

b) Headache has been reported in 33% of [trazodone](#) extended-release (mean daily dose of 310 mg over 6 weeks) recipients (n=202) compared with 27% of placebo recipients (n=204) in clinical studies of adults, ages 18 to 80 years old over a total duration of 8 weeks [19].

c) Headache has been reported in 9.9% to 19.8% of [trazodone](#) recipients (n=299) compared with 5.3% to 15.8% of placebo recipients (n=253) in clinical trials [22].

3.3.9.A.11] Hypesthesia

a) Incidence: less than 1% [19]

b) Hypesthesia has been reported in less than 1% of [trazodone](#) extended-release (mean daily dose of 310 mg over 6 weeks) recipients (n=202) in clinical studies of adults, ages 18 to 80 years old over a total duration of 8 weeks [19].

3.3.9.A.12] Impaired cognition

a) Adult Clinical Trials

1) General use (unspecified route; age 65 years or older): Systematic review identified 18 studies describing anticholinergic medication use in 124,286 elderly patients, and meta-analysis revealed a significant 45% increased risk of cognitive impairment (11 studies) [52]

3.3.9.A.13] Insomnia

a) Incidence: 6.4% to 9.9% [22]

b) Insomnia has been reported in 6.4% to 9.9% of [trazodone](#) recipients (n=299) compared with 10.5% to 12% of placebo recipients (n=253) in clinical trials [22].

c) Insomnia has been reported with [trazodone](#) use during postmarketing surveillance [22][19].

3.3.9.A.14] Memory impairment

a) Incidence: up to 1.4% [22][19]

b) [Memory impairment](#) has been reported in at least 1% of [trazodone](#) (mean daily dose of 310 mg over 6 weeks) recipients (n=202) in clinical studies of adults, ages 18 to 80 years old over a total duration of 8 weeks [19].

c) **Memory impairment** has been reported in up to 1.4% of **trazodone** recipients (n=299) compared with less than 1% of placebo recipients (n=253) in clinical trials [22].

3.3.9.A.15] Migraine

a) Incidence: at least 1% [19]

b) Migraine has been reported in at least 1% of **trazodone** extended-release (mean daily dose of 310 mg over 6 weeks) recipients (n=202) in clinical studies of adults, ages 18 to 80 years old over a total duration of 8 weeks [19].

3.3.9.A.16] Motor speech disorder

a) Incidence: less than 1% [19]

b) Speech disorder has been reported in less than 1% of **trazodone** extended-release (mean daily dose of 310 mg over 6 weeks) recipients (n=202) in clinical studies of adults, ages 18 to 80 years old over a total duration of 8 weeks [19].

3.3.9.A.17] Myoclonus

a) Summary

1) Myoclonus has been reported in patients receiving **trazodone**. The myoclonus was reversible upon withdrawal of **trazodone** [45][46].

b) Myoclonus was reported in a 38-year-old woman receiving 300 milligrams/day [45]. This may be related to serotonergic activity.

c) A high incidence of myoclonus was reported with cyclic antidepressant therapy with **imipramine**, **desipramine**, **amitriptyline**, **doxepin**, **trazodone**, **nortriptyline** and **maprotiline** [46]. Ninety-eight patients (93%) with **major depression** or **panic disorder** were treated with these agents in initial doses of 50 milligrams (mg) daily of **imipramine** or its equivalent increasing to a maximum of 300 mg daily after several weeks. Of these patients, 39 (40%) developed myoclonus after initiation of therapy, with the myoclonus being clinically significant in nine (9%) and resulting in withdrawal of the antidepressant or a medication change. Myoclonus occurred within one month of therapy in 81% of the 39 patients, with 46% of patients developing myoclonus within two weeks; the mean dose of antidepressant being administered at the time of myoclonus was 169 mg daily in **imipramine** equivalents, which was similar to the mean dose utilized by the patients not developing myoclonus (164 mg daily). Myoclonus was reversible upon withdrawal of the antidepressant but persisted if medication changes were not initiated; however, spontaneous remission of myoclonus was observed in nine patients. No predictors for the development of myoclonus were observed.

3.3.9.A.18] Neuroleptic malignant syndrome

a) **Neuroleptic malignant syndrome** (NMS)-like reactions, including life-threatening cases, have been reported with the use of antidepressants, and may occur with **trazodone** therapy. 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. 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). **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 [19].

3.3.9.A.19] Paresthesia

- a) Incidence: up to 1.4% [22][19]
- b) Paraesthesia has been reported in at least 1% of [trazodone](#) extended-release mean daily dose of 310 mg over 6 weeks) recipients (n=202) in clinical studies of adults, ages 18 to 80 years old over a total duration of 8 weeks [19].
- c) Paraesthesia has been reported in 0% to 1.4% of [trazodone](#) recipients (n=299) compared with less than 1% of placebo recipients (n=253) in clinical trials [22].

3.3.9.A.20] Parkinsonism

- a) A 57-year-old man who had undergone [hemodialysis](#) for 8 years for [end-stage renal disease](#) was given oral [trazodone](#) 100 milligrams/day for [major depression](#). His depressive symptoms disappeared, but over 18 months he gradually developed parkinsonian symptoms, including cogwheel rigidity, [akinesia](#), and gait disturbance. His [parkinsonism](#) improved within 1 week of discontinuing [trazodone](#). No serum concentrations of [trazodone](#) or its metabolites were obtained, but the clinical course strongly suggested that the parkinsonian symptoms were induced by [trazodone](#) [47].

3.3.9.A.21] Reduced concentration

- a) Incidence: 1.3% to 2.8% [22]
- b) Decreased concentration has been reported in 1.3% to 2.8% of [trazodone](#) recipients (n=299) compared with up to 2.1% of placebo recipients (n=253) in clinical trials [22].

3.3.9.A.22] Seizure

- a) General Information

- 1) [Trazodone](#) had the lowest numbers needed to harm value over 5-years of follow-up compared to other antidepressants [48].

- b) Adult Clinical Trials

- 1) Depression (oral route): A significant increase in the risk of [epilepsy](#)/seizure was reported with [trazodone](#) (more than 5 times higher) when compared with periods of no treatment in the first 5 years of follow-up [48].

- c) Adult Case Reports

- 1) A report described a 47-year-old man who developed complex partial seizures after treatment with [trazodone](#) 150 mg/day for three weeks. EEG findings were abnormal after discontinuation of [trazodone](#) and it was speculated that [trazodone](#) unmasked an underlying seizure disorder [49].
 - 2) Multiple tonic-clonic seizures occurred in a 50-year-old woman with no history of [epilepsy](#) following 18 days of [trazodone](#) therapy (50 mg daily) . The patient also had fever on admission; it was unclear if this contributed to seizure activity [50].
 - 3) Based on reports to the manufacturer, over 30 cases of seizures have occurred with [trazodone](#) administration. Sixteen reported cases had previous documented seizure problems [50][51][49].

3.3.9.A.23] Serotonin syndrome

a) **Serotonin syndrome**, including life-threatening cases have been reported with the use of antidepressants, and may occur with **trazodone** therapy. 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 [19].

3.3.9.A.24] Somnolence

- a) Incidence: 23.9% to 46% [22][19]
- b) Somnolence and sedation have been reported in 46% of **trazodone** extended-release (mean daily dose of 310 mg over 6 weeks) recipients (n=202) compared with 19% of placebo recipients (n=204) in clinical studies of adults, ages 18 to 80 years old over a total duration of 8 weeks [19].
- c) Drowsiness has been reported in 23.9% to 40.8% of **trazodone** recipients (n=299) compared with 6.3% to 19.6% of placebo recipients (n=253) in clinical trials [22].
- d) The most commonly reported adverse effects of **trazodone** therapy are drowsiness and lethargy. In a study of nine patients who received **trazodone** 200 to 600 milligrams/day for 28 days, three were lethargic and two were drowsy [42][36][37].
- e) Twelve of 50 patients who were receiving 200 to 600 milligrams/day felt drowsy, lethargic and dizzy during a four week treatment period [36]. Drowsiness was reported in 5.6% of patients in another report [37].

3.3.9.A.25] Tremor

- a) Incidence: up to 5.1% [22][19]
- b) Tremor has been reported in at least 1% of **trazodone** extended-release (mean daily dose of 310 mg over 6 weeks) recipients (n=202) in clinical studies of adults, ages 18 to 80 years old over a total duration of 8 weeks [19].
- c) Tremors have been reported in 2.8% to 5.1% of **trazodone** recipients (n=299) compared with 1.1% to 3.8% of placebo recipients (n=253) in clinical trials [22].

3.3.10] Ophthalmic Effects

3.3.10.A] **Trazodone Hydrochloride**

3.3.10.A.1] **Angle-closure glaucoma**

a) General Information

- 1) Pupillary dilation that occurs after taking antidepressants may cause an angle closure attack in patients with anatomically narrow angles without a patent **iridectomy** [1].

b) Prevention and Management

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

3.3.10.A.2] **Blurred vision**

- a) Incidence: 5% to 14.7% [22][19]

- b) Blurred vision has been reported in 5% of [trazodone](#) extended-release (mean daily dose of 310 mg over 6 weeks) recipients (n=202) compared with 0% of placebo recipients (n=204) in clinical studies of adults, ages 18 to 80 years old over a total duration of 8 weeks [19].
- c) Blurred vision has been reported in 6.3% to 14.7% of [trazodone](#) recipients (n=299) compared with 3.8% to 4.2% of placebo recipients (n=253) in clinical trials [22].
- d) In a comparative study with [imipramine](#), the incidence of blurred vision was less in [trazodone](#) patients (8%) than in [imipramine](#) patients (20%) [58].

3.3.10.A.3] Dry eye syndrome

- a) Incidence: less than 1% [19]
- b) Dry eye has been reported in 1% or less of [trazodone](#) extended-release (mean daily dose of 310 mg over 6 weeks) recipients (n=202) in clinical studies of adults, ages 18 to 80 years old over a total duration of 8 weeks [19].

3.3.10.A.4] Eye / vision finding

- a) Red, tired, and itchy eyes have been reported in 0% to 2.8% of [trazodone](#) recipients (n=299) compared with 0% of placebo recipients (n=253) in clinical trials [22].
- b) The reappearance or persistence of an image has been associated with dosage increases in patients receiving [trazodone](#) therapeutically (Hughes & Lessell, 1990).

3.3.10.A.5] Intraocular pressure finding

a) Summary

- 1) [Trazodone](#) produces a slight decrease in intraocular pressure (IOP) in patients with [open angle glaucoma](#) by increasing outflow and decreasing production of aqueous humor. Peak IOP reduction occurs in 180 minutes. However, after three hours intraocular tension stabilizes at a level slightly below pretreatment values [64]. [Trazodone's](#) effect on IOP can be beneficial in patients with [open-angle glaucoma](#) and concomitant depression. One case report associated [trazodone](#) use with increased IOP [65].
- b) A 61-year-old woman, with a 6-year history of [angle-closure glaucoma](#), experienced an increase in intraocular pressure (IOP) following the administration of [trazodone](#). She had maintained an IOP of 13 to 19 millimeters of mercury (mmHg) in both eyes for 2 years, using a regimen of daily drops of [timolol](#) 0.5% and [pilocarpine](#) 5%. Three days after taking [trazodone](#), 50 milligrams (mg) per day for depressive symptoms, she developed right conjunctival injection and eye pain and intermittent headache. Her IOP, 6 days after starting [trazodone](#), was 19 mmHg in the left eye and 40 mmHg in the right eye. [Trazodone](#) was discontinued and she received [acetazolamide](#) 500 mg/day. Two days later her IOP returned to baseline levels [65].

3.3.10.A.6] Pain in eye

- a) Incidence: less than 1% [19]
- b) Eye pain has been reported in 1% or less of [trazodone](#) extended-release (mean daily dose of 310 mg over 6 weeks) recipients (n=202) in clinical studies of adults, ages 18 to 80 years old over a total duration of 8 weeks [19].

3.3.10.A.7] Photophobia

- a) Incidence: less than 1% [19]

b) Photophobia has been reported in 1% or less of [trazodone](#) extended-release (mean daily dose of 310 mg over 6 weeks) recipients (n=202) in clinical studies of adults, ages 18 to 80 years old over a total duration of 8 weeks [19].

3.3.10.A.8] Visual disturbance

a) Incidence: at least 1% [19]

b) Visual disturbance has been reported in at least 1% of [trazodone](#) extended-release (mean daily dose of 310 mg over 6 weeks) recipients (n=202) in clinical studies of adults, ages 18 to 80 years old over a total duration of 8 weeks [19].

3.3.11] Otic Effects

3.3.11.A] [Trazodone](#) Hydrochloride

3.3.11.A.1] Hearing loss

a) Incidence: less than 1% [19]

b) Hypoacusis has been reported in less than 1% of [trazodone](#) extended-release (mean daily dose of 310 mg over 6 weeks) recipients (n=202) in clinical studies of adults, ages 18 to 80 years old over a total duration of 8 weeks [19].

3.3.11.A.2] Tinnitus

a) Incidence: up to 1.4% [22][19]

b) Tinnitus has been reported in less than 1% of [trazodone](#) extended-release (mean daily dose of 310 mg over 6 weeks) recipients (n=202) in clinical studies of adults, ages 18 to 80 years old over a total duration of 8 weeks [19].

c) Tinnitus has been reported in 0% to 1.4% of [trazodone](#) recipients (n=299) compared with 0% to less than 1% of placebo recipients (n=253) in clinical trials [22].

3.3.11.A.3] Vertigo

a) Incidence: less than 1% [19]

b) Vertigo has been reported in less than 1% of [trazodone](#) extended-release (mean daily dose of 310 mg over 6 weeks) recipients (n=202) in clinical studies of adults, ages 18 to 80 years old over a total duration of 8 weeks [19].

3.3.12] Psychiatric Effects

3.3.12.A] [Trazodone](#) Hydrochloride

3.3.12.A.1] Agitation

a) Incidence: at least 1% [19]

b) Agitation has been reported in at least 1% of [trazodone](#) extended-release (mean daily dose of 310 mg over 6 weeks) recipients (n=202) in clinical studies of adults, ages 18 to 80 years old over a total duration of 8 weeks [19].

3.3.12.A.2] [Delirium](#)

a) Trazodone-induced [delirium](#) was reported in three patients, two of whom had preexisting organic cerebral lesions and one of whom had thyroid dysfunction. [Delirium](#), manifested as hallucinations, psychomotor agitation, and cognitive changes, was observed in the three patients shortly after

initiation of [trazodone](#) therapy (with aggravation of the condition with an increase in dosage in one patient). Shortly after discontinuation of the [trazodone](#) regimen, symptoms ceased and, in one patient, symptoms recurred after reinstitution of [trazodone](#) . The authors hypothesized that the [delirium](#) might be caused by a heightened sensitivity to the major metabolite of [trazodone](#) , meta-chlorophenylpiperazine, which has specific 5-HT agonist properties [69].

b) Three cases of [delirium](#) occurred in patients with [bulimia](#) and [major depressive episodes](#) following short-term [trazodone](#) administration [70]. In two cases, [delirium](#) developed within two to three hours of the first dose. In the third case, [delirium](#) occurred after dosing adjustment from 150 to 200 milligrams daily. The authors suggest the bulimic patients may be more susceptible to [delirium](#) secondary to [trazodone](#) , possibly related to imbalances in the neuroregulatory system.

3.3.12.A.3] Dream disorder

a) Incidence: up to 5.1% [22]

b) Nightmares/vivid dreams have been reported in less than 1% to 5.1% of [trazodone](#) recipients (n=299) compared with 1.1% to 5.7% of placebo recipients (n=253) in clinical trials [22].

3.3.12.A.4] Feeling angry

a) Anger/hostility has been reported in 1.3% to 3.5% of [trazodone](#) recipients (n=299) compared with 2.5% to 6.3% of placebo recipients (n=253) in clinical trials [22].

3.3.12.A.5] Feeling nervous

a) Incidence: 6.4% to 14.8% [22]

b) Nervousness has been reported in 6.4% to 14.8% of [trazodone](#) recipients (n=299) compared with 8.2% to 10.5% of placebo recipients (n=253) in clinical trials [22].

3.3.12.A.6] Mania

a) Nine cases of mania following initiation of [trazodone](#) therapy have been described [71][72][73][74][75].

3.3.12.A.7] Panic attack

a) Panic attacks were reported at doses of 0.26 to 0.5 milligrams/kilogram of m-chlorophenylpiperazine (MCP), a [trazodone](#) metabolite and direct SHT receptor agonist [76].

3.3.12.A.8] Suicidal thoughts

a) Incidence: rare

b) Adults

1) No clinically significant differences in the risk of suicide and suicide attempts were observed across antidepressant agents and antidepressant classes in a 9-year, population-based cohort study consisting 287,543 adults. Based on the health care utilization data, the overall combined event rates of suicide death or hospitalization due to self harm ranged from 4.41 to 9.09 per 1000 person years. Among patients who received newer and atypical agents, including [trazodone](#) hydrochloride (n=28,316; 12,318 person-years), suicide occurred at an event rate of 1.14/1000 person-years (95% confidence interval (CI), 0.62 to 1.9) and suicide attempts occurred at a rate of 4.55/1000 person-years (95% CI, 3.43 to 5.9). Based on data among atypical antidepressant users who were treatment naive (no antidepressant use in the past 3 years; n=19,363; 8820 person-years), suicide occurred at a rate of 1.25/1000 person-

years (95% CI, 0.62 to 2.23) and suicide attempts occurred at a rate of 3.63/1000 person-years (95% CI, 2.48 to 5.12). Following an extensive propensity score adjustment in comparison with SSRI, atypical and newer agents had an overall hazard ratio of 1.03 (95% CI, 0.58 to 1.86). Most events were reported within the first 6 months after start of therapy [68].

c) Pediatrics

1) Compared with placebo there is an increased risk of suicidal thinking and behavior in children, adolescents, and young adults in short-term studies of [major depressive disorder](#) and other psychiatric disorders. An increase in risk of suicidality with antidepressants compared with placebo in adults older than 24 years was not demonstrated in short-term studies; in contrast, there was a reduction in risk compared with placebo in adults 65 years and older [19].

2) A causal role for antidepressants in inducing suicidality has been established in pediatric patients. Anyone considering the use of antidepressants in a child or adolescent must balance this risk with the clinical need. In pooled analyses of 24 short-term, placebo-controlled trials of nine antidepressants ([citalopram](#), [fluoxetine](#), [fluvoxamine](#), [paroxetine](#), [sertraline](#), [bupropion](#), [mirtazapine](#), [nefazodone](#), and [venlafaxine](#) extended-release) including over 4400 pediatric patients with [major depressive disorder](#), [obsessive compulsive disorder](#), or other psychiatric disorders, a greater risk of suicidal behavior or ideation during the first few months of therapy was demonstrated in patients receiving antidepressants as compared with placebo (4% vs 2%, respectively). The risk of suicidality was most consistently observed in the trials that included patients with [major depressive disorder](#), but there were signs of risk emerging from trials in other psychiatric indications, such as [obsessive compulsive disorder](#) and [social anxiety disorder](#). No suicides occurred in these trials. The risk of suicidality during longer-term use (ie, beyond several months) in pediatric patients is not known. It is also unknown whether this risk extends to adult patients [77].

d) 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](#), or mania may be at risk of [suicidal ideation](#) and behavior (SUICIDALITY). This same concern applies to treating patients with other psychiatric and nonpsychiatric disorders. If these symptoms are observed, therapy should be 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. Patients and their caregivers should be provided with the Medication Guide that is available for this drug [77]

3.3.12.A.9] Suicide

a) No clinically significant differences in the risk of suicide and suicide attempts were observed across antidepressant agents and antidepressant classes in a 9-year, population-based cohort study consisting of 287,543 adults. Based on the health care utilization data, the overall combined event rates of suicide death or hospitalization due to self harm ranged from 4.41 to 9.09 per 1000 person-years. Among patients who received newer and atypical agents, including [trazodone](#) hydrochloride (n=28,316; 12,318 person-years), suicide occurred at an event rate of 1.14/1000 person-years (95% confidence interval (CI), 0.62 to 1.9) and suicide attempts occurred at a rate of 4.55/1000 person-years (95% CI, 3.43 to 5.9). Based on data among atypical antidepressant users who were treatment naive (no antidepressant use in the past 3 years; n=19,363; 8820 person-years), suicide occurred at a rate of 1.25/1000 person-years (95% CI, 0.62 to 2.23) and suicide attempts occurred at a rate of

3.63/1000 person-years (95% CI, 2.48 to 5.12). Following an extensive propensity score adjustment in comparison with SSRI, atypical and newer agents had an overall hazard ratio of 1.03 (95% CI, 0.58 to 1.86). Most events were reported within the first 6 months after start of therapy [68].

3.3.13] Renal Effects

3.3.13.A] Trazodone Hydrochloride

3.3.13.A.1] Bladder pain

- a) Incidence: less than 1% [19]
- b) Bladder pain has been reported in less than 1% of [trazodone](#) extended-release (mean daily dose of 310 mg over 6 weeks) recipients (n=202) in clinical studies of adults, ages 18 to 80 years old over a total duration of 8 weeks [19].

3.3.13.A.2] Urgent desire to urinate

- a) Incidence: at least 1% [19]
- b) Micturition urgency has been reported in at least 1% of [trazodone](#) extended-release (mean daily dose of 310 mg over 6 weeks) recipients (n=202) in clinical studies of adults, ages 18 to 80 years old over a total duration of 8 weeks [19].

3.3.13.A.3] Urinary incontinence

- a) Incidence: less than 1% [19]
- b) [Urinary incontinence](#) has been reported in less than 1% of [trazodone](#) extended-release (mean daily dose of 310 mg over 6 weeks) recipients (n=202) in clinical studies of adults, ages 18 to 80 years old over a total duration of 8 weeks [19].

3.3.13.A.4] Urinary retention

- a) Incidence: 1% [58]
- b) Urinary hesitancy has been reported as an adverse effect of [trazodone](#) therapy. In a comparative study with [imipramine](#), the incidence of urinary hesitancy was less in [trazodone](#) patients (1%) than [imipramine](#) patients (4%) [58].

3.3.14] Reproductive Effects

3.3.14.A] Trazodone

3.3.14.A.1] Sexual dysfunction

See Drug Consult reference: Drug-Induced Sexual Dysfunction

3.3.14.B] Trazodone Hydrochloride

3.3.14.B.1] Abnormal ejaculation

- a) Incidence: 1.5% [19]
- b) [Ejaculation disorders](#) have been reported in 1.5% of [trazodone](#) extended-release (mean daily dose of 310 mg over 6 weeks) recipients (n=202) in clinical studies of adults, ages 18 to 80 years old over a total duration of 8 weeks [19].

c) Inhibition of ejaculation was reported in a 51-year-old male following oral [trazodone](#) 50 milligrams (mg) at bedtime for 3 days, then 100 mg at bedtime for 2 1/2 weeks. Withdrawal of [trazodone](#) and substitution with [doxepin](#) 50 mg at bedtime resulted in resolution of ejaculatory inhibition [84].

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

a) [Erectile dysfunction](#) has been reported in less than 1% of [trazodone](#) extended-release (mean daily dose of 310 mg over 6 weeks) recipients (n=202) in clinical studies of adults, ages 18 to 80 years old over a total duration of 8 weeks [19].

3.3.14.B.3] [Increased libido](#)

a) [Trazodone](#) administration produced an increase in libido in three women with depression. In all cases, [trazodone](#) was given in gradually increasing doses up to 150 mg daily; increases in sexual drive were observed when this dose was achieved. Two patients resisted withdrawal of the drug due to this effect [78].

3.3.14.B.4] [Orgasm disorder](#)

a) [Abnormal orgasm](#) has been reported in less than 1% of [trazodone](#) extended-release (mean daily dose of 310 mg over 6 weeks) recipients (n=202) in clinical studies of adults, ages 18 to 80 years old over a total duration of 8 weeks [19].

3.3.14.B.5] [Painful clitoral erection](#)

a) Clitorism has been reported with [trazodone](#) use during postmarketing surveillance [22][19].

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

a) Summary

1) [Trazodone](#) therapy has been associated with the occurrence of [priapism](#), sometimes requiring surgical intervention [22][79][80][81]; (Scher et al, 1983)[82]; (Carson & Mino, 1988). Predisposing conditions including [sickle cell anemia](#), [multiple myeloma](#), [leukemia](#), or anatomical deformation of the penis [22].

b) In a case report, a patient treated first with [nefazodone](#) and then with [trazodone](#), developed [priapism](#) after beginning [trazodone](#) therapy. A 51- year-old man, diagnosed with a [major depressive disorder](#), participated in a trial of [nefazodone](#) at a dose of 200 milligrams (mg) twice a day for a period of 6 weeks. After completion of the experimental protocol, the patient started therapy with [trazodone](#) 300 mg/day. After 17 days of therapy with [trazodone](#) (and three days of [allopurinol](#) for gout contracted during this period) the patient reported [priapism](#) and the [trazodone](#) was discontinued. The patient subsequently was treated with [nefazodone](#) and no further episodes of [priapism](#) were reported [79].

c) A 34-year-old woman who had received [fluoxetine](#) 40 milligrams (mg) daily for 10 months for treatment of depression was started on [trazodone](#) to combat fluoxetine-associated insomnia. The [fluoxetine](#) was decreased to 20 mg per day and [trazodone](#) 25 mg per night for 2 nights and then 50 mg at bedtime was added. Five days after starting [trazodone](#) the patient experienced a new onset irritation in the clitoral region that four days later developed into painful CLITORAL PRIAPISM. Both drugs were discontinued and she received oral [phenylpropanolamine](#) hydrochloride/[guaifenesin](#) twice daily for 2 days. The clitoral discomfort and erection resolved within 24 hours and there was no further clitoral dysfunction reported [81].

d) **Priapism** has been seen as an adverse effect from therapeutic doses (Scher et al, 1983)[82]; (Carson & Mino, 1988). Surgery was required in 26 of 84 cases reported to the manufacturer and permanent impotence has been a sequela [83].

e) In 57 cases reported to the United States Food and Drug Administration, **priapism** appeared to be mostly likely to occur during the first 28 days of therapy, with doses of 50 to 400 milligrams (mg) daily (median, 150 mg daily) [80]. The median age of patients who developed **priapism** was 40 years; however, all age groups appear to be susceptible to this adverse effect. It is suggested that patients be well informed of the potential of **priapism** when given **trazodone** and to discontinue the drug if any unusual erectile problems develop.

3.3.14.B.7] Reduced libido

a) Incidence: up to 1.5% [22][19]

b) Decreased libido has been reported in 1.5% of **trazodone** extended-release (mean daily dose of 310 mg over 6 weeks) recipients (n=202) in clinical studies of adults, ages 18 to 80 years old over a total duration of 8 weeks [19].

c) Decreased libido has been reported in less than 1% to 1.3% of **trazodone** recipients (n=299) compared with less than 1% to 1.1% of placebo recipients (n=253) in clinical trials [22].

3.3.14.B.8] Sexual dysfunction

a) Incidence: 4.9% [19]

b) Sexual dysfunction, regardless of causality, has been reported in 4.9% of **trazodone** extended-release (mean daily dose of 310 mg over 6 weeks) recipients (n=202) compared with 1.5% of placebo recipients (n=204) in clinical studies of adults, ages 18 to 80 years old over a total duration of 8 weeks [19].

3.3.15] Respiratory Effects

3.3.15.A] Trazodone Hydrochloride

3.3.15.A.1] Dyspnea

a) Incidence: at least 1% [22][19]

b) Dyspnea has been reported in at least 1% of **trazodone** extended-release (mean daily dose of 310 mg over 6 weeks) recipients (n=202) in clinical studies of adults, ages 18 to 80 years old over a total duration of 8 weeks [19].

c) Shortness of breath has been reported in less than 1% to 1.3% of **trazodone** recipients (n=299) compared with 0% to 1.1% of placebo recipients (n=253) in clinical trials [22].

3.3.15.A.2] Nasal congestion

a) Nasal/sinus congestion has been reported in 2.8% to 5.7% of **trazodone** recipients (n=299) compared with 0% to 3.2% of placebo recipients (n=253) in clinical trials [22].

3.3.16] Other

3.3.16.A] Trazodone Hydrochloride

3.3.16.A.1] Anticholinergic adverse reaction

a) **Trazodone** produces significantly fewer anticholinergic effects than the tricyclic antidepressants [85][38][58][86]. In one study, the incidence of anticholinergic effects with **trazodone** (up to 600 mg/

day) was similar to placebo, but [imipramine](#), in comparison, produced significant anticholinergic effects [58]. [Trazodone's](#) lower degree of anticholinergic effects may make the drug useful in [glaucoma](#) patients with depression [37]. There has been one case report of increased intraocular pressure associated with [trazodone](#) use [65].

3.3.16.A.2] Death

a) Adult Clinical Trials

- 1) General use (unspecified route; age 65 years or older):** A systematic review of anticholinergic medication use in the elderly (18 studies in 124,286 patients) identified one cohort study that revealed a significant 82% increased risk of all-cause mortality with [trazodone](#) [52]

3.3.16.A.3] Drug withdrawal

a) Summary

- 1) Although uncommon, a withdrawal syndrome has been reported following the gradual discontinuation of [trazodone](#).**
- b) A [trazodone](#) withdrawal syndrome has been reported following the gradual discontinuation of therapeutic doses of [trazodone](#).** It has been suggested that development of this syndrome may be due to serotonergic effects and short half-lives of [trazodone](#) and its metabolite, m-chlorophenylpiperazine, which may result in noradrenergic rebound following discontinuation. Withdrawal signs/symptoms have consisted of insomnia, vivid dreams lassitude. nausea. diarrhea, abdominal pain. anxiety, palpitations, [hypomania](#), headache. myalgia, [restless legs](#) and formication [87][88][89]; (Theilman Christenbury, 1986). Rapid withdrawal has been reported to result in predominantly gastrointestinal symptoms which respond to administration of [atropine](#). It has been suggested that a cholinergic rebound may occur following rapid withdrawal [90].

3.3.16.A.4] Falls

a) Adult Clinical Trials

- 1) General use (unspecified route; age 65 years or older):** Systematic review identified 18 studies describing anticholinergic medication use in 124,286 elderly patients, and meta-analysis revealed a significant 79% increased risk of falls with [trazodone](#) (11 studies) [52]

3.3.16.A.5] Fatigue

- a) Incidence: 5.7% to 15% [22][19]**
- b) Fatigue has been reported in 15% of [trazodone](#) extended-release (mean daily dose of 310 mg over 6 weeks) recipients (n=202) compared with 8% of placebo recipients (n=204) in clinical studies of adults, ages 18 to 80 years old over a total duration of 8 weeks [19].**
- c) Fatigue has been reported in 5.7% to 11.3% of [trazodone](#) recipients (n=299) compared with 2.5% to 4.2% of placebo recipients (n=253) in clinical trials [22].**

3.3.16.A.6] Malaise

- a) Incidence: up to 2.8% [22]**
- b) Malaise has been reported in 0% to 2.8% of [trazodone](#) recipients (n=299) compared with 0% of placebo recipients (n=253) in clinical trials [22].**

3.3.16.A.7] Shivering

- a) Chills have been reported with [trazodone](#) use during postmarketing surveillance [19].

3.4] Teratogenicity/Effects in Pregnancy/Breastfeeding**A) Teratogenicity/Effects in Pregnancy****1) U.S. Food and Drug Administration's Pregnancy Category: Category C (All Trimesters)**

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

See Drug Consult reference: PREGNANCY RISK CATEGORIES

2) Crosses Placenta: Unknown**3) Clinical Management**

- a) There are no adequate and well-controlled studies of [trazodone](#) use in pregnant women. Due to the lack of human safety information, [trazodone](#) should be used in pregnant women only if the potential benefit outweighs the potential [risk to the fetus](#) [22][19].

4) Literature Reports

- a) There are no adequate and well-controlled studies of [trazodone](#) use in pregnant women [22][19].
- b) One report describes the outcomes of 12 pregnancies exposed to [trazodone](#); two pregnancies were electively terminated, and the remaining ten resulted in children without malformations [316]. One hundred newborns (out of 229,101 births in a surveillance study of Michigan Medicaid recipients) had been exposed to [trazodone](#) during the first trimester of pregnancy. Out of one hundred exposures, one major [birth defect](#) was observed; no details are available as to the nature of the defect [317].
- c) In animal studies, [trazodone](#) has been shown to cause increased [fetal resorption](#) when rats were given [trazodone](#) doses approximately 30 to 50 times the maximum human dose. There was an increase in congenital anomalies when rabbits were given [trazodone](#) doses 15 to 50 times the maximum human dose [22][19].
- d) Early animal studies in rats indicated lower birth weights for offspring in animals receiving high doses [318][319]. These studies were designed with [trazodone](#) dosing of 10 to 300 mg/kg daily in male and female rats prior to and during mating, throughout pregnancy and lactation, and in a separate study during the last 6 to 7 days of pregnancy and throughout lactation. Additionally, rats and rabbits given 15 to 450 mg/kg daily during the middle portion of pregnancy developed no anomalies in offspring [318][319].

B) Breastfeeding

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

2)) Micromedex Lactation Rating: Infant risk 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.

3)) Clinical Management

a)) In animal studies, [trazodone](#) was excreted in the milk of lactating rats, suggesting that the drug may be excreted in human milk [22][19]. In one study, [trazodone](#) was excreted in low concentrations in breast milk following single doses [321]. Despite the absence of reports of adverse effects in breast-fed infants, the American Academy of Pediatrics classifies [trazodone](#) as a drug whose effect on nursing infants is unknown, but may be of concern [320]. Until more data are available, caution should be used when administering [trazodone](#) to a nursing mother [22][19]

4)) Literature Reports

a)) In animal studies, [trazodone](#) was excreted in the milk of lactating rats, suggesting that the drug may be excreted in human milk [22][19].

b)) In one study, [trazodone](#) was excreted in low concentrations in breast milk following single doses. Six lactating women were administered single oral doses of 50 mg, with a resultant milk-plasma ratio of 0.142. It is speculated that newborn infants would ingest less than 0.005 mg/kg of [trazodone](#) following ingestion of 50 mg by the mother and subsequent breast feeding for a 12-hour period [321].

5)) Drug Levels in Breastmilk**a)) [Trazodone](#) Hydrochloride****1)) Parent Drug****a)) Milk to Maternal Plasma Ratio**

1)) 0.142 [331]

2)) Active Metabolites

a)) m-chlorophenylpiperazine (mCCP) [330]

3.5] Drug Interactions**3.5.1] Drug-Drug Combinations****3.5.1.A] Acetophenazine**

1)) Interaction Effect: hypotension

- 2) Summary: Concomitant administration of [trazodone](#) with [chlorpromazine](#) or [trifluoperazine](#) resulted in additive hypotensive effects in two case reports. Withdrawal of [trazodone](#) resulted in resolution of the hypotension[237].
- 3) Severity: moderate
- 4) Onset: delayed
- 5) Substantiation: theoretical
- 6) Clinical Management: Monitor blood pressure, particularly in patients who might be sensitive to this effect. Advise patient to rise slowly from laying or sitting position.
- 7) Probable Mechanism: additive hypotensive effects

3.5.1.B) [Alfuzosin](#)

- 1) Interaction Effect: an increased risk of QT interval prolongation
- 2) Summary: The concomitant use of [trazodone](#) with other drugs that may prolong the QT interval, such as [alfuzosin](#)[271], may result in additive effects on QT interval prolongation and risk of [torsade de pointes](#) [95]. If coadministration is required, monitoring for QT interval prolongation may be warranted.
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: The concomitant use of [trazodone](#) with other drugs that may prolong the QT interval, such as [alfuzosin](#)[271], may result in additive effects on QT interval prolongation and risk of [torsade de pointes](#) [95]. If coadministration is required, monitoring for QT interval prolongation may be warranted.
- 7) Probable Mechanism: additive effects on QT interval prolongation
- 8) Literature Reports

a) In a postmarketing study that evaluated the effect of concomitant administration of [alfuzosin](#) with another QT interval-prolonging drug of similar effect size, the observed QT interval prolongation was greater than that seen with either drug alone, but was not more than additive. The corrected (Fridericia) QT interval (QTcF) increased by 5.9 milliseconds (upper bound of 95% confidence interval (CI), 9.4 milliseconds). The QTcF increase observed with [moxifloxacin](#) 400 mg (positive control) was 10.2 milliseconds (upper bound 95% CI, 13.8 milliseconds). The mean placebo-subtracted QTcF increase following administration of [alfuzosin](#) 10 mg alone was 1.9 milliseconds (upper bound 95% CI, 5.5 milliseconds) [271].

3.5.1.C) [Almotriptan](#)

- 1) Interaction Effect: increased risk of [serotonin syndrome](#) ([hypertension](#), [hyperthermia](#), myoclonus, mental status changes)
- 2) Summary: Both [almotriptan](#) and [trazodone](#) 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](#)[95][172]. Careful monitoring for signs and symptoms of [serotonin syndrome](#) may be warranted if [almotriptan](#) and [trazodone](#) are used concurrently, particularly during treatment initiation and dose increases [95]. 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 [96].
- 3) Severity: major
- 4) Onset: unspecified

- 5) Substantiation: theoretical
- 6) Clinical Management: Use caution with concomitant administration of [almotriptan](#) and [trazodone](#), as this may result in additive serotonergic effects and may increase the risk of [serotonin syndrome](#)[95][172]. If coadministration is required, careful monitoring is warranted, particularly during treatment initiation and dose increases.
- 7) Probable Mechanism: additive serotonergic effect

3.5.1.D) 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](#)[247].
- 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](#)[247].
- 7) Probable Mechanism: additive QT-interval prolongation

3.5.1.E) 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](#)[170].
- 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](#)[170].
- 7) Probable Mechanism: additive effects on QT interval

3.5.1.F) 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](#)[164].
- 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](#)[164].
- 7) Probable Mechanism: additive QT prolongation

3.5.1.G] Amitriptyline

- 1) Interaction Effect: an increased risk of QT interval prolongation and [serotonin syndrome](#)
- 2) Summary: QT/QTc interval prolongation and postmarketing cases of [torsade de pointes](#) have been reported with [trazodone](#). The concomitant use of [trazodone](#) with other drugs that prolong the QT interval, such as [amitriptyline](#), may result in additive effects on QT interval prolongation and an increased risk of serious [ventricular arrhythmias](#), including [torsade de pointes](#). Both [amitriptyline](#) and [trazodone](#) 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](#)[95]. 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 [96]. If coadministration is required, monitoring for QT interval prolongation and signs and symptoms of [serotonin syndrome](#) may be warranted.
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: The concomitant use of [trazodone](#) with other QT-prolonging drugs, such as [amitriptyline](#), may result in additive effects on QT interval prolongation and risk of [torsade de pointes](#). Coadministration may also result in additive serotonergic effects and may increase the risk of [serotonin syndrome](#)[95]. If coadministration is required, monitoring for QT interval prolongation and signs and symptoms of [serotonin syndrome](#) may be warranted.
- 7) Probable Mechanism: additive effects on QT interval prolongation; additive serotonergic effect

3.5.1.H] Amoxapine

- 1) Interaction Effect: an increased risk of QT interval prolongation and [serotonin syndrome](#)
- 2) Summary: QT/QTc interval prolongation and postmarketing cases of [torsade de pointes](#) have been reported with [trazodone](#). The concomitant use of [trazodone](#) with other drugs that prolong the QT interval, such as [amoxapine](#), may result in additive effects on QT interval prolongation and an increased risk of serious [ventricular arrhythmias](#), including [torsade de pointes](#). Both [amoxapine](#) and [trazodone](#) 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](#)[95]. 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 [96]. If coadministration is required, monitoring for QT interval prolongation and signs and symptoms of [serotonin syndrome](#) may be warranted.
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: The concomitant use of [trazodone](#) with other QT-prolonging drugs, such as [amoxapine](#), may result in additive effects on QT interval prolongation and risk of [torsade de pointes](#). Concomitant use may also result in additive serotonergic effects and may increase the risk of [serotonin](#)

[syndrome](#) and should be undertaken with caution[95]. If coadministration is required, appropriate monitoring may be warranted.

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

3.5.1.I] [Amphetamine](#)

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

2J) 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[156].

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[156].

7J) Probable Mechanism: additive serotonergic effect

3.5.1.J] [Amprenavir](#)

1J) Interaction Effect: an increase in [trazodone](#) plasma levels and may increase [trazodone](#) toxicity

2J) Summary: Concomitant use of [amprenavir](#) and [trazodone](#) may result in increased [trazodone](#) plasma concentrations due to [amprenavir](#) inhibition of CYP3A4-mediated [trazodone](#) metabolism. Exercise caution when using these medications together and consider a reduction of [trazodone](#) dosing. Monitor for [trazodone](#) side effects such as nausea, dizziness, hypotension, and syncope[143].

3J) Severity: moderate

4J) Onset: unspecified

5J) Substantiation: theoretical

6J) Clinical Management: Consider a lower dose of [trazodone](#) if it is used with a CYP3A4 inhibitor such as [amprenavir](#). Monitor patients receiving [trazodone](#) and [amprenavir](#) for adverse effects, including sedation, nausea, dizziness, hypotension, and syncope.

7J) Probable Mechanism: inhibition of CYP3A4-mediated [trazodone](#) metabolism by [amprenavir](#)

8J) Literature Reports

aJ) Coadministration of [trazodone](#) with [ritonavir](#), a potent CYP3A4 inhibitor pharmacologically similar to [amprenavir](#), resulted in significant [trazodone](#) pharmacokinetic changes. In 10 healthy subjects, the concurrent administration of a total of 4 doses [ritonavir](#) 200 mg twice daily with a single 50 mg dose of [trazodone](#) increased the peak plasma [trazodone](#) concentration (C_{max}) 34%, increased the area under the concentration-time curve (AUC) 2.4-fold, increased the half-life 2.2-fold, and decreased [trazodone](#) clearance 52%. During concomitant use of [trazodone](#) and [ritonavir](#), adverse effects reported included nausea, hypotension, and syncope [142].

3.5.1.K] [Anagrelide](#)

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

2J) Summary: [Anagrelide](#) has been associated with QT interval prolongation. Coadministration with another drug known to prolong the QT interval should be avoided because of risk for additive effects on the QT interval that can lead to serious cardiac adverse effects, including [torsade de pointes](#)[190].

3J) Severity: major

4J) Onset: unspecified

5J) Substantiation: theoretical

6J) Clinical Management: [Anagrelide](#) has been associated with QT interval prolongation. Coadministration with another drug known to prolong the QT interval should be avoided because of risk for additive effects on the QT interval that can lead to serious cardiac adverse effects, including [torsade de pointes](#)[190].

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

3.5.1.LJ [Apomorphine](#)

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

2J) Summary: QT/QTc interval prolongation and postmarketing cases of [torsade de pointes](#) have been reported with [trazodone](#). The concomitant use of [trazodone](#) with other drugs that prolong the QT interval, such as [apomorphine](#)[205], may result in additive effects on QT interval prolongation and an increased risk of serious [ventricular arrhythmias](#), including [torsade de pointes](#) [95]. If coadministration is required, monitoring for QT interval prolongation may be warranted.

3J) Severity: major

4J) Onset: unspecified

5J) Substantiation: theoretical

6J) Clinical Management: The concomitant use of [trazodone](#) with other QT-prolonging drugs, such as [apomorphine](#)[205], may result in additive effects on QT interval prolongation and risk of [torsade de pointes](#) [95]. If coadministration is required, monitoring for QT interval prolongation may be warranted.

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

3.5.1.MJ [Aripiprazole](#)

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

2J) Summary: [Aripiprazole](#) has been associated with QTc interval prolongation[307], 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](#).

3J) Severity: major

4J) Onset: unspecified

5J) Substantiation: theoretical

6J) Clinical Management: [Aripiprazole](#) has been associated with QTc interval prolongation[307], 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](#).

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

3.5.1.NJ [Arsenic Trioxide](#)

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

2J) Summary: [Arsenic trioxide](#) is known to prolong the QT interval and may result in [complete atrioventricular block](#) and/or [ventricular arrhythmias](#), including [torsade de pointes](#)[204]. [Trazodone](#) has also been associated with QT interval prolongation and postmarketing cases of [torsade de pointes](#) [95]. Although this interaction has not been evaluated, the concomitant use of [arsenic trioxide](#) with [trazodone](#)

may increase the risk of prolonged QT interval and [ventricular arrhythmias](#). When possible, [trazodone](#) therapy should be discontinued prior to [arsenic trioxide](#) treatment [204]; however, if coadministration is required, monitoring for QT interval prolongation may be warranted.

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Concomitant use of [arsenic trioxide](#) and [trazodone](#), both drugs that prolong the QT interval, may result in additive effects on the QT interval and an increased risk of [torsade de pointes](#)[95] [204]. When possible, [trazodone](#) therapy should be discontinued prior to [arsenic trioxide](#) treatment [204]; however, if coadministration is required, monitoring for QT interval prolongation may be warranted.

7) Probable Mechanism: additive effects on QT interval prolongation

3.5.1.O] Asenapine

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

2) Summary: QT/QTc interval prolongation and postmarketing cases of [torsade de pointes](#) have been reported with [trazodone](#)[95]. Due to the potential for additive effects on QT interval prolongation and risk of [torsade de pointes](#), the concomitant use of asenapine with [trazodone](#) should be avoided [234]. If concomitant use is required, close monitoring of cardiac function may be warranted.

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Avoid the concomitant use of asenapine with other drugs that prolong the QT interval, such as [trazodone](#)[95], as coadministration may result in additive effects on QT interval prolongation and an increased risk of [torsade de pointes](#) [234]. If concurrent therapy is required, monitor cardiac function closely.

7) Probable Mechanism: additive effects on QT interval prolongation

3.5.1.P] Astemizole

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

2) Summary: QT/QTc interval prolongation and postmarketing cases of [torsade de pointes](#) have been reported with [trazodone](#). The concomitant use of [trazodone](#) with other drugs that prolong the QT interval, such as [astemizole](#), may result in additive effects on QT interval prolongation and an increased risk of serious [ventricular arrhythmias](#), including [torsade de pointes](#)[95]. If coadministration is required, monitoring for QT interval prolongation may be warranted.

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: The concomitant use of [trazodone](#) with other QT-prolonging drugs, such as [astemizole](#), may result in additive effects on QT interval prolongation and risk of [torsade de pointes](#)[95]. If coadministration is required, monitoring for QT interval prolongation may be warranted.

7) Probable Mechanism: additive effects on QT interval prolongation

3.5.1.Q] Atazanavir

1) Interaction Effect: an increase in [trazodone](#) plasma levels and increased risk of [trazodone](#) side effects (nausea, dizziness, hypotension)

2) Summary: [Atazanavir](#) may inhibit the CYP3A-mediated metabolism of [trazodone](#). Coadministration of [atazanavir](#) (with or without [ritonavir](#)) and [trazodone](#) may elevate plasma levels of [trazodone](#). Patients

should be monitored for increased [trazodone](#) side effects including nausea, dizziness, syncope and hypotension. A reduction in [trazodone](#) dosing may be warranted[278].

3J) Severity: moderate

4J) Onset: unspecified

5J) Substantiation: probable

6J) Clinical Management: Caution is advised for the concomitant use of [atazanavir](#) (with or without [ritonavir](#)) and [trazodone](#). Patients receiving [atazanavir](#) and [trazodone](#) should be monitored for enhanced sedative effects and hypotension. Consider a reduction in [trazodone](#) dosing[278].

7J) Probable Mechanism: inhibition of CYP3A4-mediated [trazodone](#) metabolism by [atazanavir](#)

3.5.1.R| [Azithromycin](#)

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

2J) Summary: Similar to some other macrolides, [azithromycin](#) may prolong the QT interval[233]. QT/QTc interval prolongation and postmarketing cases of [torsade de pointes](#) have been reported with [trazodone](#). The concomitant use of [trazodone](#) with other drugs that prolong the QT interval may result in additive effects on QT interval prolongation and an increased risk of serious [ventricular arrhythmias](#), including [torsade de pointes](#) [95]. If coadministration is required, monitoring for QT interval prolongation may be warranted.

3J) Severity: major

4J) Onset: unspecified

5J) Substantiation: theoretical

6J) Clinical Management: The concomitant use of [trazodone](#) with other drugs that may prolong the QT interval, such as [azithromycin](#)[233], may result in additive effects on QT interval prolongation and risk of [torsade de pointes](#) [95]. If coadministration is required, monitoring for QT interval prolongation may be warranted.

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

3.5.1.S| [Benzphetamine](#)

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

2J) 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[156].

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[156].

7J) Probable Mechanism: additive serotonergic effect

3.5.1.T| [Bepridil](#)

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

2J) Summary: The concomitant use of [bepridil](#) with drugs that cause QT-interval prolongation is contraindicated[310], 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[310], as coadministration may increase the risk of [ventricular arrhythmias](#).
- 7) Probable Mechanism: additive QT-interval prolongation

3.5.1.U] Boceprevir

- 1) Interaction Effect: increased [trazodone](#) plasma concentrations
- 2) Summary: Coadministration of boceprevir, a CYP3A4 inhibitor[140] and [trazodone](#), a CYP3A4 substrate [19] may result in increased plasma concentrations of [trazodone](#). This may lead to increased [trazodone](#) adverse effects (dizziness, hypotension, syncope). A lower dose of [trazodone](#) should be considered [140].
- 3) Severity: moderate
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Concurrent administration of boceprevir and [trazodone](#) may increase [trazodone](#) plasma concentrations. Monitor patients for signs of increased [trazodone](#) adverse effects (dizziness, hypotension, syncope) and consider administering a lower [trazodone](#) dose[140].
- 7) Probable Mechanism: inhibition of CYP3A-mediated [trazodone](#) metabolism by boceprevir

3.5.1.V] 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[104].
- 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[104].
- 7) Probable Mechanism: additive extrapyramidal side effects

3.5.1.W] Brompheniramine

- 1) Interaction Effect: increased risk of [serotonin syndrome](#) ([hypertension](#), [hyperthermia](#), myoclonus, mental status changes)
- 2) Summary: Both [brompheniramine](#) and [trazodone](#) 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](#)[95]. Monitoring for signs and symptoms of [serotonin syndrome](#) may be warranted if [brompheniramine](#) and [trazodone](#) are used 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. If [serotonin syndrome](#) develops, discontinue the offending agents and provide supportive care and other therapy as necessary [96].
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical

6) Clinical Management: Use caution with concomitant administration of [brompheniramine](#) and [trazodone](#), as this may result in additive serotonergic effects and may increase the risk of [serotonin syndrome](#)[95]. If coadministration is required, appropriate monitoring may be warranted.

7) Probable Mechanism: additive serotonergic effect

3.5.1.X] 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[289][290][291]. 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[289][290][291].

7) Probable Mechanism: additive effects on the QT interval

3.5.1.Y] Buspirone

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

2) Summary: Both [busPIRone](#) and [trazodone](#) 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](#)[95]. Monitoring for signs and symptoms of [serotonin syndrome](#) may be warranted if [busPIRone](#) and [trazodone](#) are used 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. If [serotonin syndrome](#) develops, discontinue the offending agents and provide supportive care and other therapy as necessary [96].

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Use caution with concomitant administration of [busPIRone](#) and [trazodone](#), as this may result in additive serotonergic effects and may increase the risk of [serotonin syndrome](#)[95]. If coadministration is required, appropriate monitoring may be warranted.

7) Probable Mechanism: additive serotonergic effect

3.5.1.Z] Carbamazepine

1) Interaction Effect: increased [carbamazepine](#) plasma concentrations or decreased [trazodone](#) plasma concentrations and increased risk of [serotonin syndrome](#)

2) Summary: Concomitant use of [carbamazepine](#) and [trazodone](#) may increase the plasma concentrations of [carbamazepine](#) and may decrease the plasma concentrations of [trazodone](#)[264]. In addition, both [carbamazepine](#) and [trazodone](#) affect the serotonergic neurotransmitter systems and may increase the risk of [serotonin syndrome](#) [95]. Two case reports have shown increased [carbamazepine](#) levels and [carbamazepine](#) toxicity when [trazodone](#) was added to a [carbamazepine](#) regimen [265]. Additionally, a

pharmacokinetic study showed that carbamazepine decreased trazodone and m-chlorophenylpiperazine (an active metabolite of trazodone) serum levels by 76% and 60%, respectively. Concomitant use of carbamazepine and trazodone should be undertaken with caution and appropriate monitoring may be warranted [95].

3) Severity: major

4) Onset: unspecified

5) Substantiation: probable

6) Clinical Management: Use caution when prescribing trazodone to patients who takes carbamazepine. Concurrent use may result in increased carbamazepine plasma concentrations or decreased trazodone plasma concentrations. Carbamazepine levels should be monitored closely and dose adjustments made as needed[264]. Patients taking carbamazepine should also be monitored for signs of toxicity such as severe tremor and ataxia when trazodone is added [265]. If carbamazepine is added to trazodone therapy, monitor for signs or symptoms of reduced efficacy of trazodone, and consider increasing the trazodone dose as needed. Coadministration may also result in additive serotonergic effects and may increase the risk of serotonin syndrome [95]. If coadministration is required, appropriate monitoring may be warranted.

7) Probable Mechanism: inhibition of CYP3A4-mediated carbamazepine metabolism by trazodone; induction of CYP3A4-mediated trazodone metabolism by carbamazepine; additive serotonergic effects

8) Literature Reports

a) A 77-year-old female, admitted to the hospital for mood deterioration and worsening of psychotic symptoms, developed carbamazepine toxicity following the addition of trazodone to a chronic drug regimen that included carbamazepine, amiodarone, glibenclamide, and omeprazole. Upon admission, her hepatic function was normal, her carbamazepine level was stable at 8.4 mg/L, and trazodone 100 mg/day and escitalopram 100 mg/day were added to her regimen for the treatment of worsening depressive symptoms. On day 3 of admission, she began experiencing symptoms consistent with carbamazepine toxicity, including ataxic gait, and severe tremor, with a corresponding serum carbamazepine level of 11.3 mg/L. The carbamazepine level peaked at 11.6 mg/L on day 4, and trazodone was suspended. Subsequently, ataxia and severe tremor diminished. Carbamazepine levels progressively normalized, declining to 11.1 mg/L on day 6, 7.4 mg/L on day 11, and finally restabilizing at 8.9 mg/L on day 70. There were no changes to the patient's chronic drug regimen and the patient was maintained on escitalopram throughout the course of the events [265].

b) In a pharmacokinetic study, coadministration of carbamazepine 400 mg/day and trazodone 100 to 300 mg/day resulted in decreased plasma concentrations of trazodone and m-chlorophenylpiperazine (the active metabolite) that were 76% and 60% lower, respectively, compared with pre-carbamazepine levels [95].

c) A 53-year-old male diagnosed with generalized partial epilepsy was receiving carbamazepine 700 mg daily with a corresponding serum concentration of 7.9 mg/L. The concentration/dose ratio, calculated by dividing the serum concentration (mg/L) by the dose (mg/kg), was 0.89. Trazodone therapy was initiated for depression, and two months later the carbamazepine serum concentration had increased to 10.0 mg/L with a corresponding concentration/dose ratio of 1.12. The serum concentration of the main pharmacologically active metabolite of carbamazepine, carbamazepine 10,11-epoxide, was not measured. Although this patient did not show any signs or symptoms of carbamazepine toxicity, this drug interaction may be clinically significant in patients stabilized at a higher carbamazepine steady-state concentration [266].

3.5.1.AA] Ceritinib

1) Interaction Effect: increased exposure of CYP3A substrate

- 2)) Summary: Avoid concomitant use of ceritinib and a CYP3A substrate as this may increase exposure to and adverse effects of the substrate. If concurrent use cannot be avoided, consider dose reductions of the CYP3A substrate[272].
- 3)) Severity: major
- 4)) Onset: unspecified
- 5)) Substantiation: theoretical
- 6)) Clinical Management: Avoid concomitant use of ceritinib and a CYP3A substrate as this may increase exposure to and adverse effects of the substrate. If concurrent use cannot be avoided, consider dose reductions of the CYP3A substrate[272].
- 7)) Probable Mechanism: inhibition of CYP3A-mediated metabolism of drug by ceritinib

3.5.1.AB| Chloroquine

- 1)) Interaction Effect: an increased risk of QT interval prolongation
- 2)) Summary: QT/QTc interval prolongation and postmarketing cases of [torsade de pointes](#) have been reported with [trazodone](#). The concomitant use of [trazodone](#) with other drugs that prolong the QT interval, such as [chloroquine](#), may result in additive effects on QT interval prolongation and an increased risk of serious [ventricular arrhythmias](#), including [torsade de pointes](#)[95]. If coadministration is required, monitoring for QT interval prolongation may be warranted.
- 3)) Severity: major
- 4)) Onset: unspecified
- 5)) Substantiation: theoretical
- 6)) Clinical Management: The concomitant use of [trazodone](#) with other QT-prolonging drugs, such as [chloroquine](#), may result in additive effects on QT interval prolongation and risk of [torsade de pointes](#)[95]. If coadministration is required, monitoring for QT interval prolongation may be warranted.
- 7)) Probable Mechanism: additive effects on QT interval prolongation

3.5.1.AC| Chlorpheniramine

- 1)) Interaction Effect: increased risk of [serotonin syndrome](#) ([hypertension](#), [hyperthermia](#), myoclonus, mental status changes)
- 2)) Summary: Both [chlorpheniramine](#) and [trazodone](#) 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](#)[95]. Monitoring for signs and symptoms of [serotonin syndrome](#) may be warranted if [chlorpheniramine](#) and [trazodone](#) are used 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. If [serotonin syndrome](#) develops, discontinue the offending agents and provide supportive care and other therapy as necessary [96].
- 3)) Severity: major
- 4)) Onset: unspecified
- 5)) Substantiation: theoretical
- 6)) Clinical Management: Use caution with concomitant administration of [chlorpheniramine](#) and [trazodone](#), as this may result in additive serotonergic effects and may increase the risk of [serotonin syndrome](#)[95]. If coadministration is required, appropriate monitoring may be warranted.
- 7)) Probable Mechanism: additive serotonergic effect

3.5.1.AD| Chlorpromazine

- 1)) Interaction Effect: hypotension

- 2) Summary: Concomitant administration of [trazodone](#) with [chlorproMAZINE](#) or [trifluoperazine](#) resulted in additive hypotensive effects in two case reports. Withdrawal of [trazodone](#) resulted in resolution of the hypotension[115].
- 3) Severity: moderate
- 4) Onset: delayed
- 5) Substantiation: probable
- 6) Clinical Management: Monitor blood pressure, particularly in patients who might be sensitive to this effect. Advise patient to rise slowly from laying or sitting position.
- 7) Probable Mechanism: additive hypotensive effects

3.5.1.AE] [Ciprofloxacin](#)

- 1) Interaction Effect: an increased risk of QT interval prolongation
- 2) Summary: The concomitant use of [trazodone](#) with other drugs that prolong the QT interval, such as [ciprofloxacin](#)[230], may result in additive QT interval prolongation and risk of serious cardiac events, including [torsade de pointes](#) [95]. If concomitant therapy is required, monitor carefully for QT interval prolongation.
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: The concomitant use of [trazodone](#) with other drugs that prolong the QT interval, such as [ciprofloxacin](#)[230], may result in additive effects on QT interval prolongation and risk of [torsade de pointes](#) [95]. If coadministration is required, monitor for QT interval prolongation.
- 7) Probable Mechanism: additive effects on QT interval prolongation

3.5.1.AF] [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](#)[123].
- 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](#)[123].
- 7) Probable Mechanism: additive QT-interval prolongation

3.5.1.AG] [Citalopram](#)

- 1) Interaction Effect: an increased risk of QT interval prolongation and [serotonin syndrome](#) ([hypertension](#), [hyperthermia](#), myoclonus, mental status changes)
- 2) Summary: QT/QTc interval prolongation and postmarketing cases of [torsade de pointes](#) have been reported with both [citalopram](#) and [trazodone](#)[228][95]. Although this interaction has not been evaluated, concomitant use may result in additive effects on QT interval prolongation and an increased risk of serious [ventricular arrhythmias](#), including [torsade de pointes](#) [95]. A potentially life-threatening [serotonin syndrome](#) and neuroleptic malignant syndrome-like reactions (eg, hyperreflexia, incoordination, [tachycardia](#), labile blood pressure, [hyperthermia](#), agitation, hallucinations, coma) have occurred with [citalopram](#) alone, and the risk was increased when combined with other serotonergic drugs such as [trazodone](#) [95]. If coadministration is required, monitor for ECG changes. Do not exceed [citalopram](#)

doses of 40 mg/day, and discontinue [citalopram](#) in patients who have persistent QTc measurements greater than 500 milliseconds [228]. Patients should also be monitored for signs/symptoms of [serotonin syndrome](#) or neuroleptic malignant syndrome-like reactions, especially during initiation of treatment and dose increases, and therapy should be discontinued in patients who develop these symptoms [95][228].

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: The concomitant use of [citalopram](#) and [trazodone](#) is not recommended due to a potential for additive effects on QT interval prolongation with an increased risk of serious cardiovascular effects. Both agents also have the potential to cause a life-threatening [serotonin syndrome](#) or neuroleptic malignant syndrome-like reactions. If coadministration is required, monitor for ECG changes and signs/symptoms of [serotonin syndrome](#) or neuroleptic malignant syndrome-like reactions, especially during initiation of treatment and dose increases. Do not exceed [citalopram](#) doses of 40 mg/day, and discontinue [citalopram](#) in patients who have persistent QTc measurements greater than 500 milliseconds. Discontinue therapy immediately and initiate treatment in patients who have symptoms of [serotonin syndrome](#) or neuroleptic malignant-syndrome-like reactions[95][228]. 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 [96].

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

3.5.1.AH] [Clarithromycin](#)

1) Interaction Effect: an increase in [trazodone](#) plasma levels; increased risk of QT prolongation

2) Summary: Concomitant use of [clarithromycin](#) and drugs that are known to prolong the QT interval and are CYP3A4 substrates, such as [trazodone](#), may increase [trazodone](#) exposure and risk for QT interval prolongation. If concomitant use is required, consider dosage adjustments and monitoring of serum concentrations, if possible[119].

3) Severity: major

4) Onset: unspecified

5) Substantiation: established

6) Clinical Management: Concomitant use of [clarithromycin](#) and drugs that are known to prolong the QT interval and are CYP3A4 substrates, such as [trazodone](#), may increase [trazodone](#) exposure and risk for QT interval prolongation. If concomitant use is required, consider dosage adjustments and monitoring of serum concentrations, if possible[119].

7) Probable Mechanism: inhibition of CYP3A-mediated [trazodone](#) metabolism by [clarithromycin](#); additive prolongation effects on QT interval

8) Literature Reports

a) Increased plasma concentrations and pharmacodynamic effects of [trazodone](#) when coadministered with [clarithromycin](#) was demonstrated in a randomized, double-blind, 5-way crossover study of 10 healthy volunteers. The study involved five treatment protocols: (a) placebo plus placebo, (b) [zolpidem](#) (5 mg) plus placebo, (c) [zolpidem](#) (5 mg) plus [clarithromycin](#) (500 mg), (d) [trazodone](#) (50 mg) plus placebo, and (e) [trazodone](#) (50 mg) plus [clarithromycin](#) (500 mg). Blood samples were taken intermittently throughout the study to determine plasma concentrations of [zolpidem](#), [trazodone](#), and [clarithromycin](#). Coadministration of [trazodone](#) with [clarithromycin](#) compared with placebo showed an increase in [trazodone](#) C_{max} (922 +/- 161 nanogram/mL versus 681 +/- 128 nanogram/mL) and [trazodone](#) AUC (9,275 +/- 3,216 nanogram/mL per hour versus

4,668 nanogram/mL per hour). Trazodone elimination half-life increased with coadministration of clarithromycin compared to placebo (13.9 +/- 8.1 hr versus 7.1 +/- 1.6 hr), and oral clearance was reduced (89 +/- 26 mL/min versus 166 +/- 27 mL/min). The sedative effects of trazodone were also enhanced by clarithromycin. There were no significant changes in pharmacokinetics or pharmacodynamics of zolpidem in the other clarithromycin treatment groups [120].

3.5.1.AI] Clomipramine

1) Interaction Effect: an increased risk of QT interval prolongation and serotonin syndrome (hypertension, hyperthermia, myoclonus, mental status changes)

2) Summary: Postmarketing cases of abnormal ECG and arrhythmia have been infrequently reported with clomipramine[169] and QT/QTc interval prolongation and postmarketing cases of torsade de pointes have been reported with trazodone. The concomitant use of trazodone with other drugs that prolong the QT interval may result in additive effects on QT interval prolongation and an increased risk of serious ventricular arrhythmias, including torsade de pointes [95]. Both clomipramine and trazodone 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 [95]. 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 [96] If coadministration is required, monitoring for QT interval prolongation and signs and symptoms of serotonin syndrome may be warranted.

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: The concomitant use of trazodone with other drugs that may prolong the QT interval may result in additive effects on QT interval prolongation and risk of torsade de pointes. Coadministration may also result in additive serotonergic effects and may increase the risk of serotonin syndrome[95]. If coadministration is required, appropriate monitoring may be warranted.

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

3.5.1.AJ] Clozapine

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

2) Summary: QT/QTc interval prolongation and postmarketing cases of torsade de pointes have been reported with trazodone. The concomitant use of trazodone with other drugs that prolong the QT interval, such as clozapine[171], may result in additive effects on QT interval prolongation and an increased risk of serious cardiac effects, including torsade de pointes [95], ventricular arrhythmia, cardiac arrest, and sudden death [171]. If coadministration is required, monitoring for QT interval prolongation may be warranted.

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: The concomitant use of trazodone with other QT-prolonging drugs, such as clozapine[171], may result in additive effects on QT interval prolongation and risk of torsade de pointes [95], ventricular arrhythmia, cardiac arrest, and sudden death [171]. If coadministration is required, monitoring for QT interval prolongation may be warranted.

7) Probable Mechanism: additive effects on QT interval prolongation

3.5.1.AK] Cobicistat

- 1) Interaction Effect: increased concentrations of [trazodone](#)
- 2) Summary: Although the interaction between cobicistat, a CYP3A inhibitor[248], and [trazodone](#), a CYP3A4 substrate, has not been specifically evaluated, administration of [trazodone](#) concurrently with [ritonavir](#), a potent CYP3A4 inhibitor, increased [trazodone](#) Cmax by 34% and AUC by 2.4-fold [95]. If coadministration is required, the dose of [trazodone](#) should be titrated carefully [248] and a lower dose of [trazodone](#) should be considered due to an increased risk for [cardiac arrhythmias](#) when used with a CYP3A4 inhibitor, such as cobicistat, [95] Patients should be monitored for antidepressant response [248] and for [trazodone](#) toxicity, including sedation, nausea, hypotension, syncope, and/or [priapism](#).
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Concomitant use of cobicistat and [trazodone](#) may lead to increased plasma concentrations of [trazodone](#). If coadministration is necessary, titrate the dose of [trazodone](#) carefully and monitor for antidepressant response[248]. Due to the increased risk of [cardiac arrhythmias](#), consider a lower dose of [trazodone](#) when used with a CYP3A4 inhibitor, such as cobicistat [95]. Monitor patients for [trazodone](#) toxicity, including sedation, nausea, hypotension, syncope, and/or [priapism](#).
- 7) Probable Mechanism: inhibition of CYP3A-mediated metabolism of [trazodone](#) by cobicistat
- 8) Literature Reports

a) The interaction between cobicistat and [trazodone](#) has not been studied specifically. However, when [trazodone](#) (50-mg single dose), a CYP3A4 substrate, was administered concurrently with [ritonavir](#) (200 mg twice daily, 4 doses), a strong CYP3A4 inhibitor, [trazodone](#) Cmax increased by 34%, AUC increased 2.4-fold, half-life increased 2.2-fold, and clearance decreased by 52% compared with [trazodone](#) administration alone [95].

3.5.1.AL] Cocaine

- 1) Interaction Effect: increased risk of [serotonin syndrome](#) ([hypertension](#), [hyperthermia](#), myoclonus, mental status changes)
- 2) Summary: Both cocaine and [trazodone](#) 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](#)[95]. Monitoring for signs and symptoms of [serotonin syndrome](#) may be warranted if cocaine and [trazodone](#) are used 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. If [serotonin syndrome](#) develops, discontinue the offending agents and provide supportive care and other therapy as necessary [96].
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Use caution with concomitant administration of cocaine and [trazodone](#), as this may result in additive serotonergic effects and may increase the risk of [serotonin syndrome](#)[95]. If coadministration is required, appropriate monitoring may be warranted.
- 7) Probable Mechanism: additive serotonergic effect

3.5.1.AM] Conivaptan

- 1) Interaction Effect: increased exposure of CYP3A substrate
- 2) Summary: Avoid concomitant use of [conivaptan](#) (strong CYP3A inhibitor) with drugs eliminated primarily by CYP3A-mediated metabolism, as this may result in increased exposure of the CYP3A substrate. [Conivaptan](#) increased the AUC of CYP3A substrates [midazolam](#), [simvastatin](#), and [amlodipine](#). The CYP3A substrate may be initiated no sooner than 1 week after completion of [conivaptan](#) therapy[242].
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Avoid concomitant use of [conivaptan](#) (strong CYP3A inhibitor) with drugs eliminated primarily by CYP3A-mediated metabolism, as this may result in increased exposure of the CYP3A substrate. The CYP3A substrate may be initiated no sooner than 1 week after completion of [conivaptan](#) therapy[242].
- 7) Probable Mechanism: inhibition of CYP3A-mediated substrate metabolism by [conivaptan](#)
- 8) Literature Reports

a) The strong CYP3A inhibitor [conivaptan](#) 40 mg/day IV increased the AUC of [midazolam](#), a CYP3A substrate, by approximately 100% with a 1-mg IV dose and by 200% with a 2-mg oral dose [242].

b) [Conivaptan](#) 30 mg/day IV tripled the AUC of [simvastatin](#), a CYP3A substrate [242].

c) [Conivaptan](#) 40 mg orally twice daily doubled the AUC and half-life of [amlodipine](#), a CYP3A substrate [242].

3.5.1.AN] Crizotinib

- 1) Interaction Effect: increased risk of QT-interval prolongation
- 2) Summary: QT-interval prolongation has occurred during crizotinib therapy. Risk of additive QT-interval prolongation increases during coadministration with other drugs associated with QT prolongation. If concomitant use is clinically indicated, use caution and consider periodic ECG and [electrolyte monitoring](#) during therapy[163]. Dose reduction of crizotinib may be warranted.
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Use caution in coadministering crizotinib with a drug known to prolong the QT interval, as concurrent use of such agents may lead to an increased risk of serious cardiac adverse events. If concomitant use is clinically indicated, consider periodic ECG and [electrolyte monitoring](#) during therapy[163]. Dose reduction of crizotinib may be warranted.
- 7) Probable Mechanism: additive effects on QT interval

3.5.1.AO] [Cyclobenzaprine](#)

- 1) Interaction Effect: increased risk of [serotonin syndrome](#)
- 2) Summary: [Serotonin syndrome](#), a life-threatening condition, has occurred with coadministration of [cyclobenzaprine](#) and other drugs, such as [trazodone](#). 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[206][207].
- 3) Severity: major

- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Coadministration of [cyclobenzaprine](#) with [trazodone](#) 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[206][207].
- 7) Probable Mechanism: additive serotonergic effects

3.5.1.AP] Dabrafenib

- 1) Interaction Effect: decreased exposure of CYP3A4 substrates; increased risk of QT-interval prolongation
- 2) Summary: Dabrafenib is a CYP3A4 inducer known to prolong the QT interval. Use of dabrafenib with CYP3A4 substrates that also prolong the QT interval may lead to decreased exposure of the CYP3A4 substrate and an increased risk of QT-interval prolongation. Alternative therapy is recommended whenever possible. If concomitant use is required, monitor patients for loss of efficacy[261] and consider assessment and periodic monitoring for [ventricular arrhythmia](#).
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Dabrafenib is a CYP3A4 inducer capable of prolonging the QT interval. Use of dabrafenib with a CYP3A4 substrate that also prolongs the QT interval may lead to decreased exposure of the CYP3A4 substrate and an increased risk of QT-interval prolongation. Alternative therapy is recommended whenever possible. If concomitant use is required, monitor patients for loss of efficacy and[261] consider assessment and periodic monitoring for [ventricular arrhythmia](#).
- 7) Probable Mechanism: induction of CYP3A4-mediated metabolism by dabrafenib; additive QT-interval prolongation
- 8) Literature Reports
 - a) Administration of dabrafenib 150 mg twice daily for 15 days with a single 3 mg [midazolam](#) dose, decreased [midazolam](#) AUC by 74%. Dabrafenib is a CYP3A4 inducer, while [midazolam](#) is a CYP3A4 substrate [262].

3.5.1.AQ] Darunavir

- 1) Interaction Effect: increased tricyclic antidepressant exposure
- 2) Summary: Coadministration of [darunavir](#) with antidepressants (ie, tricyclic antidepressants, or [trazodone](#)) may result in increased exposure of the antidepressant. If coadministered, carefully titrate the antidepressant to the desired effect. Use the lowest effective antidepressant dose and monitor for adverse effects and antidepressant response with concurrent use[137][138].
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Coadministration of [darunavir](#) with antidepressants (ie, tricyclic antidepressants, or [trazodone](#)) may result in increased exposure of the antidepressant. If coadministered, carefully titrate the antidepressant to the desired effect. Use the lowest effective antidepressant dose and monitor for adverse effects and antidepressant response with concurrent use[137][138].
- 7) Probable Mechanism: unknown

3.5.1.AR] Dasatinib

- 1) Interaction Effect: an increased risk of QT interval prolongation
- 2) Summary: QT/QTc interval prolongation and postmarketing cases of [torsade de pointes](#) have been reported with [trazodone](#). The concomitant use of [trazodone](#) with other drugs that prolong the QT interval, such as [dasatinib](#)[166], may result in additive effects on QT interval prolongation and an increased risk of serious [ventricular arrhythmias](#), including [torsade de pointes](#) [95]. If coadministration is required, monitoring for QT interval prolongation may be warranted.
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: The concomitant use of [trazodone](#) with other QT-prolonging drugs, such as [dasatinib](#)[166], may result in additive effects on QT interval prolongation and risk of [torsade de pointes](#) [95]. If coadministration is required, monitoring for QT interval prolongation may be warranted.
- 7) Probable Mechanism: additive effects on QT interval prolongation

3.5.1.AS] 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[289][290][291]. 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[289][290][291].
- 7) Probable Mechanism: additive effects on the QT interval

3.5.1.AT] 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[267].
- 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[267].
- 7) Probable Mechanism: additive QT- interval prolongation

3.5.1.AU] Delavirdine

- 1J) Interaction Effect: increased plasma concentrations of [trazodone](#) and increased risk of [trazodone](#) adverse effects (nausea, dizziness, hypotension, syncope)
- 2J) Summary: [Trazodone](#) is metabolized in the liver by CYP3A4 enzymes. Drugs that are CYP3A4 inhibitors, such as delavirdine, may decrease the metabolism of [trazodone](#), causing increased [trazodone](#) plasma concentrations. Although, the drug interaction between delavirdine and [trazodone](#) has not been studied, adverse effects such as nausea, dizziness, hypotension and syncope have occurred following coadministration of [trazodone](#) and [ritonavir](#). Therefore, caution is advised when delavirdine and [trazodone](#) are administered concomitantly and a reduction in [trazodone](#) dosage should be considered[227].
- 3J) Severity: moderate
- 4J) Onset: delayed
- 5J) Substantiation: theoretical
- 6J) Clinical Management: Use caution with the coadministration of delavirdine and [trazodone](#). Monitor patients for signs of increased [trazodone](#) adverse effects (nausea, dizziness, hypotension, syncope). Consider reducing [trazodone](#) dosage when administering concomitantly with delavirdine.
- 7J) Probable Mechanism: inhibition of cytochrome P450 3A4-mediated [trazodone](#) metabolism

3.5.1.AV] [Desipramine](#)

- 1J) Interaction Effect: an increased risk of QT interval prolongation and [serotonin syndrome](#) ([hypertension](#), [hyperthermia](#), myoclonus, mental status changes)
- 2J) Summary: [Desipramine](#) may prolong the QT interval at very high doses[154] and QT/QTc interval prolongation and postmarketing cases of [torsade de pointes](#) have been reported with [trazodone](#). The concomitant use of [trazodone](#) with other drugs that prolong the QT interval may result in additive effects on QT interval prolongation and an increased risk of serious [ventricular arrhythmias](#), including [torsade de pointes](#) and therefore should be avoided [95]. Both [desipramine](#) and [trazodone](#) 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](#) [95]. 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 [96]. If coadministration is required, monitoring for QT interval prolongation and signs and symptoms of [serotonin syndrome](#) may be warranted.
- 3J) Severity: major
- 4J) Onset: unspecified
- 5J) Substantiation: theoretical
- 6J) Clinical Management: The concomitant use of [trazodone](#) with other drugs that may prolong the QT interval, such as [desipramine](#)[154], may result in additive effects on QT interval prolongation and risk of [torsade de pointes](#) and therefore should be avoided. Coadministration may also result in additive serotonergic effects and may increase the risk of [serotonin syndrome](#) [95]. If coadministration is required, appropriate monitoring may be warranted.
- 7J) Probable Mechanism: additive effects on QT interval prolongation; additive serotonergic effects

3.5.1.AW] [Deslorelin](#)

- 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[289][290][291].

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[289][290][291].

7) Probable Mechanism: additive effects on the QT interval

3.5.1.AX] Desvenlafaxine

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

2) Summary: Desvenlafaxine is a serotonergic drug; concomitant use with another agent that affects the serotonergic neurotransmitter system may result in an increased risk of [serotonin syndrome](#) and should be approached with extreme caution. [Serotonin syndrome](#) may be life-threatening. Symptoms may include mental status changes (eg, agitation, hallucinations, coma), autonomic instability (eg, [tachycardia](#), labile blood pressure, [hyperthermia](#)), neuromuscular aberrations (eg, hyperreflexia, incoordination), and/or gastrointestinal symptoms (eg, nausea, vomiting, diarrhea). If coadministration is required, monitor closely for signs and symptoms of [serotonin syndrome](#), especially during treatment initiation and dose increases of either drug. If [serotonin syndrome](#) develops, discontinue both agents and initiate supportive symptomatic therapy[186].

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Use extreme caution with coadministration of desvenlafaxine and another serotonergic drug, such as an SSRI, serotonin-norepinephrine reuptake inhibitor, or tricyclic antidepressant, as this may result in additive serotonergic effects and may increase the risk of [serotonin syndrome](#). If coadministration is required, careful monitoring is recommended, especially during treatment initiation and dose increases. Immediate discontinuation of both agents and supportive symptomatic treatment is warranted if [serotonin syndrome](#) develops[186].

7) Probable Mechanism: additive serotonergic effect

3.5.1.AY] 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[156].

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[156].

7J) Probable Mechanism: additive serotonergic effect

3.5.1.AZ| Dextromethorphan

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

2J) Summary: [Dextromethorphan](#) is known to cause [serotonin syndrome](#)[161] and both [dextromethorphan](#) and [trazodone](#) 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](#) [95]. Monitoring for signs and symptoms of [serotonin syndrome](#) may be warranted if [dextromethorphan](#) and [trazodone](#) are used 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. If [serotonin syndrome](#) develops, discontinue the offending agents and provide supportive care and other therapy as necessary [96].

3J) Severity: major

4J) Onset: unspecified

5J) Substantiation: theoretical

6J) Clinical Management: Use caution with concomitant administration of [dextromethorphan](#), a drug known to cause [serotonin syndrome](#)[161], and [trazodone](#), as this may result in additive serotonergic effects and may increase the risk of [serotonin syndrome](#) [95]. If coadministration is required, appropriate monitoring may be warranted.

7J) Probable Mechanism: additive serotonergic effect

3.5.1.BA| Digoxin

1J) Interaction Effect: increased [digoxin](#) serum concentrations and an increased risk of [digoxin toxicity](#) (nausea, vomiting, [arrhythmias](#))

2J) Summary: [Digoxin](#) maximum serum concentrations were increased nearly 30% compared with baseline after [nefazodone](#) (an antidepressant structurally related to [trazodone](#)) was given concurrently, in an open, randomized, crossover interaction study[256]. [Digoxin toxicity](#) occurred in a 68-year-old woman after [trazodone](#) was added to a stable treatment regimen that included [digoxin](#). Her [digoxin](#) level had remained within a stable therapeutic range for many months prior to beginning [trazodone](#) therapy [257]. Increased serum [digoxin](#) serum concentrations have also been reported in patients treated concurrently with [trazodone](#) and [digoxin](#) [258].

3J) Severity: moderate

4J) Onset: delayed

5J) Substantiation: probable

6J) Clinical Management: Monitor [digoxin](#) concentrations when [trazodone](#) is added to, changed during, or discontinued from concomitant treatment with [digoxin](#). Also, monitor patients for signs and symptoms of [digoxin toxicity](#). Adjust [digoxin](#) dose accordingly.

7J) Probable Mechanism: unknown

8J) Literature Reports

aJ) [Digoxin](#) serum concentrations were increased nearly 30% compared with baseline after [nefazodone](#) (a phenylpiperazine antidepressant structurally related to [trazodone](#)) was given concurrently with [digoxin](#). In an open, randomized, triple-crossover interaction study, healthy subjects (n=18) received an 8-day oral regimen of [digoxin](#) 0.2 milligrams (mg) daily, [nefazodone](#) 200 mg twice daily, or both drugs administered concomitantly during each 8-day trial period; all subjects crossed over to an alternate study regimen after a 10-day wash-out period. Steady-

state area under the concentration-time curve (AUC) and peak (C_{max}) and trough (C_{min}) serum concentrations of [digoxin](#) were increased by 15%, 29% and 27%, respectively (p less than 0.05, each parameter). No significant changes were observed in vital signs, heart rate, or PR, QRS, and QT intervals. The frequency and severity of adverse events did not differ between treatment groups [253].

b) [Digoxin toxicity](#) occurred in a 68-year-old woman after [trazodone](#) was added to a stable treatment regimen that included [digoxin](#). Prior to beginning [trazodone](#) therapy, her serum [digoxin](#) level had remained within therapeutic range for many months (at a dose of [digoxin](#) 125 micrograms (mcg) daily), and on admission was 0.8 nanograms/mL (1 nanomol/L). She was hospitalized for severe depression; [trazodone](#) was initiated at a dose of 50 milligrams (mg) on day 1, and then escalated to 300 mg daily by day 11. On treatment day 14, the patient complained of nausea and vomiting; her [digoxin](#) level measured at 2.8 nanograms/mL (3.6 nanomol/L). [Trazodone](#) 300 mg daily was continued and [digoxin](#) was withdrawn until therapeutic [digoxin](#) serum levels were restored. The patient's [digoxin](#) levels were sustained within therapeutic range after conversion to an every-other-day regimen of [digoxin](#) 125 mcg while she continued to receive [trazodone](#) 300 mg daily [254].

c) Increased serum concentrations of [digoxin](#) have been observed in patients receiving concurrent treatment with [trazodone](#) [255].

3.5.1.BB| [Disopyramide](#)

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

2) Summary: As with other type 1 antiarrhythmic drugs, prolongation of the QT_c interval may occur with [disopyramide](#)[151]. QT/QT_c interval prolongation and postmarketing cases of [torsade de pointes](#) have been reported with [trazodone](#). The concomitant use of [trazodone](#) with other drugs that prolong the QT interval may result in additive effects on QT interval prolongation and an increased risk of serious [ventricular arrhythmias](#), including [torsade de pointes](#) and therefore should be avoided [95]. If concomitant use of [disopyramide](#) and [trazodone](#) is required, monitor the patient closely for QT interval prolongation and consider discontinuation of [disopyramide](#) therapy if a QT interval prolongation of greater than 25% occurs with persistent ectopy [151].

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: The concomitant use of [trazodone](#) with other drugs that may prolong the QT interval, such as [disopyramide](#)[151], may result in additive effects on QT interval prolongation and risk of [torsade de pointes](#) and therefore should be avoided [95]. If concomitant use of [disopyramide](#) and [trazodone](#) is required, monitor the patient closely for QT interval prolongation and consider discontinuation of [disopyramide](#) therapy if a QT interval prolongation of greater than 25% occurs with persistent ectopy [151].

7) Probable Mechanism: additive effects on QT interval

3.5.1.BC| [Dofetilide](#)

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

2) Summary: Due to the potential for additive effects on the QT interval and increased risk of serious cardiac effects, concomitant use of [dofetilide](#) with other drugs that prolong the QT interval, such as [trazodone](#)[95], is not recommended [150]. If coadministration is required, monitoring for QT interval prolongation may be warranted.

3) Severity: major

4) Onset: unspecified

- 5) Substantiation: theoretical
- 6) Clinical Management: Coadministration of [dofetilide](#) with other drugs that prolong the QT interval, such as [trazodone](#)[95], is not recommended due to the potential for additive effects on the QT interval and increased risk of serious cardiovascular effects [150]. If coadministration is required, monitoring for QT interval prolongation may be warranted.
- 7) Probable Mechanism: additive effects on QT interval

3.5.1.BD] [Dolasetron](#)

- 1) Interaction Effect: increased risk of [serotonin syndrome](#) and QT-interval prolongation
- 2) Summary: Concomitant use of [dolasetron](#) with a drug that is a serotonergic agent with QT-interval prolonging effects may increase the risks of [serotonin syndrome](#) or QT-interval prolongation. [Serotonin syndrome](#) has been reported with the concurrent use of 5-hydroxytryptamine-3 antagonists and serotonergic drugs, primarily in infusion centers or in post-anesthesia care units. Inform patients of this increased risk and monitor for the emergence of [serotonin syndrome](#). If symptoms of [serotonin syndrome](#) occur, discontinue [dolasetron](#) and institute supportive therapy. Because [dolasetron](#) is known to prolong the QT-interval, administration with other QT-interval prolonging agents may result in additive effects, and should be undertaken with caution[121][122].
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Concomitant use of [dolasetron](#) with a drug that is a serotonergic agent with QT-interval prolonging effects may increase the risks of [serotonin syndrome](#) or QT-interval prolongation. Inform patients of the increased risk of [serotonin syndrome](#) and monitor for the emergence of [serotonin syndrome](#). If symptoms of [serotonin syndrome](#) occur, discontinue [dolasetron](#) and institute supportive therapy. Because [dolasetron](#) is known to prolong the QT-interval, coadministration with other QT-interval prolonging agents may result in additive effects, and should be undertaken with caution[121][122].
- 7) Probable Mechanism: unknown; additive QT-interval prolongation

3.5.1.BE] [Domperidone](#)

- 1) Interaction Effect: increased risk of QT interval prolongation
- 2) Summary: Use caution with coadministration of [trazodone](#), a QT prolonging drug[95], 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 of age. If coadministration is necessary, domperidone should be initiated at the lowest possible dose and titrated with caution. Discontinue domperidone if the patient experiences dizziness, palpitations, syncope, or seizure [176].
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Use caution when coadministering domperidone and [trazodone](#) as this may increase the risk of serious cardiac effects, including [ventricular arrhythmias](#) and sudden cardiac death[95], particularly at domperidone doses greater than 30 mg/day, and in patients older than 60 years. If coadministration is necessary, domperidone should be initiated at the lowest possible dose and titrated with caution. Discontinue domperidone if the patient experiences dizziness, palpitations, syncope, or seizure [176].
- 7) Probable Mechanism: additive effects on the QT interval

3.5.1.BF] [Donepezil](#)

- 1) Interaction Effect: increased risk of QT-interval prolongation and [torsade de pointes](#)
- 2) Summary: [Donepezil](#) has been associated with QT-interval prolongation[158][159]. 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[158][159]. Use caution when administering [donepezil](#) concomitantly with other drugs that cause QT-interval prolongation
- 7) Probable Mechanism: additive QT-interval prolongation

3.5.1.BG| [Doxepin](#)

- 1) Interaction Effect: increased risk of [serotonin syndrome](#) ([hypertension](#), [hyperthermia](#), myoclonus, mental status changes)
- 2) Summary: Both [doxepin](#) and [trazodone](#) 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](#)[95]. Monitoring for signs and symptoms of [serotonin syndrome](#) may be warranted if [doxepin](#) and [trazodone](#) are used 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. If [serotonin syndrome](#) develops, discontinue the offending agents and provide supportive care and other therapy as necessary [96].
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Use caution with concomitant administration of [doxepin](#) and [trazodone](#), as this may result in additive serotonergic effects and may increase the risk of [serotonin syndrome](#)[95]. If coadministration is required, appropriate monitoring may be warranted.
- 7) Probable Mechanism: additive serotonergic effect

3.5.1.BH| [Dronedarone](#)

- 1) Interaction Effect: increased risk of QT-interval prolongation
- 2) Summary: The concomitant use of dronedarone with drugs that cause QT-interval prolongation is contraindicated, as coadministration may increase the risk of QT prolongation and serious [ventricular arrhythmias](#)[260].
- 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](#)[260].
- 7) Probable Mechanism: additive QT-interval prolongation

3.5.1.BI| [Droperidol](#)

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

2) Summary: Any drug known to have the potential to prolong the QT interval should not be used together with [droperidol](#). Possible pharmacodynamic interactions can occur between [droperidol](#) and potentially arrhythmogenic agents, such as certain antidepressants that prolong the QT interval. If concomitant use cannot be avoided, treatment should be undertaken with extreme caution and [ECG monitoring](#) (prior to treatment and 2 to 3 hours after completing treatment) should be implemented[162].

3) Severity: major

4) Onset: rapid

5) Substantiation: theoretical

6) Clinical Management: Concomitant use of [droperidol](#) and other QT prolonging drugs, such as certain antidepressants, is not recommended. If concomitant use cannot be avoided, [droperidol](#) should be administered with extreme caution and [ECG monitoring](#) (prior to treatment and 2 to 3 hours after treatment is complete) is recommended[162].

7) Probable Mechanism: additive cardiac effects

3.5.1.BJ] [Duloxetine](#)

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

2) Summary: Use caution when prescribing [duloxetine](#) to patients who take [trazodone](#). Concurrent administration may result in potentially fatal [serotonin syndrome](#) or neuroleptic malignant syndrome-like reactions with symptoms including neuromuscular aberrations (eg, hyperreflexia, incoordination), autonomic instability (eg, [tachycardia](#), labile blood pressure, [hyperthermia](#)), and mental status changes (eg, agitation, hallucinations, coma). Serious reactions have been reported in patients receiving concomitant serotonergic drugs[95]. If concomitant use is necessary, monitor patients closely for signs/symptoms of [serotonin syndrome](#) or neuroleptic malignant syndrome-like reactions, especially during initiation of treatment and dose increases [269]. [Serotonin syndrome](#) can be life-threatening. If [serotonin syndrome](#) develops, discontinue the offending agents and provide supportive care and other therapy as necessary [96].

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Use caution when prescribing [duloxetine](#) to patients who take [trazodone](#). Concurrent use of [duloxetine](#), a selective serotonin and [norepinephrine](#) reuptake inhibitor, and [trazodone](#) may result in potentially fatal [serotonin syndrome](#)[95]. If concomitant use is necessary, monitor patients closely for signs/symptoms of [serotonin syndrome](#) or neuroleptic malignant syndrome-like reactions, especially during initiation of treatment and dose increases [269].

7) Probable Mechanism: additive serotonergic effect

3.5.1.BK] [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 QT_c interval prolongation was 8.7 milliseconds in subjects with the CYP2B6 *6/*6 genotype[165].

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[165].

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 Cmax in subjects with the CYP2B6 *6/*6 genotype was 2.25-fold higher than the mean Cmax 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 [165].

3.5.1.BL] [Eletriptan](#)

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

2) Summary: [Eletriptan](#) is known to cause [serotonin syndrome](#)[280] and both [eletriptan](#) and [trazodone](#) 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](#). Careful monitoring for signs and symptoms of [serotonin syndrome](#) is warranted, if [eletriptan](#) and [trazodone](#) are used concurrently, particularly during treatment initiation and dose increases [95]. 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 [96].

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Use caution with concomitant administration of [eletriptan](#), a drug known to cause [serotonin syndrome](#)[280], and [trazodone](#), as this may result in additive serotonergic effects and may increase the risk of [serotonin syndrome](#) [95]. If coadministration is required, careful monitoring is warranted, particularly during treatment initiation and dose increases [95].

7) Probable Mechanism: additive serotonergic effect

3.5.1.BM] [Erythromycin](#)

1) Interaction Effect: an increased risk of QT interval prolongation and increased [trazodone](#) plasma concentrations

2) Summary: Both [erythromycin](#) and [trazodone](#) have been associated with QT interval prolongation and [torsade de pointes](#). The concomitant use of [trazodone](#) (a CYP3A4 substrate)[95] with [erythromycin](#) (a CYP3A4 inhibitor) [147] may result in increased [trazodone](#) plasma concentrations and risk of additive QT interval prolongation and serious cardiac events, including [torsade de pointes](#). If concomitant therapy is required, consider a dose reduction of [trazodone](#) [95] and monitor carefully for QT interval prolongation.

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: The concomitant use of [trazodone](#) with other drugs that prolong the QT interval and inhibit CYP3A4, such as [erythromycin](#)[147], may result in increased [trazodone](#) plasma concentrations

and additive effects on QT interval prolongation and risk of [torsade de pointes](#). If coadministration is required, consider a dose reduction of [trazodone](#) [95] and monitor for QT interval prolongation.

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

3.5.1.BN] Escitalopram

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

2J) Summary: Escitalopram is a serotonergic drug that may prolong QT interval[175]. Use caution if concurrent use with [trazodone](#) is necessary, as coadministration may result in additive [serotonin syndrome](#), QT-interval prolongation, or both. Careful monitoring is warranted, particularly during treatment initiation and dose increases [95]. Discontinue escitalopram and any concomitant serotonergic agents immediately and initiate supportive treatment if [serotonin syndrome](#) is suspected [175].

3J) Severity: major

4J) Onset: unspecified

5J) Substantiation: theoretical

6J) Clinical Management: Escitalopram is a serotonergic drug that may prolong QT interval[175]. Use caution if concurrent use with [trazodone](#) is necessary, as coadministration may result in additive [serotonin syndrome](#), QT-interval prolongation, or both. Careful monitoring is warranted, particularly during treatment initiation and dose increases [95]. Discontinue escitalopram and any concomitant serotonergic agents immediately and initiate supportive treatment if [serotonin syndrome](#) is suspected [175].

7J) Probable Mechanism: additive serotonergic effect; additive QT-interval prolongation

3.5.1.BO] Ethopropazine

1J) Interaction Effect: hypotension

2J) Summary: Concomitant administration of [trazodone](#) with [chlorpromazine](#) or [trifluoperazine](#) resulted in additive hypotensive effects in two case reports. Withdrawal of [trazodone](#) resulted in resolution of the hypotension[263].

3J) Severity: moderate

4J) Onset: delayed

5J) Substantiation: theoretical

6J) Clinical Management: Monitor blood pressure, particularly in patients who might be sensitive to this effect. Advise patient to rise slowly from laying or sitting position.

7J) Probable Mechanism: additive hypotensive effects

3.5.1.BP] Fenfluramine

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

2J) Summary: Both [fenfluramine](#) and [trazodone](#) 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](#)[95]. Monitoring for signs and symptoms of [serotonin syndrome](#) may be warranted if [fenfluramine](#) and [trazodone](#) are used 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. If [serotonin syndrome](#) develops, discontinue the offending agents and provide supportive care and other therapy as necessary [96].

3J) Severity: major

4J) Onset: unspecified

- 5) Substantiation: theoretical
- 6) Clinical Management: Use caution with concomitant administration of [fenfluramine](#) and [trazodone](#), as this may result in additive serotonergic effects and may increase the risk of [serotonin syndrome](#)[95]. If coadministration is required, appropriate monitoring may be warranted.
- 7) Probable Mechanism: additive serotonergic effect

3.5.1.BQ| [Fentanyl](#)

- 1) Interaction Effect: increased risk of [serotonin syndrome](#)
- 2) Summary: [Fentanyl](#) is proserotonergic and has been associated with [serotonin syndrome](#) when coadministered with serotonergic drugs[282], including SSRIs [284][283][285]. [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 [282]. 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 [96].
- 3) Severity: major
- 4) Onset: delayed
- 5) Substantiation: theoretical
- 6) Clinical Management: [Fentanyl](#) is a proserotonergic, synthetic piperidine opioid and has been associated with [serotonin syndrome](#) when coadministered with other serotonergic drugs. Therefore, use caution with coadministration of [fentanyl](#) and a serotonergic drug, such as an SSRI, serotonin-norepinephrine reuptake inhibitor, tricyclic antidepressant, or another synthetic piperidine opioid, as this may result in additive serotonergic effects and may increase the risk of [serotonin syndrome](#). If possible, consider replacing serotonergic opioids (eg, [fentanyl](#)) with non-serotonergic opioids (eg, [morphine](#)) [282]. 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 [96].
- 7) Probable Mechanism: additive serotonergic effect
- 8) Literature Reports

a) [Serotonin syndrome](#) associated with [fentanyl](#) use during an [esophagogastroduodenoscopy](#) was reported in a 39-year-old woman also taking [sertraline](#) 100 mg daily as an outpatient. The patient initially presented with [hematemesis](#) and a history of [alcoholic cirrhosis](#). Prior to the [esophagogastroduodenoscopy](#), an [octreotide](#) and [pantoprazole](#) drip was started, 2 doses of [fentanyl](#) 50 micrograms, and 2 doses of [midazolam](#) 1 mg were administered. The patient became somnolent and extremely rigid in all four extremities following the procedure, and [vecuronium](#) and [etomidate](#) were given for immediate intubation. The rigidity progressed with diffuse diaphoresis, horizontal [roving eye movements](#), and a fever of 105 degrees F. Due to the potential for seizure activity, [lorazepam](#) 2 mg IV was given with no improvement and a [propofol](#) drip was started for continued sedation during intubation. A CPK value of 2800 units/L and an ammonia level of 340 micromols/L indicated [rhabdomyolysis](#). An acute intracranial process was ruled out on a [CT scan](#) of the brain and the neurology team made the diagnosis of [serotonin syndrome](#) secondary to an interaction between [fentanyl](#) and [sertraline](#). [Propofol](#) was continued for sedation and the patient received supportive treatment with a cooling blanket and [ciproheptadine](#). After 3 days, the patient's temperature and CPK level normalized and she later extubated with no further complications [283].

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 [284].

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 [285].

3.5.1.BR] Fingolimod

1) Interaction Effect: an increased risk of QT interval prolongation and **torsade de pointes**

2) Summary: QT interval prolongation and postmarketing cases of **torsade de pointes** (with immediate-release tablets) have been reported with **trazodone**[95] and dose-related QT interval prolongation has been reported with fingolimod. As initiation of fingolimod therapy may decrease the heart rate and prolong the QT interval, the coadministration of fingolimod with **trazodone** may increase the risk of additive QT interval prolongation and **torsade de pointes**. If concomitant use is necessary, observe patients who are receiving **trazodone** with **continuous ECG monitoring** overnight in a medical facility when initiating fingolimod [157].

3) Severity: major

- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: The concomitant use of fingolimod and [trazodone](#) may increase the risk of QT interval prolongation[157] and [torsade de pointes](#) [95]. If coadministration is necessary, observe the trazodone-treated patient with [continuous ECG monitoring](#) overnight in a medical facility when initiating fingolimod therapy [157].
- 7) Probable Mechanism: additive QT interval prolongation

3.5.1.BS] [Flecainide](#)

- 1) Interaction Effect: an increased risk of QT interval prolongation
- 2) Summary: QT/QTc interval prolongation and postmarketing cases of [torsade de pointes](#) have been reported with [trazodone](#). The concomitant use of [trazodone](#) with other drugs that prolong the QT interval, such as [flecainide](#)[145], may result in additive effects on QT interval prolongation and an increased risk of serious [ventricular arrhythmias](#), including [torsade de pointes](#) and therefore should be avoided [95]. If coadministration is required, monitoring for QT interval prolongation may be warranted.
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: The concomitant use of [trazodone](#) with other QT-prolonging drugs, such as [flecainide](#)[145], may result in additive effects on QT interval prolongation and risk of [torsade de pointes](#) and therefore should be avoided [95]. If coadministration is required, monitoring for QT interval prolongation may be warranted.
- 7) Probable Mechanism: additive effects on QT interval prolongation

3.5.1.BT] [Fluconazole](#)

- 1) Interaction Effect: increased [trazodone](#) exposure and an increased risk of QT interval prolongation
- 2) Summary: Concomitant use of [fluconazole](#) (moderate CYP3A4 inhibitor) with other drugs that are known to prolong the QT interval and are CYP3A4 substrates, such as [trazodone](#), is contraindicated because of increased exposure to the CYP3A4 substrate and risk for additive QT-interval prolongation. Fluconazole-mediated CYP3A4 inhibition may continue for 4 to 5 days after discontinuation because of the long half-life[203]. QT/QTc interval prolongation and postmarketing cases of [torsade de pointes](#) have been reported with [trazodone](#) [95].
- 3) Severity: contraindicated
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Concomitant use of [fluconazole](#) (moderate CYP3A4 inhibitor) with other drugs that are known to prolong the QT interval and are CYP3A4 substrates, such as [trazodone](#), is contraindicated because of increased exposure to the CYP3A4 substrate and risk for additive QT-interval prolongation. Fluconazole-mediated CYP3A4 inhibition may continue for 4 to 5 days after discontinuation because of the long half-life[203].
- 7) Probable Mechanism: additive effects on QT interval prolongation; inhibition of CYP3A4-mediated [trazodone](#) metabolism by [fluconazole](#)

3.5.1.BU] [Fluoxetine](#)

- 1) Interaction Effect: increased risk of [serotonin syndrome](#) ([hypertension](#), [hyperthermia](#), myoclonus, mental status changes); increased risk of QT-interval prolongation
- 2) Summary: Both [fluoxetine](#) and [trazodone](#) affect the serotonergic neurotransmitter systems. Concomitant use may increase the risk of [serotonin syndrome](#)[212][95]. There have been several

reports of [serotonin syndrome](#) due to interactions between selective serotonin reuptake inhibitors and antidepressants [217][218][219]. Additionally, concomitant administration of [fluoxetine](#) and [trazodone](#) may result in additive effects on the QT interval and should be avoided [212]. Monitoring for [serotonin syndrome](#) is warranted [95] and periodic [ECG monitoring](#) should be considered [212].

3) Severity: major

4) Onset: unspecified

5) Substantiation: probable

6) Clinical Management: Concomitant administration of [fluoxetine](#) and [trazodone](#) may result in additive serotonergic effects and may increase the risk of [serotonin syndrome](#)[212][95]. Additionally, concomitant administration of [fluoxetine](#) and [trazodone](#) may result in additive effects on the QT interval and should be avoided [212]. If coadministration is required, appropriate monitoring is warranted (including periodic [ECG monitoring](#)), particularly during treatment initiation and dose increases [95][212].

7) Probable Mechanism: additive serotonergic effects; additive QT-interval prolongation effects

8) Literature Reports

a) Five cases of elevated antidepressant levels, four involving tricyclic antidepressants ([nortriptyline](#), [imipramine](#), [desipramine](#)) and one involving [trazodone](#), have been reported. After the addition of [fluoxetine](#), the ratio of antidepressant level to dose increased by 109% to 486% in the patients on tricyclics and by 31% in the patient on [trazodone](#). The trazodone-treated patient developed sedation and unstable gait [213].

b) A 44-year-old man developed symptoms characteristic of [serotonin syndrome](#) due to a possible interaction between [fluoxetine](#) and [trazodone](#). The patient had been taking [fluoxetine](#) 40 mg daily and [trazodone](#) 100 mg daily for approximately two months before symptoms occurred. The patient experienced disorientation, tremor, diaphoresis, and anxiety, followed by uncontrollable shaking and loss of consciousness. After the patient was treated with [cyproheptadine](#) 4 mg orally, symptoms resolved over the next 30 minutes. [Trazodone](#) was discontinued and the patient continued to take [fluoxetine](#) 40 mg daily without further complications [214].

c) A 43-year-old male with [traumatic brain injury](#) developed speech dysfunction during therapy with [fluoxetine](#) and [trazodone](#). The patient was being treated with [trazodone](#) 150 mg at bedtime for chronic pain as a result of a fall. After undergoing a comprehensive psychiatric evaluation as part of rehabilitation, [fluoxetine](#) 20 mg every morning was added to the patient's regimen for treatment of symptoms of depression. Within one week of starting therapy with [fluoxetine](#), the patient began to slur his speech and later exhibited a slow rate of speech, increased pause length, prolongation of initial phonemes, and word-finding difficulties. After discontinuation of [fluoxetine](#) and tapering of [trazodone](#) therapy, the patient had marked improvement in speech difficulty and returned to normal over the next week [215].

d) The pharmacokinetic effect of [trazodone](#) and [fluoxetine cotherapy](#) was studied in 27 inpatients with a [major depressive episode](#). All were treated with [trazodone](#) 100 mg daily, followed one week later with the addition of [fluoxetine](#) 20 mg daily, [pindolol](#) 7.5 mg daily, or placebo for four weeks. [Pindolol](#) and placebo had no significant effect on the plasma concentrations of [trazodone](#) or its active metabolite, meta-chlorophenylpiperazine (mCPP). However, when [fluoxetine](#) was combined with [trazodone](#), levels of mCPP increased from a mean baseline value of 11.3 ng/mL to 38.3 ng/mL (57.5 nanomol/L to 194.7 nanomol/L) in four weeks. This increase was also associated with an improvement in the clinical response to the antidepressants [216].

3.5.1.BV] [Fluphenazine](#)

1) Interaction Effect: hypotension

- 2)) Summary: Concomitant administration of [trazodone](#) with [chlorpromazine](#) or [trifluoperazine](#) resulted in additive hypotensive effects in two case reports. Withdrawal of [trazodone](#) resulted in resolution of the hypotension[268].
- 3)) Severity: moderate
- 4)) Onset: delayed
- 5)) Substantiation: theoretical
- 6)) Clinical Management: Monitor blood pressure, particularly in patients who might be sensitive to this effect. Advise patient to rise slowly from laying or sitting position.
- 7)) Probable Mechanism: additive hypotensive effects

3.5.1.BW] [Fluvoxamine](#)

- 1)) Interaction Effect: increased risk of [serotonin syndrome](#) ([hypertension](#), [hyperthermia](#), myoclonus, mental status changes)
- 2)) Summary: Both [fluvoxamine](#) and [trazodone](#) 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](#)[246][95]. Close monitoring for signs and symptoms of [serotonin syndrome](#) is warranted if [fluvoxamine](#) and [trazodone](#) are used concurrently, particularly during treatment initiation and dose increases [95]. 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 [96].
- 3)) Severity: major
- 4)) Onset: unspecified
- 5)) Substantiation: theoretical
- 6)) Clinical Management: Use caution with concomitant administration of [fluvoxamine](#), a selective serotonin reuptake inhibitor, and [trazodone](#), as this may result in additive serotonergic effects and may increase the risk of [serotonin syndrome](#)[246][95]. If coadministration is required, close monitoring is warranted, particularly during treatment initiation and dose increases [95].
- 7)) Probable Mechanism: additive serotonergic effect

3.5.1.BX] [Fosamprenavir](#)

- 1)) Interaction Effect: an increase in [trazodone](#) plasma levels
- 2)) Summary: Concomitant use of [amprenavir](#), the active metabolite of [fosamprenavir](#), and [trazodone](#) may result in increased [trazodone](#) plasma concentrations due to [amprenavir](#) inhibition of CYP3A4-mediated [trazodone](#) metabolism. Exercise caution when using these medications together and consider a reduction of [trazodone](#) dosing. Monitor for [trazodone](#) side effects such as nausea, dizziness, hypotension, and syncope[141][143].
- 3)) Severity: moderate
- 4)) Onset: unspecified
- 5)) Substantiation: theoretical
- 6)) Clinical Management: Concomitant use of [fosamprenavir](#) (with or without [ritonavir](#)) and [trazodone](#) may cause increased [trazodone](#) plasma concentrations, and should be used with caution. Consider a lower dose of [trazodone](#) if it is used with a CYP3A4 inhibitor such as [fosamprenavir](#). Monitor patients receiving [fosamprenavir](#) and [trazodone](#) for adverse effects, including sedation, nausea, dizziness, hypotension, and syncope[141].

- 7J) Probable Mechanism: inhibition of CYP3A4-mediated [trazodone](#) metabolism by [amprenavir](#), the active metabolite of [fosamprenavir](#)
- 8J) Literature Reports

aJ) Coadministration of [trazodone](#) with [ritonavir](#), a potent CYP3A4 inhibitor pharmacologically similar to [fosamprenavir](#), resulted in significant [trazodone](#) pharmacokinetic changes. In 10 healthy subjects, the concurrent administration of a total of 4 doses [ritonavir](#) 200 mg twice daily with a single 50-mg dose of [trazodone](#) increased the peak plasma [trazodone](#) concentration (C_{max}) 34%, increased the AUC 2.4-fold, increased the half-life 2.2-fold, and decreased [trazodone](#) clearance 52%. During concomitant use of [trazodone](#) and [ritonavir](#), adverse effects reported included nausea, hypotension, and syncope [142].

3.5.1.BY] [Fosphenytoin](#)

- 1J) Interaction Effect: increased [phenytoin](#) serum concentrations and an increased risk of [phenytoin](#) toxicity (ataxia, hyperreflexia, [nystagmus](#), tremor)
- 2J) Summary: Increased [phenytoin](#) serum concentrations have occurred in patients receiving concomitant treatment with [trazodone](#) and [phenytoin](#)[125]. [Phenytoin](#) toxicity has occurred in a patient receiving concurrent treatment with the 2 drugs [124].
- 3J) Severity: moderate
- 4J) Onset: unspecified
- 5J) Substantiation: probable
- 6J) Clinical Management: Measure serum levels of [phenytoin](#) after initiation, changes in dose, or discontinuation of [trazodone](#); adjust dosage accordingly.
- 7J) Probable Mechanism: unknown
- 8J) Literature Reports

aJ) In 1 case concomitant administration of [phenytoin](#) and [trazodone](#) was reported to result in increases in [phenytoin](#) serum concentrations and [phenytoin](#) toxicity. It is speculated that [trazodone](#) may competitively inhibit the metabolism of [phenytoin](#), binding of [phenytoin](#) to plasma proteins, or renal [phenytoin](#) excretion. It may be prudent to monitor [phenytoin](#) serum concentrations in patients receiving the combination until further data is available [124].

3.5.1.BZ] [Foxglove](#)

- 1J) Interaction Effect: increased risk of [digitalis toxicity](#)
- 2J) Summary: A single case report documents [digoxin toxicity](#) resulting from [trazodone](#) administration[185]. Theoretically, foxglove may be similarly affected by [trazodone](#) due to its similarity to [digoxin](#).
- 3J) Severity: moderate
- 4J) Onset: delayed
- 5J) Substantiation: probable
- 6J) Clinical Management: Avoid concomitant use of foxglove and [trazodone](#). It is possible that even intermittent [trazodone](#) doses will affect foxglove clearance (i.e., delayed excretion predisposing the patient to [digitalis toxicity](#)). Patients who choose to combine foxglove with [trazodone](#) should be advised to monitor closely for signs and symptoms of toxicity (e.g., nausea, vomiting, drowsiness, changes in vision, dizziness, muscle weakness, hallucinations).
- 7J) Probable Mechanism: not specified
- 8J) Literature Reports

a) Trazodone added to a previously stable dose of digoxin resulted in a toxic digoxin level within 14 days. A 68-year-old woman with a 30-year history of unipolar affective illness was admitted for inpatient psychiatric service. Medical history was significant for congestive heart failure, hypertension, atrial tachyarrhythmias, and impaired renal function presumed secondary to hypertensive nephropathy. She was stabilized on digoxin (125 mcg/day) and quinidine with achievement of therapeutic blood levels for each drug. Digoxin level on admission was 0.8 ng/mL (therapeutic range 1.2 to 1.7 ng/mL) and quinidine level was 4.0 mcg/mL (therapeutic range 1.5 to 5.0 mcg/mL). Trazodone 50 mg at bedtime was begun and increased in 50 mg increments every other day until 300 mg/day was reached on Day 11. On Day 14 she complained of nausea and vomiting. A digoxin level was toxic at 2.8 ng/mL. The quinidine level remained within therapeutic limits at 1.6 mcg/mL. With digoxin discontinuation, the nausea and vomiting resolved within 3 days. She continued trazodone 300 mg daily. Digoxin was resumed at 125 mcg every other day resulting in therapeutic levels [184].

3.5.1.CA] Frovatriptan

- 1) Interaction Effect: increased risk of serotonin syndrome (hypertension, hyperthermia, myoclonus, mental status changes)
- 2) Summary: Both frovatriptan and trazodone 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[95][243]. Careful monitoring for signs and symptoms of serotonin syndrome is warranted, if frovatriptan and trazodone are used concurrently, particularly during treatment initiation and dose increases [95]. 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 [96].
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Use caution with concomitant administration of frovatriptan and trazodone, as this may result in additive serotonergic effects and may increase the risk of serotonin syndrome[95][243]. If coadministration is required, careful monitoring is warranted, particularly during treatment initiation and dose increases [95].
- 7) Probable Mechanism: additive serotonergic effect

3.5.1.CB] Furazolidone

- 1) Interaction Effect: an increased risk of serotonin syndrome (hypertension, hyperthermia, myoclonus, mental status changes)
- 2) Summary: Trazodone exerts inhibitory effects on serotonin reuptake. Serotonin syndrome has been reported with the use of trazodone and the risk is increased with concurrent administration or overlapping therapy with an MAOI intended to treat psychiatric disorders. Serotonin syndrome is a hyperserotonergic state characterized by symptoms such as agitation and restlessness, myoclonus, changes in mental status, hyperreflexia, diaphoresis, shivering, and tremor. Serious, even fatal, reactions have been reported with concomitant use of serotonergic drugs and MAOIs. A minimum of 14 days should elapse after discontinuing an MAOI intended to treat psychiatric disorders before initiating therapy with trazodone, and a minimum of 14 days should elapse after discontinuing trazodone before initiating therapy with an MAOI intended to treat psychiatric disorders[23].

- 3)) Severity: contraindicated
- 4)) Onset: unspecified
- 5)) Substantiation: theoretical
- 6)) Clinical Management: Concurrent use of [trazodone](#) and an MAOI intended to treat psychiatric disorders is contraindicated. Wait at least 14 days after discontinuing an MAOI before initiating [trazodone](#). Wait at least 14 days after discontinuing [trazodone](#) before initiating therapy with an MAOI intended to treat psychiatric disorders[23].
- 7)) Probable Mechanism: additive serotonergic effect

3.5.1.CC] [Gatifloxacin](#)

- 1)) Interaction Effect: an increased risk of QT interval prolongation
- 2)) Summary: [Gatifloxacin](#) prolongs the QT interval in a dose-related manner[192] and QT/QTc interval prolongation and postmarketing cases of [torsade de pointes](#) have been reported with [trazodone](#) [95]. The concomitant use of [gatifloxacin](#) with [trazodone](#) may result in additive effects on QT interval prolongation and an increased risk of serious [ventricular arrhythmias](#), including [torsade de pointes](#) [95]. If coadministration is required, do not exceed the recommended dose or infusion rate of [gatifloxacin](#) [192].
- 3)) Severity: major
- 4)) Onset: unspecified
- 5)) Substantiation: theoretical
- 6)) Clinical Management: The concomitant use of [trazodone](#) with other QT-prolonging drugs, such as [gatifloxacin](#)[192], may result in additive effects on QT interval prolongation and risk of [torsade de pointes](#) [95]. If coadministration is required, do not exceed the recommended dose or infusion rate of [gatifloxacin](#) [192].
- 7)) Probable Mechanism: additive effects on QT interval prolongation

3.5.1.CD] [Gemifloxacin](#)

- 1)) Interaction Effect: an increased risk of QT interval prolongation
- 2)) Summary: Like other fluoroquinolones, gemifloxacin may prolong the QT interval[193]. QT/QTc interval prolongation and postmarketing cases of [torsade de pointes](#) have been reported with [trazodone](#). The concomitant use of [trazodone](#) with other drugs that prolong the QT interval may result in additive effects on QT interval prolongation and an increased risk of serious [ventricular arrhythmias](#), including [torsade de pointes](#) and therefore should be avoided [95]. If coadministration is required, monitoring for QT interval prolongation may be warranted.
- 3)) Severity: major
- 4)) Onset: unspecified
- 5)) Substantiation: theoretical
- 6)) Clinical Management: The concomitant use of [trazodone](#) with other drugs that may prolong the QT interval, such as gemifloxacin[193], may result in additive effects on QT interval prolongation and risk of [torsade de pointes](#) and therefore should be avoided [95]. If coadministration is required, monitoring for QT interval prolongation may be warranted.
- 7)) Probable Mechanism: additive effects on QT interval prolongation

3.5.1.CE] [Ginkgo](#)

- 1)) Interaction Effect: excessive sedation and potential coma
- 2)) Summary: A single case report has described a semicomatose state following use of ginkgo with [trazodone](#). Since no rechallenge of either agent alone or together was performed, it is inconclusive if the reaction was due to the combination or an unusual reaction to either agent alone. Ginkgo may have partial agonist activity at [GABA](#) receptors[301][302], as well as the ability to induce cytochrome P450 3A4

(CYP3A4) activity, producing more of the active metabolite of [trazodone](#), mCPP, which further enhances the release of [GABA](#) [303]. In contrast, ginkgo inhibited CYP3A4 in vitro [304]. However, in vitro findings may not translate into the same in vivo findings, therefore the clinical significance of this in vitro finding is unknown.

3) Severity: major

4) Onset: rapid

5) Substantiation: probable

6) Clinical Management: A single case report has described a semicomatose state following use of ginkgo with [trazodone](#). Since no rechallenge of either agent alone or together was performed, it is inconclusive if the reaction was due to the combination or an unusual adverse reaction to either agent alone. Until more is known about this potential interaction, avoid concomitant use of ginkgo and [trazodone](#). If the use of both cannot be avoided, use a low dose of [trazodone](#) and monitor the patient carefully for signs of excessive sedation.

7) Probable Mechanism: induction of cytochrome P450 3A4 by ginkgo to produce more of the active metabolite mCPP of [trazodone](#)

8) Literature Reports

a) An 80-year-old female diagnosed with probable [Alzheimer's disease](#) was prescribed ginkgo biloba 80 mg twice daily and [trazodone](#) 20 mg twice daily following treatment failure after 3 months with bromazepam 3.5 mg daily, [donepezil](#) 5 mg at bedtime, and [vitamin E](#) 600 mg twice daily. Bromazepam, [donepezil](#), and [vitamin E](#) were discontinued. On the third day of treatment with ginkgo and [trazodone](#), the patient developed gait instability and drowsiness, fell asleep one hour later, and was unable to be awakened. Blood pressure was 120/55, Glasgow coma scale was 6/15. [Flumazenil](#) 1 mg was given and the patient woke immediately. [Trazodone](#) and ginkgo were discontinued, replaced by bromazepam. At evaluation 2 months later, cognitive function and behavior were unchanged. The mechanism of the interaction between ginkgo and [trazodone](#) was hypothesized to be due to a combination of weak [GABA](#) agonist activity of ginkgo, and induction of CYP 3A4 by ginkgo, leading to increased production of the active metabolite of [trazodone](#), mCPP which further increased [GABA](#) release [299].

b) Ginkgo biloba inhibited CYP3A4 in vitro with an IC₅₀ of 4.75 mmol. [Ketoconazole](#), a known CYP3A4 inhibitor, was compared with ginkgo and other phytochemicals, had an IC₅₀ of 7.18 x 10⁻⁴ mmol, making it 23.3 times more inhibitory than the most inhibitory plant phytochemical (goldenseal) with an IC₅₀ of 0.03 mmol. Ginkgo was a much weaker inhibitor of CYP3A4; however, clinically significant drug interactions may occur with the inhibitory phytochemicals tested and drugs metabolized by CYP3A4 [300].

3.5.1.CF] [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[289][290][291]. 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[289][290][291].

7) Probable Mechanism: additive effects on the QT interval

3.5.1.CG| 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[289][290][291]. 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[289][290][291].

7) Probable Mechanism: additive effects on the QT interval

3.5.1.CH| Granisetron

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

2) Summary: Concomitant use of [granisetron](#) with a drug that is a serotonergic and QT-interval prolonging drug may increase the risk of [serotonin syndrome](#)[167] and the risk of QT-interval prolongation [168]. [Serotonin syndrome](#) has been reported with the cocurrent use of 5-hydroxytryptamine-3 antagonists and serotonergic drugs, primarily in infusion centers or in post-anesthesia care units. Inform patients of this increased risk. Monitor for the emergence of [serotonin syndrome](#) and discontinue treatment with [granisetron](#) and institute supportive therapy if symptoms of [serotonin syndrome](#) occur [167]. Coadministration with other drugs that prolong the QT-interval may result in additive effects on the QT-interval, therefore use with caution [168].

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Concomitant use of [granisetron](#) with a drug that is a serotonergic and QT-interval prolonging drug may increase the risk of [serotonin syndrome](#)[167] and the risk of QT-interval prolongation [168]. Inform patients of the increased risk of [serotonin syndrome](#). Monitor for the emergence of [serotonin syndrome](#) and discontinue treatment with [granisetron](#) and institute supportive therapy if symptoms of [serotonin syndrome](#) occur [167]. Coadministration with other drugs that prolong the QT-interval may result in additive effects on the QT-interval, therefore use with caution [168].

7) Probable Mechanism: unknown; additive QT-interval prolongation

3.5.1.CI| Halofantrine

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

2) Summary: QT/QTc interval prolongation and postmarketing cases of [torsade de pointes](#) have been reported with [trazodone](#)[95] and QT interval prolongation and serious ventricular [dysrhythmias](#), sometimes associated with death, have occurred with recommended therapeutic doses of [halofantrine](#). The coadministration of [halofantrine](#) and other drugs known to prolong the QT interval, such as [trazodone](#),

is not recommended due to the potential for additive QT interval prolongation and/or [torsade de pointes](#) [194]. If coadministration is required, monitoring for QT interval prolongation may be warranted.

3J) Severity: major

4J) Onset: unspecified

5J) Substantiation: theoretical

6J) Clinical Management: Due to the potential for additive effects on the QT interval and increased risk of [torsade de pointes](#), the concurrent administration of [halofantrine](#) and other drugs that prolong the QT interval, such as [trazodone](#)[95], is not recommended [194]. If concomitant therapy is required, closely monitor for QT interval prolongation.

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

3.5.1.CJ| [Haloperidol](#)

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

2J) Summary: QT-interval prolongation, [torsade de pointes](#) (TdP), and sudden death have been reported with [haloperidol](#). A higher risk of QT prolongation and TdP is associated with higher-than-recommended doses of any formulation and IV administration of [haloperidol](#)[182]. QT/QTc interval prolongation and postmarketing cases of TdP have also been reported with [trazodone](#). The concomitant use of [haloperidol](#) with [trazodone](#) may result in additive effects on QT-interval prolongation and an increased risk of serious [ventricular arrhythmias](#), including TdP [95]. If coadministration is required, monitoring for QT interval prolongation may be warranted.

3J) Severity: major

4J) Onset: unspecified

5J) Substantiation: theoretical

6J) Clinical Management: The concomitant use of [trazodone](#) with other drugs that prolong the QT interval, such as [haloperidol](#)[182], may result in additive effects on QT interval prolongation and risk of [torsade de pointes](#) [95]. If coadministration is required, monitoring for QT interval prolongation may be warranted.

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

3.5.1.CK| [Histrelin](#)

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[289][290][291]. 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[289][290][291].

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

3.5.1.CL| [Hydroxychloroquine](#)

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

2J) Summary: [Hydroxychloroquine](#) has been associated with QT interval prolongation[231][232], [ventricular premature contractions](#), and [torsade de pointes](#) [232]. 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[231] [232]. 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 [231].

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 [232].

3.5.1.CM] Hydroxytryptophan

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

2) Summary: Both hydroxytryptophan and [trazodone](#) affect the serotonergic neurotransmitter systems. Concomitant use is not recommended due to the additive effects and the potential for increased risk of [serotonin syndrome](#)[95]. Monitoring for signs and symptoms of [serotonin syndrome](#) is warranted if hydroxytryptophan and [trazodone](#) are used 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. If [serotonin syndrome](#) develops, discontinue the offending agents and provide supportive care and other therapy as necessary [96].

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: The concomitant administration of hydroxytryptophan and [trazodone](#) is not recommended, as this may result in additive serotonergic effects and may increase the risk of [serotonin syndrome](#)[95]. If coadministration is required, careful monitoring is warranted.

7) Probable Mechanism: additive serotonergic effect

3.5.1.CN] [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[287]. 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[287]. 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.CO] [Ibutilide](#)

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

2) Summary: QT/QTc interval prolongation and postmarketing cases of [torsade de pointes](#) have been reported with [trazodone](#). The concomitant use of [trazodone](#) with other drugs that prolong the QT interval, such as [ibutilide](#)[181], may result in additive effects on QT interval prolongation and an increased risk of serious [ventricular arrhythmias](#), including [torsade de pointes](#) [95]. If coadministration is required, monitoring for QT interval prolongation may be warranted.

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: The concomitant use of [trazodone](#) with other QT-prolonging drugs, such as [ibutilide](#)[181], may result in additive effects on QT interval prolongation and risk of [torsade de pointes](#) [95]. If coadministration is required, monitoring for QT interval prolongation may be warranted.

7) Probable Mechanism: additive effects on QT interval prolongation

3.5.1.CP] [Idelalisib](#)

1) Interaction Effect: increased exposure of CYP3A substrate

2) Summary: Avoid coadministration of idelalisib (a strong CYP3A inhibitor) and a CYP3A substrate as this may increase exposure of the CYP3A substrate and increase the risk of adverse effects. During a drug interaction study, coadministration of idelalisib and [midazolam](#) (CYP3A substrate) resulted in a 5.4-fold increase in [midazolam](#) AUC and a 2.4 fold increase in [midazolam](#) Cmax[191].

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Coadministration of idelalisib (a strong CYP3A inhibitor) and a CYP3A substrate should be avoided, as this may increase exposure of the CYP3A substrate and increase the risk of adverse effects[191].

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

8) Literature Reports

a) During a drug interaction study, administration of idelalisib 150 mg for 15 doses followed by a single dose of [midazolam](#) 5 mg (a CYP3A substrate) in healthy volunteers, resulted in a 5.4-fold increase in [midazolam](#) AUC and a 2.4 fold increase in [midazolam](#) Cmax [191].

3.5.1.CQ| Iloperidone

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

2) Summary: Both [iloperidone](#) and [trazodone](#) may prolong QT interval[95][187]. Due to the potential for additive effects on QT interval prolongation and an increased risk of [cardiotoxicity](#) (QT prolongation, [torsades de pointes](#), [cardiac arrest](#)), avoid using [iloperidone](#) with other QT interval-prolonging drugs [187]. If concurrent therapy is required, monitor carefully for QT interval prolongation.

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Avoid the concomitant use of [iloperidone](#) with other drugs that prolong the QT interval, such as [trazodone](#)[95], as coadministration may result in additive effects on QT interval prolongation and an increased risk of [cardiotoxicity](#) (QT prolongation, [torsades de pointes](#), [cardiac arrest](#)) [187]. If concurrent therapy is required, monitor carefully for QT interval prolongation.

7) Probable Mechanism: additive effects on QT interval prolongation

3.5.1.CR| Imipramine

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

2) Summary: QT/QTc interval prolongation and postmarketing cases of [torsade de pointes](#) have been reported with [trazodone](#). The concomitant use of [trazodone](#) with other drugs that prolong the QT interval may result in additive effects on QT interval prolongation and an increased risk of serious [ventricular arrhythmias](#), including [torsade de pointes](#). Both [imipramine](#) and [trazodone](#) 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](#)[95]. 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 [96]. If coadministration of [imipramine](#) and [trazodone](#) is required, monitoring for QT interval prolongation and signs and symptoms of [serotonin syndrome](#) may be warranted.

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: The concomitant use of [trazodone](#) with other drugs that may prolong the QT interval, such as [imipramine](#), may result in additive effects on QT interval prolongation and risk of [torsade de pointes](#). Coadministration may also result in additive serotonergic effects and may increase the risk of [serotonin syndrome](#)[95]. If coadministration is required, appropriate monitoring may be warranted.

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

3.5.1.CS| Indinavir

- 1) Interaction Effect: an increase in [trazodone](#) plasma levels
- 2) Summary: Coadministration of [trazodone](#) with [ritonavir](#) (an indinavir-related [protease](#) inhibitor capable of potent CYP3A4 inhibition) produced increases in peak plasma [trazodone](#) concentration, prolongation of elimination half-life, increased area under the concentration-time curve, and decreased [trazodone](#) clearance. During concomitant use of [trazodone](#) and [ritonavir](#), adverse effects reported included nausea, hypotension, and syncope. Other signs and symptoms associated with excess [trazodone](#) exposure have included [priapism](#), respiratory arrest, seizures, and EKG changes[125].
- 3) Severity: moderate
- 4) Onset: unspecified
- 5) Substantiation: probable
- 6) Clinical Management: Consider a lower dose of [trazodone](#) if it is used with a CYP3A4 inhibitor such as [indinavir](#). Monitor patients receiving [trazodone](#) and [indinavir](#) for adverse effects, including sedation, nausea, hypotension, syncope, and/or [priapism](#).
- 7) Probable Mechanism: inhibition of CYP3A-mediated [trazodone](#) metabolism by [indinavir](#)

3.5.1.CT] Iproniazid

- 1) Interaction Effect: an increased risk of [serotonin syndrome](#) ([hypertension](#), [hyperthermia](#), myoclonus, mental status changes)
- 2) Summary: [Trazodone](#) exerts inhibitory effects on serotonin reuptake. [Serotonin syndrome](#) has been reported with the use of [trazodone](#) and the risk is increased with concurrent administration or overlapping therapy with an MAOI intended to treat psychiatric disorders. [Serotonin syndrome](#) is a hyperserotonergic state characterized by symptoms such as agitation and restlessness, myoclonus, changes in mental status, hyperreflexia, diaphoresis, shivering, and tremor. Serious, even fatal, reactions have been reported with concomitant use of serotonergic drugs and MAOIs. A minimum of 14 days should elapse after discontinuing an MAOI intended to treat psychiatric disorders before initiating therapy with [trazodone](#), and a minimum of 14 days should elapse after discontinuing [trazodone](#) before initiating therapy with an MAOI intended to treat psychiatric disorders[23].
- 3) Severity: contraindicated
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Concurrent use of [trazodone](#) and an MAOI intended to treat psychiatric disorders is contraindicated. Wait at least 14 days after discontinuing an MAOI before initiating [trazodone](#). Wait at least 14 days after discontinuing [trazodone](#) before initiating therapy with an MAOI intended to treat psychiatric disorders[23].
- 7) Probable Mechanism: additive serotonergic effect

3.5.1.CU] Isocarboxazid

- 1) Interaction Effect: an increased risk of [serotonin syndrome](#) ([hypertension](#), [hyperthermia](#), myoclonus, mental status changes)
- 2) Summary: [Trazodone](#) exerts inhibitory effects on serotonin reuptake. [Serotonin syndrome](#) has been reported with the use of [trazodone](#) and the risk is increased with concurrent administration or overlapping therapy with an MAOI intended to treat psychiatric disorders. [Serotonin syndrome](#) is a hyperserotonergic state characterized by symptoms such as agitation and restlessness, myoclonus, changes in mental status, hyperreflexia, diaphoresis, shivering, and tremor. Serious, even fatal, reactions have been reported with concomitant use of serotonergic drugs and MAOIs. A minimum of 14 days should elapse after discontinuing an MAOI intended to treat psychiatric disorders before initiating therapy with [trazodone](#), and a minimum of 14 days should elapse after discontinuing [trazodone](#) before initiating therapy with an MAOI intended to treat psychiatric disorders[23].

- 3J) Severity: contraindicated
- 4J) Onset: unspecified
- 5J) Substantiation: theoretical
- 6J) Clinical Management: Concurrent use of [trazodone](#) and an MAOI intended to treat psychiatric disorders is contraindicated. Wait at least 14 days after discontinuing an MAOI before initiating [trazodone](#). Wait at least 14 days after discontinuing [trazodone](#) before initiating therapy with an MAOI intended to treat psychiatric disorders[23].
- 7J) Probable Mechanism: additive serotonergic effect

3.5.1.CV] Ivabradine

- 1J) Interaction Effect: increased risk of QT prolongation
- 2J) Summary: Use caution with the concomitant administration of ivabradine and other drugs that prolong the QT interval due to the potential for additive QT prolongation[235].
- 3J) Severity: major
- 4J) Onset: unspecified
- 5J) Substantiation: theoretical
- 6J) Clinical Management: Use caution with the concomitant administration of ivabradine and other drugs that prolong the QT interval due to the potential for additive QT prolongation[235].
- 7J) Probable Mechanism: additive QT-interval prolongation

3.5.1.CW] Ketoconazole

- 1J) Interaction Effect: an increase in [trazodone](#) plasma levels; increased risk for QT interval prolongation
- 2J) Summary: Using [ketoconazole](#) together with a CYP3A4 substrate known to prolong the QT interval, such as [trazodone](#), may be contraindicated[226] and should be avoided [23]. Concomitant use may result in elevated plasma concentrations of [trazodone](#), increasing the risk for QT prolongation and life-threatening ventricular [tachyarrhythmias](#), including [torsades de pointes](#) [226] Patients receiving [trazodone](#) concurrently with [ketoconazole](#) are at risk for increased exposure to [trazodone](#) due to ketoconazole-mediated inhibition of CYP3A4 metabolism. Coadministration of [trazodone](#) with [ritonavir](#) (another potent CYP3A4 inhibitor) produced increases in peak plasma [trazodone](#) concentration, prolongation of elimination half-life, increases in AUC and decreased [trazodone](#) clearance. During concomitant use of [trazodone](#) and [ritonavir](#), adverse effects reported included nausea, hypotension, and syncope. Other signs and symptoms associated with excess [trazodone](#) exposure have included QT interval prolongation, [priapism](#), respiratory arrest, seizures, and EKG changes [23].
- 3J) Severity: contraindicated
- 4J) Onset: unspecified
- 5J) Substantiation: probable
- 6J) Clinical Management: Using [ketoconazole](#) together with a CYP3A4 substrate known to prolong the QT interval, such as [trazodone](#), may be contraindicated[226] and should be avoided [23]. Concomitant use may result in elevated plasma concentrations of [trazodone](#), increasing the risk for QT prolongation and life-threatening ventricular [tachyarrhythmias](#), including [torsades de pointes](#) [226].
- 7J) Probable Mechanism: inhibition of CYP3A-mediated [trazodone](#) metabolism by [ketoconazole](#); increased/additive effects on the QT interval

3.5.1.CX] Lapatinib

- 1J) Interaction Effect: an increased risk of QT interval prolongation
- 2J) Summary: QT/QTc interval prolongation and postmarketing cases of [torsade de pointes](#) have been reported with [trazodone](#). The concomitant use of [trazodone](#) with other drugs that prolong the QT interval, such as lapatinib[178], may result in additive effects on QT interval prolongation and an increased risk

of serious [ventricular arrhythmias](#), including [torsade de pointes](#) and therefore should be avoided [95]. If coadministration is required, monitoring for QT interval prolongation may be warranted.

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: The concomitant use of [trazodone](#) with other QT-prolonging drugs, such as lapatinib[178], may result in additive effects on QT interval prolongation and risk of [torsade de pointes](#) and therefore should be avoided [95]. If coadministration is required, monitoring for QT interval prolongation may be warranted.

7) Probable Mechanism: additive effects on QT interval prolongation

3.5.1.CY] [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[289][290][291]. 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[289][290][291].

7) Probable Mechanism: additive effects on the QT interval

3.5.1.CZ] [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[308].

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[308].

7) Probable Mechanism: additive effects on QT interval

3.5.1.DA] [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[309].

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[309].

7) Probable Mechanism: additive serotonergic effects

3.5.1.DB| [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 [trazodone](#) is contraindicated due to the potential for [serotonin syndrome](#). If urgent treatment with [linezolid](#) is necessary in a patient receiving [trazodone](#) and alternatives are not available, promptly discontinue [trazodone](#) and administer [linezolid](#) after a risk/benefit evaluation. Monitor for [serotonin syndrome](#) for 14 days or for 24 hours after the last dose of [linezolid](#), whichever comes first. [Trazodone](#) therapy may resume 24 hours after the last dose of [linezolid](#)[23].

3) Severity: contraindicated

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Concurrent use of [linezolid](#), an MAOI, and [trazodone](#) is contraindicated due to the potential for [serotonin syndrome](#). If urgent treatment with [linezolid](#) is necessary in a patient receiving [trazodone](#) and alternatives are not available, promptly discontinue [trazodone](#) and administer [linezolid](#) after a risk/benefit evaluation. Monitor for [serotonin syndrome](#) for 14 days or for 24 hours after the last dose of [linezolid](#), whichever comes first. [Trazodone](#) therapy may resume 24 hours after the last dose of [linezolid](#)[23].

7) Probable Mechanism: additive serotonergic effects

3.5.1.DC| [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[156].

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[156].

7J) Probable Mechanism: additive serotonergic effect

3.5.1.DD] Lithium

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

2J) Summary: Both [lithium](#) and [trazodone](#) 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](#)[95]. Monitoring for signs and symptoms of [serotonin syndrome](#) may be warranted if [lithium](#) and [trazodone](#) are used 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. If [serotonin syndrome](#) develops, discontinue the offending agents and provide supportive care and other therapy as necessary [96].

3J) Severity: major

4J) Onset: unspecified

5J) Substantiation: theoretical

6J) Clinical Management: Use caution with concomitant administration of [lithium](#) and [trazodone](#), as this may result in additive serotonergic effects and may increase the risk of [serotonin syndrome](#)[95]. If coadministration is required, appropriate monitoring may be warranted.

7J) Probable Mechanism: additive serotonergic effect

3.5.1.DE] Lopinavir

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

2J) Summary: Postmarketing cases of QT interval prolongation and [torsade de pointes](#) have been reported with both [lopinavir/ritonavir](#)[99] and [trazodone](#) [95]. Due to the potential for additive effects on the QT interval and increased risk of [torsade de pointes](#), avoid the concomitant use of [lopinavir/ritonavir](#) with [trazodone](#) [99]. If concurrent therapy is required, monitor carefully for QT interval prolongation.

3J) Severity: major

4J) Onset: unspecified

5J) Substantiation: theoretical

6J) Clinical Management: Avoid the concomitant use of [lopinavir/ritonavir](#) with other drugs that prolong the QT interval, such as [trazodone](#)[95], as coadministration may result in additive effects on QT-interval prolongation and an increased risk of [torsade de pointes](#) [99]. If concurrent therapy is required, monitor carefully for QT interval prolongation.

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

3.5.1.DF] Lorcaserin

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

2J) Summary: Lorcaserin is a serotonergic drug and concomitant use with another agent that affects the serotonergic neurotransmitter system, such as an SSRI, serotonin-norepinephrine reuptake inhibitor, or tricyclic antidepressant, may result in an increased risk of [serotonin syndrome](#) and should be approached with extreme caution. [Serotonin syndrome](#) may be life threatening and symptoms may include mental status changes (eg, agitation, hallucinations, coma), autonomic instability (eg, [tachycardia](#), labile blood pressure, [hyperthermia](#)), neuromuscular aberrations (eg, hyperreflexia, incoordination), and/or gastrointestinal symptoms (eg, nausea, vomiting, diarrhea). If coadministration is required, monitor closely for signs and symptoms of [serotonin syndrome](#), especially during initiation of the coadministered

drug and during dosage increases of either drug. If [serotonin syndrome](#) develops, discontinue both agents and initiate supportive symptomatic therapy[128].

3J) Severity: major

4J) Onset: unspecified

5J) Substantiation: theoretical

6J) Clinical Management: Use extreme caution with concomitant administration of lorcaserin and another serotonergic drug, such as an SSRI, serotonin-norepinephrine reuptake inhibitor, or tricyclic antidepressant, as this may result in additive serotonergic effects and may increase the risk of [serotonin syndrome](#). If coadministration is required, careful monitoring is recommended, especially during treatment initiation and dose increases. Drug discontinuation and supportive symptomatic treatment is recommended if [serotonin syndrome](#) develops[128].

7J) Probable Mechanism: additive serotonergic effects

3.5.1.DGJ Lumefantrine

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

2J) Summary: QT/QTc interval prolongation and postmarketing cases of [torsade de pointes](#) have been reported with [trazodone](#)[95]. Due to the potential for additive effects on QT interval prolongation, concomitant use of artemether/lumefantrine with other drugs that prolong the QT interval should be avoided. Additionally, caution is advised when administering drugs that prolong the QT interval after completing artemether/lumefantrine therapy due to the long half-life of lumefantrine (3 to 6 days) [101]. If coadministration is required, monitoring for QT interval prolongation may be warranted.

3J) Severity: major

4J) Onset: unspecified

5J) Substantiation: theoretical

6J) Clinical Management: Avoid the coadministration of artemether/lumefantrine with other drugs that prolong the QT interval, such as [trazodone](#)[95], due to the potential for additive effects on QT interval prolongation. Additionally, caution is advised when administering drugs that prolong the QT interval after completing artemether/lumefantrine therapy due to the long half-life of lumefantrine (3 to 6 days) [101]. If coadministration is required, monitoring for QT interval prolongation may be warranted.

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

3.5.1.DHJ Mefloquine

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

2J) Summary: QT/QTc interval prolongation and postmarketing cases of [torsade de pointes](#) have been reported with [trazodone](#). The concomitant use of [trazodone](#) with other drugs that prolong the QT interval, such as [mefloquine](#)[102], may result in additive effects on QT interval prolongation and an increased risk of serious [ventricular arrhythmias](#), including [torsade de pointes](#) [95]. If coadministration is required, monitoring for QT interval prolongation may be warranted.

3J) Severity: major

4J) Onset: unspecified

5J) Substantiation: theoretical

6J) Clinical Management: The concomitant use of [trazodone](#) with other QT-prolonging drugs, such as [mefloquine](#)[102], may result in additive effects on QT interval prolongation and risk of [torsade de pointes](#) [95]. If coadministration is required, monitoring for QT interval prolongation may be warranted.

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

3.5.1.DIJ Meperidine

- 1) Interaction Effect: increased risk of [serotonin syndrome](#) ([hypertension](#), [hyperthermia](#), myoclonus, mental status changes)
- 2) Summary: Both [meperidine](#) and [trazodone](#) 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](#)[95]. Monitoring for signs and symptoms of [serotonin syndrome](#) may be warranted if [meperidine](#) and [trazodone](#) are used 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. If [serotonin syndrome](#) develops, discontinue the offending agents and provide supportive care and other therapy as necessary [96].
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Use caution with concomitant administration of [meperidine](#) and [trazodone](#), as this may result in additive serotonergic effects and may increase the risk of [serotonin syndrome](#)[95]. If coadministration is required, appropriate monitoring may be warranted.
- 7) Probable Mechanism: additive serotonergic effect

3.5.1.DJ] [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](#)[259].
- 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](#)[259].
- 7) Probable Mechanism: additive QT-interval prolongation

3.5.1.DK] [Methadone](#)

- 1) Interaction Effect: an increased risk of QT interval prolongation and [serotonin syndrome](#) ([hypertension](#), [hyperthermia](#), myoclonus, mental status changes)
- 2) Summary: Use extreme caution with the concomitant use of [methadone](#) with other drugs that prolong the QT interval, such as [trazodone](#)[95] as coadministration may result in additive effects on QT interval prolongation and an increased risk of serious [ventricular arrhythmias](#). If concomitant use of [methadone](#) and [trazodone](#) is required, closely monitor cardiovascular status, including QT prolongation and [dysrhythmia](#), during treatment [106]. Both [methadone](#) and [trazodone](#) 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](#) [95]. 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 [96].
- 3) Severity: major

- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Use extreme caution with the concomitant use of [methadone](#) with other drugs that prolong the QT interval, such as [trazodone](#)[95] as coadministration may result in additive effects on QT interval prolongation and an increased risk of serious [ventricular arrhythmias](#). Coadministration may also result in additive serotonergic effects and may increase the risk of [serotonin syndrome](#) [95]. If concomitant use of [methadone](#) and [trazodone](#) is required, closely monitor for QT interval prolongation and signs and symptoms of [serotonin syndrome](#) [106][95].
- 7) Probable Mechanism: additive effects on QT interval prolongation; additive serotonergic effects

3.5.1.DL] [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[156].
- 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[156].
- 7) Probable Mechanism: additive serotonergic effect

3.5.1.DM] [Methotrimeprazine](#)

- 1) Interaction Effect: hypotension
- 2) Summary: Concomitant administration of [trazodone](#) with [chlorpromazine](#) or [trifluoperazine](#) resulted in additive hypotensive effects in two case reports. Withdrawal of [trazodone](#) resulted in resolution of the hypotension[306].
- 3) Severity: moderate
- 4) Onset: delayed
- 5) Substantiation: theoretical
- 6) Clinical Management: Monitor blood pressure, particularly in patients who might be sensitive to this effect. Advise patient to rise slowly from laying or sitting position.
- 7) Probable Mechanism: additive hypotensive effects

3.5.1.DN] [Methylene Blue](#)

- 1) Interaction Effect: an increased risk of [serotonin syndrome](#) ([hypertension](#), [hyperthermia](#), myoclonus, mental status changes)
- 2) Summary: Concurrent use of methylene blue IV, an MAOI, and [trazodone](#) is contraindicated due to the potential for [serotonin syndrome](#). Reports have involved methylene blue administered intravenously in doses of 1 mg/kg to 8 mg/kg. Reports have not included lower doses or other routes of administration, such as oral or local tissue injection; however, the potential for [serotonin syndrome](#) may exist in these cases. If urgent treatment with methylene blue IV is necessary in a patient receiving [trazodone](#) and alternatives are not available, promptly discontinue [trazodone](#) and administer methylene blue IV after a risk/benefit

evaluation[23]. Use the lowest possible dose of methylene blue [110]. Monitor for [serotonin syndrome](#) for 14 days or 24 hours after the last dose of methylene blue IV, whichever comes first. [Trazodone](#) therapy may resume 24 hours after the last dose of methylene blue IV [23]

3) Severity: contraindicated

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Concurrent use of IV methylene blue (an MAOI) and [trazodone](#) is contraindicated due to the potential for [serotonin syndrome](#). If urgent treatment with methylene blue IV is necessary in a patient receiving [trazodone](#) and alternatives are not available, promptly discontinue [trazodone](#) and administer methylene blue IV after a risk/benefit evaluation[23]. Use the lowest possible dose of methylene blue [110]. Monitor for [serotonin syndrome](#) for 14 days or 24 hours after the last dose of methylene blue IV, whichever comes first. [Trazodone](#) therapy may resume 24 hours after the last dose of methylene blue. While the risk of concurrent [trazodone](#) 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 [23].

7) Probable Mechanism: additive serotonergic effects

3.5.1.DO| [Metoclopramide](#)

1) Interaction Effect: an increased risk of extrapyramidal reactions

2) Summary: Concomitant use of [trazodone](#) with [metoclopramide](#) may increase the risk of extrapyramidal symptoms, such as [tardive dyskinesia](#), and is contraindicated[201]. If concurrent therapy is required, monitor patients for signs and symptoms of extrapyramidal reactions. Discontinue [metoclopramide](#) if patient develops signs and symptoms. Injection of [diphenhydramine](#) 50 mg intramuscularly or [benztropine](#) 1 to 2 mg intramuscularly may reverse the extrapyramidal reactions [202].

3) Severity: contraindicated

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Concomitant use of [trazodone](#) with [metoclopramide](#) is contraindicated[201]. If concurrent therapy is required, monitor patients for signs and symptoms of extrapyramidal reactions. Discontinue [metoclopramide](#) if patient develops signs and symptoms of extrapyramidal reactions. Injection of [diphenhydramine](#) 50 mg intramuscularly or [benztropine](#) 1 to 2 mg intramuscularly may reverse the extrapyramidal reactions [202].

7) Probable Mechanism: unknown

3.5.1.DP| [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[126].

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[126].

7j) Probable Mechanism: additive QT-interval prolongation**8j) 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 [126].

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 [127].

3.5.1.DQ| Mifepristone

1j) Interaction Effect: increased [trazodone](#) plasma concentrations and an increased risk of QT interval prolongation

2j) Summary: [Trazodone](#) is primarily metabolized by CYP3A4[95], and [mifepristone](#) is a CYP3A substrate and inhibitor [220]. Both agents have been associated with QT interval prolongation [220] [95]. Concomitant use of [mifepristone](#) (Korlym(TM)) with [trazodone](#) should be avoided due to a risk of increased [trazodone](#) plasma concentrations and additive QT interval prolongation. Due to the long half-life of [mifepristone](#), wait at least 2 weeks after stopping [mifepristone](#) (Korlym(TM)) before initiating [trazodone](#). However, if concomitant use is necessary, use the lowest effective dose possible for both agents and monitor closely for QT interval prolongation; additionally, wait at least 2 weeks after stopping [mifepristone](#) (Korlym(TM)) before increasing the [trazodone](#) dose [220].

3j) Severity: major

4j) Onset: unspecified

5j) Substantiation: theoretical

6j) Clinical Management: Avoid the concomitant use of [mifepristone](#) (Korlym(TM)) with [trazodone](#) as it may result in increased [trazodone](#) plasma concentrations and risk of additive QT interval prolongation[220][95]. Due to the long half-life of [mifepristone](#), wait at least 2 weeks after stopping [mifepristone](#) (Korlym(TM)) before initiating [trazodone](#). However, if concomitant use is necessary, use the lowest effective dose possible for both agents and monitor closely for QT interval prolongation; additionally, wait at least 2 weeks after stopping [mifepristone](#) (Korlym(TM)) before increasing the [trazodone](#) dose [220].

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

3.5.1.DR| Milnacipran

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

2) Summary: Both milnacipran and [trazodone](#) 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](#)[236][95]. Careful monitoring for signs and symptoms of [serotonin syndrome](#) is warranted, if milnacipran and [trazodone](#) are used concurrently, particularly during treatment initiation and dose increases [95]. 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 [96].

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Use caution with concomitant administration of milnacipran, a selective serotonin reuptake inhibitor, and [trazodone](#), as this may result in additive serotonergic effects and may increase the risk of [serotonin syndrome](#)[236][95]. If coadministration is required, careful monitoring is warranted, particularly during treatment initiation and dose increases [95].

7) Probable Mechanism: additive serotonergic effect

3.5.1.DS] [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[221]. 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 [96].

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](#)[221].

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 [222].

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 [223].

3.5.1.DT] Moclobemide

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

2)) Summary: [Trazodone](#) exerts inhibitory effects on serotonin reuptake. [Serotonin syndrome](#) has been reported with the use of [trazodone](#) and the risk is increased with concurrent administration or overlapping therapy with an MAOI intended to treat psychiatric disorders. [Serotonin syndrome](#) is a hyperserotonergic state characterized by symptoms such as agitation and restlessness, myoclonus, changes in mental status, hyperreflexia, diaphoresis, shivering, and tremor. Serious, even fatal, reactions have been reported with concomitant use of serotonergic drugs and MAOIs. A minimum of 14 days should elapse after discontinuing an MAOI intended to treat psychiatric disorders before initiating therapy with [trazodone](#), and a minimum of 14 days should elapse after discontinuing [trazodone](#) before initiating therapy with an MAOI intended to treat psychiatric disorders[23].

3)) Severity: contraindicated

4)) Onset: unspecified

5)) Substantiation: theoretical

6)) Clinical Management: Concurrent use of [trazodone](#) and an MAOI intended to treat psychiatric disorders is contraindicated. Wait at least 14 days after discontinuing an MAOI before initiating [trazodone](#). Wait at least 14 days after discontinuing [trazodone](#) before initiating therapy with an MAOI intended to treat psychiatric disorders[23].

7)) Probable Mechanism: additive serotonergic effect

3.5.1.DU] 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](#)[229] 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](#)[229] and monitor for changes in the QT-interval.

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

3.5.1.DV] Nafarelin

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[289][290][291]. 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[289][290][291].

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

3.5.1.DW] Naratriptan

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

2J) Summary: [Naratriptan](#) is known to cause [serotonin syndrome](#)[238] and both [naratriptan](#) and [trazodone](#) 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](#) [95]. Careful monitoring for signs and symptoms of [serotonin syndrome](#) is warranted, if [naratriptan](#) and [trazodone](#) are used concurrently, particularly during treatment initiation and dose increases [95]. 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 [96].

3J) Severity: major

4J) Onset: unspecified

5J) Substantiation: theoretical

6J) Clinical Management: Use caution with concomitant administration of [naratriptan](#), a drug known to cause [serotonin syndrome](#)[238], and [trazodone](#), as this may result in additive serotonergic effects and may increase the risk of [serotonin syndrome](#). If coadministration is required, careful monitoring is warranted, particularly during treatment initiation and dose increases [95].

7J) Probable Mechanism: additive serotonergic effect

3.5.1.DX] Nefazodone

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

2J) Summary: Both [nefazodone](#) and [trazodone](#) 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](#)[95]. Monitoring for signs and symptoms of [serotonin syndrome](#) may be warranted if [nefazodone](#) and [trazodone](#) are used concurrently, particularly during treatment initiation and dose increases [95]. 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 [96].

3) Severity: major

4) Onset: unspecified

5) Substantiation: probable

6) Clinical Management: Use caution with concomitant administration of [nefazodone](#), a selective serotonin reuptake inhibitor[118], and [trazodone](#), as this may result in additive serotonergic effects and may increase the risk of [serotonin syndrome](#) [95]. If coadministration is required, appropriate monitoring may be warranted, particularly during treatment initiation and dose increases [95].

7) Probable Mechanism: additive serotonergic effect

3.5.1.DY] [Nelfinavir](#)

1) Interaction Effect: increased exposure of CYP3A4 substrate; increased risk of QT-interval prolongation

2) Summary: [Nelfinavir](#) is a strong CYP3A inhibitor. Coadministration of [nelfinavir](#) and a CYP3A4 substrate that may have serious or life-threatening consequences with increased plasma concentrations is contraindicated[252]. [Nelfinavir](#) and these selected CYP3A4 substrates are each independently associated with QT-interval prolongation. Coadministration may result in additive risk for QT-interval prolongation and serious cardiac adverse effects.

3) Severity: contraindicated

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: The concomitant use of [nelfinavir](#) and a CYP3A4 substrate that may have serious or life-threatening consequences with increased plasma concentrations is contraindicated[252].

7) Probable Mechanism: inhibition of CYP3A4-mediated metabolism by [nelfinavir](#); additive QT interval effects

3.5.1.DZ] [Nilotinib](#)

1) Interaction Effect: increased exposure of CYP3A4 substrate and increased risk of QT-interval prolongation

2) Summary: Nilotinib is a moderate CYP3A4 inhibitor and is independently capable of prolonging the QT interval. Avoid use of nilotinib with CYP3A4 substrates that also prolong the QT interval as concomitant use may lead to increased exposure to the CYP3A4 substrate and an increased risk of QT-interval prolongation and [torsade de pointes](#). If possible, treatment with nilotinib should be interrupted. If concurrent treatment is required, close monitoring for QT interval prolongation is recommended and dose adjustments of the CYP3A4 substrate may be necessary[311]. Monitoring for toxic effects should be considered.

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Nilotinib is a moderate CYP3A4 inhibitor and is independently capable of prolonging the QT interval. Use of nilotinib with CYP3A4 substrates that also prolong the QT interval should be avoided, as concomitant use may lead to increased exposure to the CYP3A4 substrate and an increased risk of QT-interval prolongation and [torsade de pointes](#). If possible, treatment with nilotinib should be interrupted. If concurrent treatment is required, close monitoring for QT interval prolongation is recommended and dose adjustments of the CYP3A4 substrate may be necessary[311]. Monitoring for toxic effects should be considered.

7J) Probable Mechanism: inhibition of CYP3A4-mediated metabolism of this drug by nilotinib; additive QT-interval prolongation

3.5.1.EA] **Norfloxacin**

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

2J) Summary: Rare postmarketing cases of QT interval prolongation and **ventricular arrhythmia**, including **torsade de pointes** (TdP), have been reported with **norfloxacin**[114]. QT/QTc interval prolongation and postmarketing cases of TdP have also been reported with **trazodone**. The concomitant use of **trazodone** with other drugs that may prolong the QT interval, such as **norfloxacin**, may result in additive effects on QT interval prolongation and an increased risk of serious **ventricular arrhythmias**, including TdP [95]. If coadministration is required, monitoring for QT interval prolongation may be warranted.

3J) Severity: major

4J) Onset: unspecified

5J) Substantiation: theoretical

6J) Clinical Management: The concomitant use of **trazodone** with other drugs that may prolong the QT interval, such as **norfloxacin**[114], may result in additive effects on QT interval prolongation and risk of **torsade de pointes** [95]. If coadministration is required, monitoring for QT interval prolongation may be warranted.

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

3.5.1.EB] **Nortriptyline**

1J) Interaction Effect: an increased risk of QT interval prolongation and **serotonin syndrome**

2J) Summary: QT/QTc interval prolongation and postmarketing cases of **torsade de pointes** have been reported with **trazodone**. The concomitant use of **trazodone** with other drugs that may prolong the QT interval, such as **nortriptyline**, may result in additive effects on QT interval prolongation and an increased risk of serious **ventricular arrhythmias**, including **torsade de pointes**. Both **nortriptyline** and **trazodone** 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**[95]. 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 [96]. If coadministration is required, monitoring for QT interval prolongation and signs and symptoms of **serotonin syndrome** may be warranted.

3J) Severity: major

4J) Onset: unspecified

5J) Substantiation: theoretical

6J) Clinical Management: Use caution with concomitant administration of **nortriptyline** and **trazodone**, as this may result in additive serotonergic effects and may increase the risk of **serotonin syndrome**. The concomitant use of **trazodone** with **nortriptyline** may also result in additive effects on QT interval prolongation and increased risk of **torsade de pointes**[95]. If coadministration is required, monitoring for signs and symptoms of **serotonin syndrome** and QT interval prolongation may be warranted.

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

3.5.1.EC] **Octreotide**

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

2) Summary: QT/QTc interval prolongation and postmarketing cases of [torsade de pointes](#) have been reported with [trazodone](#). The concomitant use of [trazodone](#) with other drugs that prolong the QT interval, such as [octreotide](#)[139], may result in additive effects on QT interval prolongation and an increased risk of serious [ventricular arrhythmias](#), including [torsade de pointes](#) [95]. If coadministration is required, monitoring for QT interval prolongation may be warranted.

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: The concomitant use of [trazodone](#) with other QT interval-prolonging drugs, such as [octreotide](#)[139], may result in additive effects on QT interval prolongation and risk of [torsade de pointes](#) [95]. If coadministration is required, monitoring for QT interval prolongation may be warranted.

7) Probable Mechanism: additive effects on QT interval prolongation

3.5.1.ED] [Ondansetron](#)

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

2) Summary: QT/QTc interval prolongation and postmarketing cases of [torsade de pointes](#) have been reported with [trazodone](#). The concomitant use of [trazodone](#) with other drugs that prolong the QT interval, such as [ondansetron](#)[188], may result in additive effects on QT interval prolongation and an increased risk of serious [ventricular arrhythmias](#), including [torsade de pointes](#) and therefore should be avoided [95]. If concurrent therapy is required, [ECG monitoring](#) is recommended [188].

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: The concomitant use of [trazodone](#) with other QT-prolonging drugs, such as [ondansetron](#)[188], may result in additive effects on QT interval prolongation and risk of [torsade de pointes](#) and therefore should be avoided [95]. If concurrent therapy is required, [ECG monitoring](#) is recommended [188].

7) Probable Mechanism: additive effects on QT interval prolongation

3.5.1.EE] [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[208].

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[208].

7) Probable Mechanism: additive serotonergic effect

3.5.1.EF] [Paliperidone](#)

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

2) Summary: Both [paliperidone](#) and [trazodone](#) are associated with prolonged QT interval[180][95]. Due to the potential for additive effects on QT interval prolongation and an increased risk of serious cardiac events, including [torsade de pointes](#) and/or sudden death, avoid using these drugs concomitantly [180]. If concomitant therapy is required, monitoring for QT interval prolongation may be warranted.

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Avoid concomitant use of [paliperidone](#) with other drugs that prolong the QT interval, such as [trazodone](#)[95], as it may result in additive effects on QT interval prolongation and an increased risk of serious cardiac events, including [torsade de pointes](#) and/or sudden death [180]. If concomitant therapy is required, closely monitor for QT interval prolongation.

7) Probable Mechanism: additive effects on QT interval prolongation

3.5.1.EG| [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](#)[270].

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](#)[270].

7) Probable Mechanism: unknown

3.5.1.EH| [Panobinostat](#)

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

2) Summary: Concurrent use of panobinostat with QT-prolonging drugs is not recommended, as additive effects on the QT interval may develop. Conduct frequent [ECG monitoring](#) if concurrent use with antiemetics known to prolong the QT interval is warranted. Interrupt treatment if the Fridericia-corrected QT interval increases to 480 msec or more. Discontinue panobinostat if QT-interval prolongation does not resolve after any electrolyte abnormalities are corrected[189].

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Concurrent use of panobinostat with QT-prolonging drugs is not recommended, as additive effects on the QT interval may develop. Conduct frequent [ECG monitoring](#) if concurrent use with antiemetics known to prolong the QT interval is warranted. Interrupt treatment if the Fridericia-corrected QT interval increases to 480 msec or more. Discontinue panobinostat if QT-interval prolongation does not resolve after any electrolyte abnormalities are corrected[189].

7) Probable Mechanism: additive QT effects

3.5.1.EI| [Pargyline](#)

- 1) Interaction Effect: an increased risk of [serotonin syndrome](#) ([hypertension](#), [hyperthermia](#), myoclonus, mental status changes)
- 2) Summary: [Trazodone](#) exerts inhibitory effects on serotonin reuptake. [Serotonin syndrome](#) has been reported with the use of [trazodone](#) and the risk is increased with concurrent administration or overlapping therapy with an MAOI intended to treat psychiatric disorders. [Serotonin syndrome](#) is a hyperserotonergic state characterized by symptoms such as agitation and restlessness, myoclonus, changes in mental status, hyperreflexia, diaphoresis, shivering, and tremor. Serious, even fatal, reactions have been reported with concomitant use of serotonergic drugs and MAOIs. A minimum of 14 days should elapse after discontinuing an MAOI intended to treat psychiatric disorders before initiating therapy with [trazodone](#), and a minimum of 14 days should elapse after discontinuing [trazodone](#) before initiating therapy with an MAOI intended to treat psychiatric disorders[23].
- 3) Severity: contraindicated
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Concurrent use of [trazodone](#) and an MAOI intended to treat psychiatric disorders is contraindicated. Wait at least 14 days after discontinuing an MAOI before initiating [trazodone](#). Wait at least 14 days after discontinuing [trazodone](#) before initiating therapy with an MAOI intended to treat psychiatric disorders[23].
- 7) Probable Mechanism: additive serotonergic effect

3.5.1.EJ] [Paroxetine](#)

- 1) Interaction Effect: increased risk of [serotonin syndrome](#) ([hypertension](#), [hyperthermia](#), myoclonus, mental status changes)
- 2) Summary: Both [paroxetine](#) and [trazodone](#) 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](#)[293][95]. There have been several reports of [serotonin syndrome](#) due to interactions between selective serotonin reuptake inhibitors and antidepressants, including one case report due to [paroxetine](#) and [trazodone](#) coadministration [296][297][298]. 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 [96]. Monitoring for signs and symptoms of [serotonin syndrome](#) may be warranted if [paroxetine](#) and [trazodone](#) are used concurrently, particularly during treatment initiation and dose increases [95].
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: probable
- 6) Clinical Management: Use caution with concomitant administration of [paroxetine](#) and [trazodone](#), as this may result in additive serotonergic effects and may increase the risk of [serotonin syndrome](#)[293][95]. If coadministration is required, appropriate monitoring may be warranted, particularly during treatment initiation and dose increases [95].
- 7) Probable Mechanism: additive serotonergic effects
- 8) Literature Reports

a) [Serotonin syndrome](#) was reported in a 29-year old woman taking [trazodone](#) and [paroxetine](#). The patient was treated with [trazodone](#) 200 mg daily at bedtime for approximately three months for depression and insomnia. The patient's depressive symptoms were unresponsive to this treatment, so [trazodone](#) was subsequently decreased to 50 mg daily at bedtime for two weeks

before [paroxetine](#) 20 mg every morning was added. Within 24 hours after the first dose of [paroxetine](#), the patient became agitated, confused, shaky, and diaphoretic. Upon examination, the patient had impaired concentration, intermittent myoclonus in all extremities, hyperreflexia, tremor, and diaphoresis. After discontinuation of antidepressant medications, the patient's symptoms resolved [294].

b) A 44-year old man developed symptoms characteristic of [serotonin syndrome](#) due to a possible interaction between [fluoxetine](#) and [trazodone](#). The patient had been taking [fluoxetine](#) 40 mg daily and [trazodone](#) 100 mg daily for approximately two months before symptoms occurred. The patient experienced disorientation, tremor, diaphoresis, and anxiety, followed by uncontrollable shaking and loss of consciousness. After the patient was treated with [cyproheptadine](#) 4 mg orally, symptoms resolved over the next 30 minutes. [Trazodone](#) was discontinued and the patient continued to take [fluoxetine](#) 40 mg daily without further complications [295].

3.5.1.EK] Pasireotide

- 1) Interaction Effect: increased risk of QT prolongation
- 2) 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[239].
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) 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[239].
- 7) Probable Mechanism: additive QT-interval prolongation

3.5.1.EL] Pazopanib

- 1) Interaction Effect: an increased risk of QT interval prolongation
- 2) Summary: QT/QTc interval prolongation and postmarketing cases of [torsade de pointes](#) have been reported with [trazodone](#). The concomitant use of [trazodone](#) with other drugs that prolong the QT interval, such as pazopanib[183], may result in additive effects on QT interval prolongation and an increased risk of serious [ventricular arrhythmias](#), including [torsade de pointes](#) and should be avoided [95]. If coadministration is required, monitoring for QT interval prolongation may be warranted.
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: The concomitant use of [trazodone](#) with other QT-prolonging drugs, such as pazopanib[183], may result in additive effects on QT interval prolongation and risk of [torsade de pointes](#) and should be avoided [95]. If coadministration is required, monitoring for QT interval prolongation may be warranted.
- 7) Probable Mechanism: additive effects on QT interval prolongation

3.5.1.EM] Pentazocine

- 1) Interaction Effect: increased risk of [serotonin syndrome](#) ([hypertension](#), [hyperthermia](#), myoclonus, mental status changes)
- 2) Summary: Both [pentazocine](#) and [trazodone](#) 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](#)[95]. Monitoring for signs and symptoms of [serotonin syndrome](#) may be warranted if [pentazocine](#) and [trazodone](#) are used 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. If [serotonin syndrome](#) develops, discontinue the offending agents and provide supportive care and other therapy as necessary [96].
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Use caution with concomitant administration of [pentazocine](#) and [trazodone](#), as this may result in additive serotonergic effects and may increase the risk of [serotonin syndrome](#)[95]. If coadministration is required, appropriate monitoring may be warranted.
- 7) Probable Mechanism: additive serotonergic effect

3.5.1.EN] Perflutren Lipid Microsphere

- 1) Interaction Effect: an increased risk of QT interval prolongation
- 2) Summary: QT/QTc interval prolongation and postmarketing cases of [torsade de pointes](#) have been reported with [trazodone](#). The concomitant use of [trazodone](#) with other drugs that prolong the QT interval, such as perflutren, may result in additive effects on QT interval prolongation and an increased risk of serious [ventricular arrhythmias](#), including [torsade de pointes](#)[95]. If coadministration is required, monitoring for QT interval prolongation may be warranted.
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: The concomitant use of [trazodone](#) with other QT-prolonging drugs, such as perflutren, may result in additive effects on QT interval prolongation and risk of [torsade de pointes](#)[95]. If coadministration is required, monitoring for QT interval prolongation may be warranted.
- 7) Probable Mechanism: additive effects on QT interval prolongation
- 8) Literature Reports

a) Serious cardiopulmonary reactions, including fatalities, have been reported during or after administration of perflutren-containing microspheres; most serious reactions occurred within 30 minutes of administration. In 221 subjects receiving a perflutren-containing microsphere bolus injection of up to 10 microL/kg, measurement of ECG parameters from 1 hour to 72 hours after administration revealed QTc prolongations of greater than 30 milliseconds in 29% (64/221) of subjects. Among 46 subjects who were further evaluated, 39% experienced associated cardiac rhythm changes. The effects of concomitant drugs on ECG changes has not been studied [113]

3.5.1.EO] Perphenazine

- 1) Interaction Effect: hypotension
- 2) Summary: Concomitant administration of [trazodone](#) with [chlorpromazine](#) or [trifluoperazine](#) resulted in additive hypotensive effects in two case reports. Withdrawal of [trazodone](#) resulted in resolution of the hypotension[292].
- 3) Severity: moderate

- 4) Onset: delayed
- 5) Substantiation: theoretical
- 6) Clinical Management: Monitor blood pressure, particularly in patients who might be sensitive to this effect. Advise patient to rise slowly from laying or sitting position.
- 7) Probable Mechanism: additive hypotensive effects

3.5.1.EP] Phenelzine

- 1) Interaction Effect: an increased risk of **serotonin syndrome** (**hypertension**, **hyperthermia**, myoclonus, mental status changes)
- 2) Summary: **Trazodone** exerts inhibitory effects on serotonin reuptake. **Serotonin syndrome** has been reported with the use of **trazodone** and the risk is increased with concurrent administration or overlapping therapy with an MAOI intended to treat psychiatric disorders. **Serotonin syndrome** is a hyperserotonergic state characterized by symptoms such as agitation and restlessness, myoclonus, changes in mental status, hyperreflexia, diaphoresis, shivering, and tremor. Serious, even fatal, reactions have been reported with concomitant use of serotonergic drugs and MAOIs. A minimum of 14 days should elapse after discontinuing an MAOI intended to treat psychiatric disorders before initiating therapy with **trazodone**, and a minimum of 14 days should elapse after discontinuing **trazodone** before initiating therapy with an MAOI intended to treat psychiatric disorders[23].
- 3) Severity: contraindicated
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Concurrent use of **trazodone** and an MAOI intended to treat psychiatric disorders is contraindicated. Wait at least 14 days after discontinuing an MAOI before initiating **trazodone**. Wait at least 14 days after discontinuing **trazodone** before initiating therapy with an MAOI intended to treat psychiatric disorders[23].
- 7) Probable Mechanism: additive serotonergic effect

3.5.1.EQ] Phenytoin

- 1) Interaction Effect: increased **phenytoin** serum concentrations and an increased risk of **phenytoin** toxicity (ataxia, hyperreflexia, **nystagmus**, tremor)
- 2) Summary: Increased **phenytoin** serum concentrations have occurred in patients receiving concomitant treatment with **trazodone** and **phenytoin**[125]. **Phenytoin** toxicity has occurred in a patient receiving concurrent treatment with the 2 drugs [124].
- 3) Severity: moderate
- 4) Onset: unspecified
- 5) Substantiation: probable
- 6) Clinical Management: Measure serum levels of **phenytoin** after initiation, changes in dose, or discontinuation of **trazodone**; adjust dosage accordingly.
- 7) Probable Mechanism: unknown
- 8) Literature Reports

a) In 1 case concomitant administration of **phenytoin** and **trazodone** was reported to result in increases in **phenytoin** serum concentrations and **phenytoin** toxicity. It is speculated that **trazodone** may competitively inhibit the metabolism of **phenytoin**, binding of **phenytoin** to plasma proteins, or renal **phenytoin** excretion. It may be prudent to monitor **phenytoin** serum concentrations in patients receiving the combination until further data is available [124].

3.5.1.ER] 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](#)[103].
- 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](#)[103].
- 7) Probable Mechanism: additive effects on the QT interval

3.5.1.ES] [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](#)[136].
- 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](#)[136].
- 7) Probable Mechanism: additive QT-interval prolongation

3.5.1.ET] [Piperaquine](#)

- 1) Interaction Effect: increased exposure of CYP3A4 substrates and increased risk of QT-interval prolongation
- 2) Summary: Concomitant administration of piperaquine and QT-interval prolonging drugs may result in additive prolongation effects on the QT interval and is contraindicated. Additionally, recent use of QT-interval prolonging drugs, that may still be circulating at the time of piperaquine administration, is contraindicated. Concurrent administration of piperaquine (a CYP3A4 inhibitor) and a CYP3A4 substrate may increase the exposure of the CYP3A4 substrate. Due to the long half-life of piperaquine, caution is advised when administering a CYP3A4 substrate for up to 3 months after discontinuation of piperaquine therapy[130].
- 3) Severity: contraindicated
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Concomitant administration of piperaquine (a QT-interval prolonging drug) with other QT-interval prolonging drugs may result in additive prolongation effects on the QT interval and is contraindicated. Additionally, recent use of QT-interval prolonging drugs, that may still be circulating at the time of piperaquine administration, is contraindicated. Concurrent administration of piperaquine (a CYP3A4 inhibitor) and a CYP3A4 substrate may increase the exposure of the CYP3A4 substrate. Due to the long half-life of piperaquine, caution is advised when administering a CYP3A4 substrate for up to 3 months after discontinuation of piperaquine therapy[130].
- 7) Probable Mechanism: inhibition of CYP3A4-mediated metabolism of this drug by piperaquine; additive QT-interval prolongation

3.5.1.EU] Pipotiazine

- 1) Interaction Effect: hypotension
- 2) Summary: Concomitant administration of [trazodone](#) with [chlorpromazine](#) or [trifluoperazine](#) resulted in additive hypotensive effects in two case reports. Withdrawal of [trazodone](#) resulted in resolution of the hypotension[288].
- 3) Severity: moderate
- 4) Onset: delayed
- 5) Substantiation: theoretical
- 6) Clinical Management: Monitor blood pressure, particularly in patients who might be sensitive to this effect. Advise patient to rise slowly from laying or sitting position.
- 7) Probable Mechanism: additive hypotensive effects

3.5.1.EV] 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[249].
- 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[249].
- 7) Probable Mechanism: additive QT prolongation

3.5.1.EW] Posaconazole

- 1) Interaction Effect: increased [trazodone](#) plasma concentrations and increased risk of QT interval prolongation
- 2) Summary: The metabolism of [trazodone](#), a CYP3A4 substrate, may be inhibited by concomitant administration of [posaconazole](#), a strong CYP3A4 inhibitor. Increased [trazodone](#) plasma concentrations can lead to QT interval prolongation and [torsade de pointes](#)[95][210]. Prolongation of the QT interval and rare cases of [torsade de pointes](#) have also been reported in patients receiving [posaconazole](#). Therefore, concomitant use of [posaconazole](#) and CYP3A4 substrates that prolong the QT interval is contraindicated [210].
- 3) Severity: contraindicated
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Concomitant use of [posaconazole](#) with CYP3A4 substrates that prolong the QT interval, such as [trazodone](#)[95], is contraindicated due to the potential for increased [propafenone](#) plasma concentrations, thereby increasing the risk for QT interval prolongation and [torsades de pointes](#) [210].
- 7) Probable Mechanism: inhibition of CYP3A4-mediated [trazodone](#) metabolism by [posaconazole](#) and additive effects on QT interval prolongation

3.5.1.EX] Procainamide

- 1) Interaction Effect: an increased risk of QT interval prolongation
- 2) Summary: QT/QTc interval prolongation and postmarketing cases of [torsade de pointes](#) have been reported with [trazodone](#)[95]. The concomitant use of [trazodone](#) with other drugs that prolong the QT interval, such as [procainamide](#) (a class IA antiarrhythmic) [179], may result in additive effects on QT

interval prolongation and an increased risk of serious [ventricular arrhythmias](#), including [torsade de pointes](#) [95]. If coadministration is required, monitoring for QT interval prolongation may be warranted.

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: The concomitant use of [trazodone](#) with other drugs that may prolong the QT interval, such as [procainamide](#)[179], may result in additive effects on QT interval prolongation and risk of [torsade de pointes](#) [95]. If coadministration is required, monitoring for QT interval prolongation may be warranted.

7) Probable Mechanism: additive effects on QT interval prolongation

3.5.1.EY] [Procarbazine](#)

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

2) Summary: [Trazodone](#) exerts inhibitory effects on serotonin reuptake. [Serotonin syndrome](#) has been reported with the use of [trazodone](#) and the risk is increased with concurrent administration or overlapping therapy with an MAOI intended to treat psychiatric disorders. [Serotonin syndrome](#) is a hyperserotonergic state characterized by symptoms such as agitation and restlessness, myoclonus, changes in mental status, hyperreflexia, diaphoresis, shivering, and tremor. Serious, even fatal, reactions have been reported with concomitant use of serotonergic drugs and MAOIs. A minimum of 14 days should elapse after discontinuing an MAOI intended to treat psychiatric disorders before initiating therapy with [trazodone](#), and a minimum of 14 days should elapse after discontinuing [trazodone](#) before initiating therapy with an MAOI intended to treat psychiatric disorders[23].

3) Severity: contraindicated

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Concurrent use of [trazodone](#) and an MAOI intended to treat psychiatric disorders is contraindicated. Wait at least 14 days after discontinuing an MAOI before initiating [trazodone](#). Wait at least 14 days after discontinuing [trazodone](#) before initiating therapy with an MAOI intended to treat psychiatric disorders[23].

7) Probable Mechanism: additive serotonergic effect

3.5.1.EZ] [Prochlorperazine](#)

1) Interaction Effect: hypotension

2) Summary: Concomitant administration of [trazodone](#) with [chlorpromazine](#) or [trifluoperazine](#) resulted in additive hypotensive effects in two case reports. Withdrawal of [trazodone](#) resulted in resolution of the hypotension[286].

3) Severity: moderate

4) Onset: delayed

5) Substantiation: theoretical

6) Clinical Management: Monitor blood pressure, particularly in patients who might be sensitive to this effect. Advise patient to rise slowly from laying or sitting position.

7) Probable Mechanism: additive hypotensive effects

3.5.1.FA] [Promazine](#)

1) Interaction Effect: hypotension

- 2)) Summary: Concomitant administration of [trazodone](#) with [chlorpromazine](#) or [trifluoperazine](#) resulted in additive hypotensive effects in two case reports. Withdrawal of [trazodone](#) resulted in resolution of the hypotension[91].
- 3)) Severity: moderate
- 4)) Onset: delayed
- 5)) Substantiation: theoretical
- 6)) Clinical Management: Monitor blood pressure, particularly in patients who might be sensitive to this effect. Advise patient to rise slowly from laying or sitting position.
- 7)) Probable Mechanism: additive hypotensive effects

3.5.1.FB| [Promethazine](#)

- 1)) Interaction Effect: hypotension
- 2)) Summary: Concomitant administration of [trazodone](#) with [chlorpromazine](#) or [trifluoperazine](#) resulted in additive hypotensive effects in two case reports. Withdrawal of [trazodone](#) resulted in resolution of the hypotension[92].
- 3)) Severity: moderate
- 4)) Onset: delayed
- 5)) Substantiation: theoretical
- 6)) Clinical Management: Monitor blood pressure, particularly in patients who might be sensitive to this effect. Advise patient to rise slowly from laying or sitting position.
- 7)) Probable Mechanism: additive hypotensive effects

3.5.1.FC| [Propafenone](#)

- 1)) Interaction Effect: an increased risk of QT interval prolongation
- 2)) Summary: [Propafenone](#) may prolong the QT interval and has caused serious cardiac events, including sudden death and life-threatening [ventricular arrhythmias](#) (eg, [ventricular fibrillation](#), [ventricular tachycardia](#), [asystole](#), and [torsade de pointes](#))[177]. QT/QTc interval prolongation and postmarketing cases of [torsade de pointes](#) have been reported with [trazodone](#). The concomitant use of [trazodone](#) with other drugs that prolong the QT interval may result in additive effects on QT interval prolongation and an increased risk of serious [ventricular arrhythmias](#), including [torsade de pointes](#) [95]. If coadministration is required, monitoring for QT interval prolongation may be warranted.
- 3)) Severity: major
- 4)) Onset: unspecified
- 5)) Substantiation: theoretical
- 6)) Clinical Management: The concomitant use of [trazodone](#) with other drugs that may prolong the QT interval, such as [propafenone](#)[177], may result in additive effects on QT interval prolongation and risk of [torsade de pointes](#) [95]. If coadministration is required, monitoring for QT interval prolongation may be warranted.
- 7)) Probable Mechanism: additive effects on QT interval prolongation

3.5.1.FD| [Propiomazine](#)

- 1)) Interaction Effect: hypotension
- 2)) Summary: Concomitant administration of [trazodone](#) with [chlorpromazine](#) or [trifluoperazine](#) resulted in additive hypotensive effects in two case reports. Withdrawal of [trazodone](#) resulted in resolution of the hypotension[98].
- 3)) Severity: moderate
- 4)) Onset: delayed
- 5)) Substantiation: theoretical

- 6) Clinical Management: Monitor blood pressure, particularly in patients who might be sensitive to this effect. Advise patient to rise slowly from laying or sitting position.
- 7) Probable Mechanism: additive hypotensive effects

3.5.1.FE] Propoxyphene

- 1) Interaction Effect: increased risk of [serotonin syndrome](#) ([hypertension](#), [hyperthermia](#), myoclonus, mental status changes)
- 2) Summary: Both [propoxyphene](#) and [trazodone](#) 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](#)[95]. Monitoring for signs and symptoms of [serotonin syndrome](#) may be warranted if [propoxyphene](#) and [trazodone](#) are used 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. If [serotonin syndrome](#) develops, discontinue the offending agents and provide supportive care and other therapy as necessary [96].
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Use caution with concomitant administration of [propoxyphene](#) and [trazodone](#), as this may result in additive serotonergic effects and may increase the risk of [serotonin syndrome](#)[95]. If coadministration is required, appropriate monitoring may be warranted.
- 7) Probable Mechanism: additive serotonergic effect

3.5.1.FF] Protriptyline

- 1) Interaction Effect: an increased risk of QT interval prolongation
- 2) Summary: QT/QTc interval prolongation and postmarketing cases of [torsade de pointes](#) have been reported with [trazodone](#). The concomitant use of [trazodone](#) with other drugs that may prolong the QT interval, such as [protriptyline](#), may result in additive effects on QT interval prolongation and an increased risk of serious [ventricular arrhythmias](#), including [torsade de pointes](#)[95]. If coadministration is required, monitoring for QT interval prolongation may be warranted.
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: The concomitant use of [trazodone](#) with other drugs that may prolong the QT interval, such as [protriptyline](#), may result in additive effects on QT interval prolongation and risk of [torsade de pointes](#)[95]. If coadministration is required, monitoring for QT interval prolongation may be warranted.
- 7) Probable Mechanism: additive effects on QT interval prolongation

3.5.1.FG] 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[153].
- 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[153].

7) Probable Mechanism: additive effects on QT interval

3.5.1.FH] [Quinidine](#)

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

2) Summary: QT/QTc interval prolongation and postmarketing cases of [torsade de pointes](#) have been reported with [trazodone](#). The concomitant use of [trazodone](#) with other drugs that prolong the QT interval, such as [quinidine](#)[200], may result in additive effects on QT interval prolongation and an increased risk of serious [ventricular arrhythmias](#), including [torsade de pointes](#) [95]. If coadministration is required, monitoring for QT interval prolongation may be warranted.

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: The concomitant use of [trazodone](#) with other drugs that may prolong the QT interval, such as [quinidine](#)[200], may result in additive effects on QT interval prolongation and risk of [torsade de pointes](#) [95]. If coadministration is required, monitoring for QT interval prolongation may be warranted.

7) Probable Mechanism: additive effects on QT interval prolongation

3.5.1.FI] [Quinine](#)

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

2) Summary: Both oral and parenteral [quinine](#) have been associated with QT interval prolongation, and rarely, fatal [cardiac arrhythmias](#), including [torsade de pointes](#), have occurred with [quinine](#) sulfate. Due to the potential for additive effects on QT interval prolongation and an increased risk of serious cardiac events, concomitant use of [quinine](#) with other drugs that prolong the QT interval, such as [trazodone](#)[95], is not recommended [199]. If concomitant therapy is required, monitor carefully for QT interval prolongation.

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Concomitant use of [quinine](#) with other drugs that prolong the QT interval, such as [trazodone](#)[95], is not recommended as it may result in additive effects on QT interval prolongation and an increased risk of serious cardiac events, including [torsade de pointes](#) [199]. If concomitant therapy is required, closely monitor for QT interval prolongation.

7) Probable Mechanism: additive effects on QT interval prolongation

3.5.1.FJ] [Ranolazine](#)

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

2) Summary: [Ranolazine](#) prolongs the QTc interval in a dose-related manner[148] and QT/QTc interval prolongation and postmarketing cases of [torsade de pointes](#) have been reported with [trazodone](#). The concomitant use of [trazodone](#) with other drugs that prolong the QT interval, such as [ranolazine](#), may result in additive effects on QT interval prolongation and an increased risk of serious [ventricular arrhythmias](#), including [torsade de pointes](#) [95]. If coadministration is required, monitoring for QT interval prolongation may be warranted.

3) Severity: major

4) Onset: unspecified

- 5J) Substantiation: theoretical
- 6J) Clinical Management: The concomitant use of [trazodone](#) with other drugs that may prolong the QT interval, such as [ranolazine](#)[148], may result in additive effects on QT interval prolongation and risk of [torsade de pointes](#) [95]. If coadministration is required, monitoring for QT interval prolongation may be warranted.
- 7J) Probable Mechanism: additive effects on QT interval prolongation

3.5.1.FK] [Rasagiline](#)

- 1J) Interaction Effect: an increased risk of [serotonin syndrome](#) ([hypertension](#), [hyperthermia](#), myoclonus, mental status changes)
- 2J) Summary: [Trazodone](#) exerts inhibitory effects on serotonin reuptake. [Serotonin syndrome](#) has been reported with the use of [trazodone](#) and the risk is increased with concurrent administration or overlapping therapy with an MAOI intended to treat psychiatric disorders. [Serotonin syndrome](#) is a hyperserotonergic state characterized by symptoms such as agitation and restlessness, myoclonus, changes in mental status, hyperreflexia, diaphoresis, shivering, and tremor. Serious, even fatal, reactions have been reported with concomitant use of serotonergic drugs and MAOIs. A minimum of 14 days should elapse after discontinuing an MAOI intended to treat psychiatric disorders before initiating therapy with [trazodone](#), and a minimum of 14 days should elapse after discontinuing [trazodone](#) before initiating therapy with an MAOI intended to treat psychiatric disorders[23].
- 3J) Severity: contraindicated
- 4J) Onset: unspecified
- 5J) Substantiation: theoretical
- 6J) Clinical Management: Concurrent use of [trazodone](#) and an MAOI intended to treat psychiatric disorders is contraindicated. Wait at least 14 days after discontinuing an MAOI before initiating [trazodone](#). Wait at least 14 days after discontinuing [trazodone](#) before initiating therapy with an MAOI intended to treat psychiatric disorders[23].
- 7J) Probable Mechanism: additive serotonergic effect

3.5.1.FL] [Ritonavir](#)

- 1J) Interaction Effect: an increase in [trazodone](#) plasma levels and increased risk of [trazodone](#) side effects
- 2J) Summary: [Ritonavir](#) inhibits the CYP3A-mediated metabolism of [trazodone](#). Coadministration of [ritonavir](#) with [trazodone](#) produced a 34% (95% CI) increase in peak plasma [trazodone](#) concentrations, a 2.4-fold (95%CI) increase in total area under the concentration-time curve, and a prolongation of elimination half-life. Patients should be monitored for increased [trazodone](#) side effects including nausea, dizziness, syncope and hypotension. A reduction in [trazodone](#) dosing may be warranted[195][196].
- 3J) Severity: moderate
- 4J) Onset: unspecified
- 5J) Substantiation: probable
- 6J) Clinical Management: Patients receiving [trazodone](#) and [ritonavir](#) should be monitored for enhanced sedative effects and hypotension. Consider a reduction in [trazodone](#) dosing.
- 7J) Probable Mechanism: inhibition of CYP3A-mediated [trazodone](#) metabolism by [ritonavir](#)
- 8J) Literature Reports

aJ) Coadministration of [ritonavir](#) and [trazodone](#) produces a significant increase in peak plasma [trazodone](#) concentration (C_{max}), prolongation of elimination half-life, increase in total AUC, and reduction in oral clearance. Ten subjects participated in a randomized, four-way crossover design study with 7 days elapsing between treatments. The four treatment conditions were: Treatment A: placebo to match [trazodone](#), plus placebo to match [ritonavir](#); Treatment B: [trazodone](#) 50 mg plus [ritonavir](#) placebo; Treatment C: placebo to match [trazodone](#) plus [ritonavir](#) 200 mg X 4

doses; Treatment D: [trazodone](#) 50 mg plus [ritonavir](#) 200 mg X 4 doses. [Ritonavir](#) and [trazodone](#) coadministration produced a significant increase in [trazodone](#) C_{max} with the mean +/- SE value being 842 +/- 64 ng/mL (treatment B) and 1125 +/- 111 ng/mL (treatment D) (p less than 0.05). The mean +/- SE elimination half-life in treatment B was 6.7 +/- 0.7 h and in treatment D was 14.9 +/- 3.9 (p less than 0.05). The mean +/- SE total AUC for treatment B was 5.86 +/- 0.83 mcg/mL X h and for treatment D was 13.88 +/- 2.89 (p less than 0.01). The mean +/- SE apparent oral clearance (mL/min) for treatment B was 155 +/- 23 and for treatment D was 75 +/- 12 (p less than 0.001). Sedation, [impairment of psychomotor](#) performance (the DSST), and a quantitatively small increase in beta amplitude on the EEG caused by [trazodone](#) were all enhanced by coadministration of [ritonavir](#) [109].

3.5.1.FM] [Rizatriptan](#)

- 1) Interaction Effect: increased risk of [serotonin syndrome](#) ([hypertension](#), [hyperthermia](#), myoclonus, mental status changes)
- 2) Summary: [Rizatriptan](#) is known to cause [serotonin syndrome](#)[160] and both [rizatriptan](#) and [trazodone](#) 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](#). Careful monitoring for signs and symptoms of [serotonin syndrome](#) is warranted, if [rizatriptan](#) and [trazodone](#) are used concurrently, particularly during treatment initiation and dose increases [95]. 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 [96].
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Use caution with concomitant administration of [rizatriptan](#), a drug known to cause [serotonin syndrome](#)[160], and [trazodone](#), as this may result in additive serotonergic effects and may increase the risk of [serotonin syndrome](#). If coadministration is required, careful monitoring is warranted, particularly during treatment initiation and dose increases [95].
- 7) Probable Mechanism: additive serotonergic effect

3.5.1.FN] [Safinamide](#)

- 1) Interaction Effect: Risk of [serotonin syndrome](#)
- 2) Summary: Concomitant use of serotonergic agents with safinamide (a MAOI-type B) is contraindicated due to the potential for [serotonin syndrome](#). Use of serotonergic agents within 14 days of discontinuing a MAOI is also contraindicated[174].
- 3) Severity: contraindicated
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Concomitant use of serotonergic agents with safinamide (a MAOI-type B) is contraindicated due to the potential for [serotonin syndrome](#). Use of serotonergic agents within 14 days of discontinuing a MAOI is also contraindicated[174].
- 7) Probable Mechanism: Additive serotonergic effects

3.5.1.FO] [Salmeterol](#)

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

2) Summary: Clinically significant prolongation of the QTc interval has been reported with very large oral and inhalation doses of salmeterol (12 to 20 times the recommended dose)[149]. QT/QTc interval prolongation and postmarketing cases of **torsade de pointes** have been reported with **trazodone**. The concomitant use of **trazodone** with other drugs that prolong the QT interval may result in additive effects on QT interval prolongation and an increased risk of serious **ventricular arrhythmias**, including **torsade de pointes** [95]. If coadministration is required, monitoring for QT interval prolongation may be warranted.

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: The concomitant use of **trazodone** with other drugs that may prolong the QT interval, such as salmeterol[149], may result in additive effects on QT interval prolongation and risk of **torsade de pointes** [95]. If coadministration is required, monitoring for QT interval prolongation may be warranted.

7) Probable Mechanism: additive effects on QT interval prolongation

3.5.1.FP] **Saquinavir**

1) Interaction Effect: increased **trazodone** exposure and increased risk of QT interval prolongation

2) Summary: **Saquinavir** and **trazodone** are both metabolized primarily by CYP3A and using these agents together may increase the exposure of **trazodone** resulting in additive effects on QT interval prolongation and **Torsades de pointes**. Therefore, the concomitant use of **saquinavir** and **trazodone** is contraindicated[277].

3) Severity: contraindicated

4) Onset: delayed

5) Substantiation: theoretical

6) Clinical Management: Concomitant use of **saquinavir** and **trazodone** is contraindicated. Both **saquinavir** and **trazodone** are metabolized primarily by CYP3A4 and using these agents together may cause increased levels of **trazodone**, and an increased risk of QT interval prolongation and **Torsades de pointes**[277].

7) Probable Mechanism: inhibition of CYP3A4-mediated **trazodone** metabolism

3.5.1.FQ] **Selegiline**

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

2) Summary: **Trazodone** exerts inhibitory effects on serotonin reuptake. **Serotonin syndrome** has been reported with the use of **trazodone** and the risk is increased with concurrent administration or overlapping therapy with an MAOI intended to treat psychiatric disorders. **Serotonin syndrome** is a hyperserotonergic state characterized by symptoms such as agitation and restlessness, myoclonus, changes in mental status, hyperreflexia, diaphoresis, shivering, and tremor. Serious, even fatal, reactions have been reported with concomitant use of serotonergic drugs and MAOIs. A minimum of 14 days should elapse after discontinuing an MAOI intended to treat psychiatric disorders before initiating therapy with **trazodone**, and a minimum of 14 days should elapse after discontinuing **trazodone** before initiating therapy with an MAOI intended to treat psychiatric disorders[23].

3) Severity: contraindicated

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Concurrent use of **trazodone** and an MAOI intended to treat psychiatric disorders is contraindicated. Wait at least 14 days after discontinuing an MAOI before initiating

[trazodone](#). Wait at least 14 days after discontinuing [trazodone](#) before initiating therapy with an MAOI intended to treat psychiatric disorders[23].

7J) Probable Mechanism: additive serotonergic effect

3.5.1.FR| [Sertraline](#)

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

2J) Summary: Caution is advised with concomitant use of [sertraline](#) and [trazodone](#) should be avoided due to an increased risk of [serotonin syndrome](#), especially during treatment initiation and dose increases. Discontinue any concomitant serotonergic agents immediately and initiate supportive treatment if [serotonin syndrome](#) is suspected. Monitor patients closely for [serotonin syndrome](#), especially during treatment initiation and dose increases. Symptoms of [serotonin syndrome](#) include neuromuscular abnormalities (eg, hyperreflexia, tremor, and ataxia), autonomic instability (eg, [tachycardia](#), diaphoresis, and [hyperthermia](#)), gastrointestinal symptoms (eg, nausea, vomiting, diarrhea), or mental status changes (eg, agitation and confusion)[211][1].

3J) Severity: major

4J) Onset: unspecified

5J) Substantiation: theoretical

6J) Clinical Management: Exercise caution with concomitant use of [sertraline](#) and [trazodone](#) due to an increased risk of [serotonin syndrome](#), especially during treatment initiation and dose increases. Discontinue any concomitant serotonergic agents immediately and initiate supportive treatment if [serotonin syndrome](#) is suspected. Monitor patients closely for [serotonin syndrome](#), especially during treatment initiation and dose increases. Symptoms of [serotonin syndrome](#) include neuromuscular abnormalities (eg, hyperreflexia, tremor, and ataxia), autonomic instability (eg, [tachycardia](#), diaphoresis, and [hyperthermia](#)), gastrointestinal symptoms (eg, nausea, vomiting, diarrhea), or mental status changes (eg, agitation and confusion)[211][1].

7J) Probable Mechanism: additive serotonergic effects

3.5.1.FS| [Sevoflurane](#)

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

2J) 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](#)[129].

3J) Severity: major

4J) Onset: unspecified

5J) Substantiation: theoretical

6J) 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](#)[129].

7J) Probable Mechanism: additive effects on QT interval

3.5.1.FT| [Sibutramine](#)

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

2J) Summary: Both [sibutramine](#) and [trazodone](#) 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](#)[241][95]. Careful monitoring for signs and symptoms of [serotonin syndrome](#) is warranted, if [sibutramine](#) and [trazodone](#) are used concurrently, particularly during treatment initiation and dose increases [95]. 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 [96].

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Use caution with concomitant administration of [sibutramine](#), a selective serotonin reuptake inhibitor, and [trazodone](#), as this may result in additive serotonergic effects and may increase the risk of [serotonin syndrome](#)[241][95]. If coadministration is required, careful monitoring is warranted, particularly during treatment initiation and dose increases [95].

7) Probable Mechanism: additive serotonergic effect

3.5.1.FU] [Sodium Phosphate](#)

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

2) Summary: QT/QTc interval prolongation and postmarketing cases of [torsade de pointes](#) have been reported with [trazodone](#). The concomitant use of [trazodone](#) with other drugs that prolong the QT interval, such as [sodium phosphate](#)[152], may result in additive effects on QT interval prolongation and an increased risk of serious [ventricular arrhythmias](#), including [torsade de pointes](#) [95]. If coadministration is required, monitoring for QT interval prolongation may be warranted.

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: The concomitant use of [trazodone](#) with other QT-prolonging drugs, such as [sodium phosphate](#), may result in additive effects on QT interval prolongation[152] and risk of [torsade de pointes](#) [95]. If coadministration is required, monitoring for QT interval prolongation may be warranted.

7) Probable Mechanism: additive effects on QT interval prolongation

3.5.1.FV] [Sodium Phosphate, Dibasic](#)

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

2) Summary: QT/QTc interval prolongation and postmarketing cases of [torsade de pointes](#) have been reported with [trazodone](#). The concomitant use of [trazodone](#) with other drugs that prolong the QT interval, such as [sodium phosphate](#)[152], may result in additive effects on QT interval prolongation and an increased risk of serious [ventricular arrhythmias](#), including [torsade de pointes](#) [95]. If coadministration is required, monitoring for QT interval prolongation may be warranted.

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: The concomitant use of [trazodone](#) with other QT-prolonging drugs, such as [sodium phosphate](#), may result in additive effects on QT interval prolongation[152] and risk of [torsade de pointes](#) [95]. If coadministration is required, monitoring for QT interval prolongation may be warranted.

7) Probable Mechanism: additive effects on QT interval prolongation

3.5.1.FW] [Sodium Phosphate, Monobasic](#)

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

2) Summary: QT/QTc interval prolongation and postmarketing cases of [torsade de pointes](#) have been reported with [trazodone](#). The concomitant use of [trazodone](#) with other drugs that prolong the QT interval,

such as [sodium phosphate](#)[152], may result in additive effects on QT interval prolongation and an increased risk of serious [ventricular arrhythmias](#), including [torsade de pointes](#) [95]. If coadministration is required, monitoring for QT interval prolongation may be warranted.

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: The concomitant use of [trazodone](#) with other QT-prolonging drugs, such as [sodium phosphate](#), may result in additive effects on QT interval prolongation[152] and risk of [torsade de pointes](#) [95]. If coadministration is required, monitoring for QT interval prolongation may be warranted.

7) Probable Mechanism: additive effects on QT interval prolongation

3.5.1.FX] [Solifenacin](#)

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

2) Summary: QT/QTc interval prolongation and postmarketing cases of [torsade de pointes](#) have been reported with [trazodone](#). The concomitant use of [trazodone](#) with other drugs that prolong the QT interval, such as [solifenacin](#)[155], may result in additive effects on QT interval prolongation and an increased risk of serious [ventricular arrhythmias](#), including [torsade de pointes](#) [95]. If coadministration is required, monitoring for QT interval prolongation may be warranted.

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: The concomitant use of [trazodone](#) with other drugs that may prolong the QT interval, such as [solifenacin](#)[155], may result in additive effects on QT interval prolongation and risk of [torsade de pointes](#) [95]. If coadministration is required, monitoring for QT interval prolongation may be warranted.

7) Probable Mechanism: additive effects on QT interval prolongation

3.5.1.FY] [Sorafenib](#)

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

2) Summary: QT/QTc interval prolongation and postmarketing cases of [torsade de pointes](#) have been reported with [trazodone](#). The concomitant use of [trazodone](#) with other drugs that prolong the QT interval, such as [sorafenib](#)[144], may result in additive effects on QT interval prolongation and an increased risk of serious [ventricular arrhythmias](#), including [torsade de pointes](#) [95]. If concomitant use is required, [monitoring of ECG](#) and electrolytes ([calcium](#), magnesium, and potassium) is recommended [144].

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: The concomitant use of [trazodone](#) with other drugs that may prolong the QT interval, such as [sorafenib](#)[144], may result in additive effects on QT interval prolongation and risk of [torsade de pointes](#) [95]. If concomitant use of [sorafenib](#) with [trazodone](#) is required, [monitoring of ECG](#) and electrolytes ([calcium](#), magnesium, and potassium) is recommended [144].

7) Probable Mechanism: additive effects on QT interval prolongation

3.5.1.FZ] [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[131][132]. There have been isolated reports of QTc

prolongation and **torsade de pointes** temporally related to the concomitant administration of **ciprofloxacin** and **sotalol** [134][133].

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[131][132].

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 [133].

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 [134].

3.5.1.GA] 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**[198].

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**[198].

7) Probable Mechanism: additive QT interval effects

3.5.1.GB] St John's Wort

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

2) Summary: Both St. John's wort and [trazodone](#) 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](#)[95]. Monitoring for signs and symptoms of [serotonin syndrome](#) may be warranted if St. John's wort and [trazodone](#) are used 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. If [serotonin syndrome](#) develops, discontinue the offending agents and provide supportive care and other therapy as necessary [96].

3) Severity: major

4) Onset: unspecified

5) Substantiation: probable

6) Clinical Management: Use caution with concomitant administration of St. John's wort and [trazodone](#), as this may result in additive serotonergic effects and may increase the risk of [serotonin syndrome](#)[95]. If coadministration is required, appropriate monitoring may be warranted.

7) Probable Mechanism: additive serotonergic effects

3.5.1.GC] 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[111].

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[111].

7) Probable Mechanism: additive effects on the QT interval

3.5.1.GD] Sumatriptan

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

2) Summary: Both [sumatriptan](#) and [trazodone](#) 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](#). Careful monitoring for signs and symptoms of [serotonin syndrome](#) is warranted, if [sumatriptan](#) and [trazodone](#) are used concurrently, particularly during treatment initiation and dose increases[95]. 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 [96].

3) Severity: major

- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Use caution with concomitant administration of [sumatriptan](#) and [trazodone](#), as this may result in additive serotonergic effects and may increase the risk of [serotonin syndrome](#)[95]. If coadministration is required, careful monitoring is warranted, particularly during treatment initiation and dose increases [95].
- 7) Probable Mechanism: additive serotonergic effect

3.5.1.GE] [Sunitinib](#)

- 1) Interaction Effect: an increased risk of QT interval prolongation
- 2) Summary: [Sunitinib](#) has been associated with prolongation of the QT interval in a dose-dependent manner, with [torsade de pointes](#) occurring in less than 0.1% of patients exposed to [sunitinib](#)[146]. QT/QTc interval prolongation and postmarketing cases of [torsade de pointes](#) have also been reported with [trazodone](#). The concomitant use of [trazodone](#) with other drugs that prolong the QT interval may result in additive effects on QT interval prolongation and an increased risk of serious [ventricular arrhythmias](#) [95]. If coadministration is required, consideration should be given to monitoring cardiac function periodically with on-treatment ECGs and evaluating electrolyte (ie, magnesium, potassium) levels [146].
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: The concomitant use of [trazodone](#) with other drugs that prolong the QT interval, such as [sunitinib](#)[146], may result in additive effects on QT interval prolongation and risk of [torsade de pointes](#) [95]. If coadministration is required, consider monitoring cardiac function periodically with on-treatment ECGs and evaluating electrolyte (ie, magnesium, potassium) levels [146].
- 7) Probable Mechanism: additive effects on QT interval prolongation

3.5.1.GF] [Suvorexant](#)

- 1) Interaction Effect: additive sedative effects
- 2) Summary: Avoid concomitant use of suvorexant and this drug as potentiation of sedative effects may occur[240].
- 3) Severity: moderate
- 4) Onset: rapid
- 5) Substantiation: theoretical
- 6) Clinical Management: Concomitant use of suvorexant and this drug is not recommended as potentiation of sedative effects may occur[240].
- 7) Probable Mechanism: additive CNS depression

3.5.1.GG] [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[244][245].
- 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[244][245].

7J) Probable Mechanism: additive effects on QT interval

3.5.1.GHJ Telaprevir

1J) Interaction Effect: increased trazodone plasma concentrations

2J) Summary: Coadministration of trazodone, a CYP3A4 substrate[19] and telaprevir, a CYP3A4 inhibitor, may result in increased plasma concentrations of trazodone. This may lead to increased trazodone adverse effects (eg, nausea, dizziness, hypotension, syncope). Therefore, exercise caution and consider a lower trazodone dose [93].

3J) Severity: moderate

4J) Onset: unspecified

5J) Substantiation: theoretical

6J) Clinical Management: Concurrent administration of telaprevir and trazodone may increase trazodone plasma concentrations and increase risk for trazodone adverse effects (eg, nausea, dizziness, hypotension, syncope). Therefore, exercise caution and consider a lower trazodone dose[93].

7J) Probable Mechanism: inhibition of CYP3A4-mediated metabolism of trazodone

3.5.1.GI Telithromycin

1J) Interaction Effect: an increased risk of QT interval prolongation and increased trazodone plasma concentrations

2J) Summary: Both telithromycin and trazodone have been associated with QT interval prolongation and postmarketing cases of torsade de pointes. The concomitant use of trazodone (a CYP3A4 substrate) [95] with telithromycin (a strong CYP3A4 inhibitor) [173] may result in increased trazodone plasma concentrations and risk of additive QT interval prolongation and serious cardiac events, including torsade de pointes. If concomitant therapy is required, consider a dose reduction of trazodone [95] and monitor carefully for QT interval prolongation.

3J) Severity: major

4J) Onset: unspecified

5J) Substantiation: theoretical

6J) Clinical Management: The concomitant use of trazodone with other drugs that prolong the QT interval and inhibit CYP3A4, such as telithromycin[173], may result in increased trazodone plasma concentrations and additive effects on QT interval prolongation and risk of torsade de pointes. If coadministration is required, consider a dose reduction of trazodone [95] and monitor for QT interval prolongation.

7J) Probable Mechanism: additive effects on QT interval prolongation; inhibition of CYP3A4-mediated trazodone metabolism by telithromycin

3.5.1.GJ Terfenadine

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

2J) 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[197].

3J) Severity: contraindicated

4J) Onset: unspecified

5J) Substantiation: theoretical

6J) 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[197].

7J) Probable Mechanism: additive QT interval effects

3.5.1.GK] Tetrabenazine

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

2J) Summary: Concomitant use of tetrabenazine with other drugs that prolong the QT interval, such as [trazodone](#)[95], should be avoided as both drugs prolong the QT interval and may increase the risk for serious cardiac events, including [torsade de pointes](#) [281]. If concomitant therapy is required, monitor carefully for QT interval prolongation.

3J) Severity: major

4J) Onset: unspecified

5J) Substantiation: theoretical

6J) Clinical Management: Avoid concomitant use of tetrabenazine with other drugs that prolong the QT interval, such as [trazodone](#)[95], as this may result in additive effects on QT interval prolongation and an increased risk of serious cardiac events, including [torsade de pointes](#) [281]. If concomitant therapy is required, monitor ECG carefully for QT interval prolongation.

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

3.5.1.GL] Thiethylperazine

1J) Interaction Effect: hypotension

2J) Summary: Concomitant administration of [trazodone](#) with [chlorpromazine](#) or [trifluoperazine](#) resulted in additive hypotensive effects in two case reports. Withdrawal of [trazodone](#) resulted in resolution of the hypotension[100].

3J) Severity: moderate

4J) Onset: delayed

5J) Substantiation: theoretical

6J) Clinical Management: Monitor blood pressure, particularly in patients who might be sensitive to this effect. Advise patient to rise slowly from laying or sitting position.

7J) Probable Mechanism: additive hypotensive effects

3.5.1.GM] Thioridazine

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

2J) 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](#)[116].

3J) Severity: contraindicated

4J) Onset: unspecified

5J) Substantiation: theoretical

6J) 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](#)[116].

7J) Probable Mechanism: additive QT interval effects

3.5.1.GN] Tipranavir

1J) Interaction Effect: increased plasma concentrations of [trazodone](#) and increased risk of [trazodone](#) adverse effects (nausea, dizziness, hypotension, syncope)

2J) Summary: Coadministration of [tipranavir](#)/[ritonavir](#) with [trazodone](#) may inhibit the CYP3A4-mediated [trazodone](#) metabolism, causing increased [trazodone](#) plasma concentrations. Although the drug interaction

between [tipranavir](#) and [trazodone](#) has not been studied, adverse effects such as nausea, dizziness, hypotension and syncope have occurred following coadministration of [trazodone](#) and [ritonavir](#). Therefore, caution is advised when [tipranavir/ritonavir](#) and [trazodone](#) are administered concomitantly. Consider using a lower dose of [trazodone](#)[108].

3) Severity: moderate

4) Onset: unspecified

5) Substantiation: probable

6) Clinical Management: Concurrent administration of [tipranavir/ritonavir](#) and [trazodone](#) may increase [trazodone](#) plasma concentrations. Use caution when these agents are coadministered and consider using a lower [trazodone](#) dose[108]. Monitor patients for signs of increased [trazodone](#) adverse effects (nausea, dizziness, hypotension, syncope).

7) Probable Mechanism: inhibition of CYP3A4-mediated [trazodone](#) metabolism

8) Literature Reports

a) Coadministration of [ritonavir](#) and [trazodone](#) produces a significant increase in peak plasma [trazodone](#) concentration (C_{max}), prolongation of elimination half-life, increase in total AUC, and reduction in oral clearance. Ten subjects participated in a randomized, four-way crossover design study with 7 days elapsing between treatments. The four treatment conditions were: Treatment A: placebo to match [trazodone](#), plus placebo to match [ritonavir](#); Treatment B: [trazodone](#) 50 mg plus [ritonavir](#) placebo; Treatment C: placebo to match [trazodone](#) plus [ritonavir](#) 200 mg X 4 doses; Treatment D: [trazodone](#) 50 mg plus [ritonavir](#) 200 mg X 4 doses. [Ritonavir](#) and [trazodone](#) coadministration produced a significant increase in [trazodone](#) C_{max} with the mean +/- SE value being 842 +/- 64 ng/mL (treatment B) and 1125 +/- 111 ng/mL (treatment D) (p less than 0.05). The mean +/- SE elimination half-life in treatment B was 6.7 +/- 0.7 h and in treatment D was 14.9 +/- 3.9 (p less than 0.05). The mean +/- SE total AUC for treatment B was 5.86 +/- 0.83 mcg/mL X h and for treatment D was 13.88 +/- 2.89 (p less than 0.01). The mean +/- SE apparent oral clearance (mL/min) for treatment B was 155 +/- 23 and for treatment D was 75 +/- 12 (p less than 0.001). Sedation, [impairment of psychomotor](#) performance (the DSST), and a quantitatively small increase in beta amplitude on the EEG caused by [trazodone](#) were all enhanced by coadministration of [ritonavir](#) [109].

3.5.1.GO] [Toremifene](#)

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

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 other QT interval-prolonging drugs, such as [trazodone](#)[95], should be avoided. If treatment with [trazodone](#) is warranted, interrupt [toremifene](#) therapy; however, if coadministration of [trazodone](#) with [toremifene](#) is required, monitor for QT prolongation. Consider [monitoring ECG](#) at baseline and during treatment as indicated in patients at increased risk of QT prolongation [275].

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Concomitant use of [toremifene](#) with other drugs that prolong the QT interval, such as [trazodone](#)[95], may result in additive effects on the QT interval and should be avoided. If treatment with [trazodone](#) is required, interruption of [toremifene](#) is recommended; however, if concomitant use is necessary, closely monitor for QT prolongation [275].

7) Probable Mechanism: additive effects on QT interval prolongation

3.5.1.GP] [Tramadol](#)

- 1) Interaction Effect: increased risk of [serotonin syndrome](#) ([hypertension](#), [hyperthermia](#), myoclonus, mental status changes)
- 2) Summary: Both [tramadol](#) and [trazodone](#) 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](#)[274][95]. Careful monitoring for signs and symptoms of [serotonin syndrome](#) is warranted, if [tramadol](#) and [trazodone](#) are used concurrently, particularly during treatment initiation and dose increases [274]. 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 [96].
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Use caution with concomitant administration of [tramadol](#) and [trazodone](#), as this may result in additive serotonergic effects and may increase the risk of [serotonin syndrome](#)[274][95]. If coadministration is required, careful monitoring is warranted, particularly during treatment initiation and dose increases [274].
- 7) Probable Mechanism: additive serotonergic effect

3.5.1.GQ| [Tranlycypromine](#)

- 1) Interaction Effect: an increased risk of [serotonin syndrome](#) ([hypertension](#), [hyperthermia](#), myoclonus, mental status changes)
- 2) Summary: [Trazodone](#) exerts inhibitory effects on serotonin reuptake. [Serotonin syndrome](#) has been reported with the use of [trazodone](#) and the risk is increased with concurrent administration or overlapping therapy with an MAOI intended to treat psychiatric disorders. [Serotonin syndrome](#) is a hyperserotonergic state characterized by symptoms such as agitation and restlessness, myoclonus, changes in mental status, hyperreflexia, diaphoresis, shivering, and tremor. Serious, even fatal, reactions have been reported with concomitant use of serotonergic drugs and MAOIs. A minimum of 14 days should elapse after discontinuing an MAOI intended to treat psychiatric disorders before initiating therapy with [trazodone](#), and a minimum of 14 days should elapse after discontinuing [trazodone](#) before initiating therapy with an MAOI intended to treat psychiatric disorders[23].
- 3) Severity: contraindicated
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Concurrent use of [trazodone](#) and an MAOI intended to treat psychiatric disorders is contraindicated. Wait at least 14 days after discontinuing an MAOI before initiating [trazodone](#). Wait at least 14 days after discontinuing [trazodone](#) before initiating therapy with an MAOI intended to treat psychiatric disorders[23].
- 7) Probable Mechanism: additive serotonergic effect

3.5.1.GR| [Trifluoperazine](#)

- 1) Interaction Effect: hypotension
- 2) Summary: Concomitant administration of [trazodone](#) with [chlorpromazine](#) or [trifluoperazine](#) resulted in additive hypotensive effects in two case reports. Withdrawal of [trazodone](#) resulted in resolution of the hypotension[105].
- 3) Severity: moderate

- 4) Onset: delayed
- 5) Substantiation: probable
- 6) Clinical Management: Monitor blood pressure, particularly in patients who might be sensitive to this effect. Advise patient to rise slowly from laying or sitting position.
- 7) Probable Mechanism: additive hypotensive effects

3.5.1.GS] Triflupromazine

- 1) Interaction Effect: hypotension
- 2) Summary: Concomitant administration of [trazodone](#) with [chlorpromazine](#) or [trifluoperazine](#) resulted in additive hypotensive effects in two case reports. Withdrawal of [trazodone](#) resulted in resolution of the hypotension[107].
- 3) Severity: moderate
- 4) Onset: delayed
- 5) Substantiation: theoretical
- 6) Clinical Management: Monitor blood pressure, particularly in patients who might be sensitive to this effect. Advise patient to rise slowly from laying or sitting position.
- 7) Probable Mechanism: additive hypotensive effects

3.5.1.GT] Trimipramine

- 1) Interaction Effect: an increased risk of QT interval prolongation
- 2) Summary: QT/QTc interval prolongation and postmarketing cases of [torsade de pointes](#) have been reported with [trazodone](#). The concomitant use of [trazodone](#) with other drugs that may prolong the QT interval, such as [trimipramine](#), may result in additive effects on QT interval prolongation and an increased risk of serious [ventricular arrhythmias](#), including [torsade de pointes](#)[95]. If coadministration of [trazodone](#) and [trimipramine](#) is required, monitoring for QT interval prolongation may be warranted.
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: The concomitant use of [trazodone](#) with other drugs that may prolong the QT interval, such as [trimipramine](#), may result in additive effects on QT interval prolongation and risk of [torsade de pointes](#)[95]. If coadministration is required, monitoring for QT interval prolongation may be warranted.
- 7) Probable Mechanism: additive effects on QT interval prolongation

3.5.1.GU] Triptorelin

- 1) Interaction Effect: increased risk of QT-interval prolongation
- 2) Summary: Use caution with coadministration of gonadotropin-releasing hormone (GnRH) agonists with QT-interval prolonging drugs. Androgen deprivation caused by GnRH agonists may prolong the QT interval and cause additive effects when administered with QT-interval prolonging drugs[289][290][291]. 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[289][290][291].
- 7) Probable Mechanism: additive effects on the QT interval

3.5.1.GV] Tryptophan

- 1) Interaction Effect: increased risk of [serotonin syndrome](#) ([hypertension](#), [hyperthermia](#), myoclonus, mental status changes)
- 2) Summary: Both [trazodone](#) and tryptophan affect the serotonergic neurotransmitter systems. Concomitant use is not recommended due to the additive effects and the potential for increased risk of [serotonin syndrome](#)[95]. Monitoring for signs and symptoms of [serotonin syndrome](#) may be warranted if [trazodone](#) and tryptophan are used 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. If [serotonin syndrome](#) develops, discontinue the offending agents and provide supportive care and other therapy as necessary [96].
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Concomitant administration of [trazodone](#) and tryptophan is not recommended, as this may result in additive serotonergic effects and may increase the risk of [serotonin syndrome](#)[95]. If coadministration is required, appropriate monitoring may be warranted.
- 7) Probable Mechanism: additive serotonergic effect

3.5.1.GW] Vandetanib

- 1) Interaction Effect: increased risk of QT interval prolongation
- 2) Summary: QT/QTc interval prolongation and postmarketing cases of [torsade de pointes](#) have been reported with [trazodone](#)[95]. Due to the potential for additive effects on QT interval prolongation and an increased risk of [cardiotoxicity](#) (QT prolongation, [torsade de pointes](#), [cardiac arrest](#)), the concomitant use of [trazodone](#) with vandetanib should be avoided. If coadministration of [trazodone](#) and vandetanib is required, more frequent [monitoring of ECG](#) is recommended [279].
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: The concomitant use of vandetanib with other drugs that may prolong the QT interval, such as [trazodone](#)[95] should be avoided as coadministration may result in additive effects on QT interval prolongation. If concomitant use of [trazodone](#) with vandetanib is required, more frequent [monitoring of ECG](#) is recommended [279].
- 7) Probable Mechanism: additive effects on QT interval

3.5.1.GX] Vardenafil

- 1) Interaction Effect: an increased risk of QT interval prolongation
- 2) Summary: QT/QTc interval prolongation and postmarketing cases of [torsade de pointes](#) have been reported with [trazodone](#). The concomitant use of [trazodone](#) with other drugs that prolong the QT interval, such as [vardenafil](#)[276], may result in additive effects on QT interval prolongation and an increased risk of serious [ventricular arrhythmias](#), including [torsade de pointes](#) [95]. If coadministration is required, monitoring for QT interval prolongation may be warranted.
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical

6) Clinical Management: The concomitant use of [trazodone](#) with other drugs that may prolong the QT interval, such as [vardenafil](#)[276], may result in additive effects on QT interval prolongation and risk of [torsade de pointes](#) [95]. If coadministration is required, monitoring for QT interval prolongation may be warranted.

7) Probable Mechanism: additive effects on QT interval prolongation

3.5.1.GY] [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](#)[112].

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](#)[112].

7) Probable Mechanism: additive effects on QT interval

3.5.1.GZ] [Venlafaxine](#)

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](#)[97]. 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](#) [94][95]. If [trazodone](#) and [venlafaxine](#) are used concomitantly, monitor closely for symptoms of [serotonin syndrome](#), particularly during treatment initiation and dose increases [94][96]. Symptoms of [serotonin syndrome](#) include neuromuscular abnormalities (including hyperreflexia, tremor, muscle rigidity, clonus, peripheral hypertonicity, and shivering), autonomic hyperactivity (including [tachycardia](#), mydriasis, diaphoresis, the presence of bowel sounds, and diarrhea), and mental status changes (including agitation and [delirium](#)). [Serotonin syndrome](#) can be life-threatening. If [serotonin syndrome](#) develops, discontinue the offending agents and provide supportive care and other therapy as necessary [96].

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[94], 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 [95][94][96]

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 [97].

3.5.1.HA| 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](#)[117]. 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 [96]. 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 [117].

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[117].

7) Probable Mechanism: additive serotonergic effects

3.5.1.HB| 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[135]. 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[135]. If concomitant use is required, consider a baseline ECG and on-treatment monitoring.

7) Probable Mechanism: additive QT interval effects

3.5.1.HC| Voriconazole

1) Interaction Effect: an increased risk of QT interval prolongation and increased [trazodone](#) plasma concentrations

2) Summary: The concomitant use of [trazodone](#) (a CYP3A4 substrate)[95] with [voriconazole](#) (a CYP3A4 inhibitor) [273] may result in increased [trazodone](#) plasma concentrations and risk of additive QT interval prolongation and serious cardiac events, including [torsade de pointes](#). If concomitant therapy is required, consider a dose reduction of [trazodone](#) [95] and monitor carefully for QT interval prolongation.

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: The concomitant use of [trazodone](#) with other drugs that prolong the QT interval and inhibit CYP3A4, such as [voriconazole](#)[273], may result in increased [trazodone](#) plasma concentrations and additive effects on QT interval prolongation and risk of [torsade de pointes](#). If coadministration is required, consider a dose reduction of [trazodone](#) [95] and monitor for QT interval prolongation.

7) Probable Mechanism: additive effects on QT interval prolongation and inhibition of CYP3A4-mediated [trazodone](#) metabolism by [voriconazole](#)

3.5.1.HD] 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[305].

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[305].

7) Probable Mechanism: additive serotonergic effects

3.5.1.HE] 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[224][225]; coadministration with another serotonergic drug may increase the risk for [serotonin syndrome](#).

3) Severity: contraindicated

4) Onset: unspecified

5) Substantiation: theoretical

6J) Clinical Management: The concomitant use of ziprasidone with other drugs that prolong the QT interval is contraindicated because coadministration may result in additive risk for QT-interval prolongation. Serotonin syndrome has also been reported with ziprasidone monotherapy and in combination with other serotonergic drugs[224][225]; coadministration with another serotonergic drug may increase the risk for serotonin syndrome.

7J) Probable Mechanism: additive QT interval effects; additive serotonergic effect

3.5.1.HF] Zolmitriptan

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

2J) Summary: Both trazodone and zolmitriptan 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[95][209]. Careful monitoring for signs and symptoms of serotonin syndrome is warranted if trazodone and zolmitriptan are used concurrently, particularly during treatment initiation and dose increases [95]. 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 [96].

3J) Severity: major

4J) Onset: unspecified

5J) Substantiation: theoretical

6J) Clinical Management: Use caution with concomitant administration of trazodone and zolmitriptan, as this may result in additive serotonergic effects and may increase the risk of serotonin syndrome[95][209]. If coadministration is required, careful observation is warranted, particularly during treatment initiation and dose increases [95].

7J) Probable Mechanism: additive serotonergic effect

3.5.1.HG] Zuclopenthixol

1J) Interaction Effect: increased risk of QT prolongation

2J) 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[250][251].

3J) Severity: major

4J) Onset: unspecified

5J) Substantiation: theoretical

6J) 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[250][251].

7J) Probable Mechanism: additive QT prolongation

3.5.2] Drug-Food Combinations

3.5.2.A] Food

- 1]) Interaction Effect: increased time to peak levels
- 2]) Summary: Although the rate of absorption of [trazodone](#) is reduced when there is food in the gut, there may be a slight increase in the total amount of drug absorbed. The maximum concentration is reduced by up to 30%, and the time to reach peak levels is prolonged[312][313][314]. [Trazodone](#) should be taken shortly after a meal or light snack [315].
- 3]) Severity: minor
- 4]) Onset: rapid
- 5]) Substantiation: probable
- 6]) Clinical Management: [Trazodone](#) should be taken shortly after a meal or light snack.
- 7]) Probable Mechanism: delayed absorption

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] [Trazodone](#) Hydrochloride

1]) Therapeutic

a]) Physical Findings

- 1]) Improvement in signs and symptoms of depression is indicative of efficacy.

2]) Toxic

a]) Physical Findings

- 1]) Monitor for clinical worsening, suicidality, or unusual changes in behavior, particularly during the initial few months of therapy or at times of dose changes, either increases or decreases. Such monitoring should include daily observation by families and caregivers [19][142].
- 2]) Assess for irregular heart rates, particularly among patients with cardiovascular disorders and/or risk factors associated with QTc prolongation [19][142].

4.2] Patient Instructions

A] [Trazodone](#) (By mouth)

[Trazodone](#)

Treats depression.

When This Medicine Should Not Be Used:

This medicine is not right for everyone. Do not use it if you had an [allergic reaction](#) to [trazodone](#).

How to Use This Medicine:

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.

Regular tablet: Take it with or shortly after a meal or light snack.

Extended-release tablet: Take it at the same time each day, preferably at bedtime, without food.

The tablet can be swallowed whole, or you may break the tablet in half along the score line. Do not break the tablet unless your doctor tells you to. Do not crush or chew the tablet.

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 [trazodone](#) if you currently take an MAO inhibitor (MAOI) or have used an MAOI in the past 14 days.

Tell your doctor if you also use any of the following:

[Carbamazepine](#), [digoxin](#), [phenytoin](#), [indinavir](#), [ritonavir](#), [buspirone](#), [fentanyl](#), [lithium](#), tryptophan, St John's wort, [tramadol](#)

Medicine to treat a [fungal infection](#) (such as [itraconazole](#), [ketoconazole](#)), a diuretic (water pill), blood pressure medicine, an NSAID pain or [arthritis](#) medicine (such as [aspirin](#), [celecoxib](#), [diclofenac](#), [ibuprofen](#), [naproxen](#)), a blood thinner (such as [warfarin](#)), other medicine for depression, or triptan medicine to treat migraine headaches

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, bleeding problems, [glaucoma](#), [heart disease](#), heart rhythm problems, or low blood pressure. Tell your doctor if you recently had a [heart attack](#).

For some children, teenagers, and young adults, this medicine may increase mental or emotional problems. This may lead to thoughts of suicide and violence. Talk with your doctor right away if you have any thoughts or behavior changes that concern you. Tell your doctor if you or anyone in your family has a history of [bipolar disorder](#) or suicide attempts.

This medicine may cause the following problems:

[Serotonin syndrome](#) (more likely when used with certain other medicines)

Heart rhythm problems (QT prolongation)

Low sodium levels

Higher risk of bleeding

Do not stop using this medicine suddenly. Your doctor will need to slowly decrease your dose before you stop it completely.

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. Stand or sit up slowly if you are dizzy.

Tell any doctor or dentist who treats you that you are using this medicine. You may need to stop using this medicine several days before you have surgery or medical tests.

Your doctor will check your progress and the effects of this medicine at regular visits. Keep all appointments.

Keep all medicine out of the reach of children. Never share your medicine with anyone.

Possible Side Effects While Using This Medicine:

Call your doctor right away if you notice any of these side effects:

Allergic reaction: Itching or hives, swelling in your face or hands, swelling or tingling in your mouth or throat, chest tightness, trouble breathing

Anxiety, restlessness, fever, sweating, muscle spasms, nausea, vomiting, diarrhea, seeing or hearing things that are not there

Confusion, weakness, muscle twitching

Fast, pounding, or uneven heartbeat

Lightheadedness, dizziness, fainting

Painful, prolonged erection of your penis

Sudden increase in energy, feeling irritable, trouble sleeping

Thoughts of hurting yourself or others, unusual behavior

Unusual bleeding or bruising

If you notice these less serious side effects, talk with your doctor:

Constipation, mild nausea

Dry mouth

Eye pain, vision changes, seeing halos around lights

Headache

Sleepiness or unusual drowsiness

If you notice other side effects that you think are caused by this medicine, tell your doctor.

4.3] Place In Therapy

A) Trazodone Hydrochloride

1) Trazodone is indicated for the treatment of depression with or without prominent anxiety [19], including major depressive disorder in adults [19].

2) In most clinical trials, trazodone has been shown to be more effective than placebo in treating major depression; however, its effectiveness relative to other classes of antidepressants remains unclear [338]. In mild typical or endogenous depression, trazodone has been shown to be equally effective as standard tricyclic antidepressants [339][340][341][342][343], but in moderate-to-severe endogenous depression, patients seem to have difficulty tolerating adequate doses. Trazodone possesses the unique property of sedation without anticholinergic effects and in patients with initial insomnia, the sedating effect of trazodone may prove to be beneficial [338].

3) The recent introduction of an extended-release tablet will allow once-daily dosing [19]. Other advantageous characteristics include successful treatment of anxiety disorders [344][345] and a comparatively safe adverse effects profile following overdoses [19][19]. Disadvantages of trazodone include a higher incidence of priapism, orthostatic hypotension, and reports of cardiac arrhythmias during therapy [19][19].

4.4] Mechanism of Action / Pharmacology

A) Trazodone Hydrochloride

1) Mechanism of Action

a) Trazodone, which was first synthesized in 1966, represents a different class of antidepressants, the triazolopyridines. Structurally, it does not bear any similarity to tricyclic antidepressants, tetracyclic antidepressants, or MAO inhibitors [332][333]. The mechanism of antidepressant action is not fully understood, but suspected to be related to its potentiation of serotonergic activity in the CNS. Preclinical studies have shown that trazodone selectively inhibits neuronal reuptake of serotonin and acts as an antagonist at 5-HT-2A/2C serotonin receptors [19]. At low doses, trazodone appears to act as a serotonin antagonist and at higher doses as an agonist [332][333].

b) Unlike other antidepressants, trazodone does not potentiate catecholamines or inhibit monoamine oxidase. It does appear to have a sedative effect and slight muscle relaxant properties, but no anticonvulsant activity [334]. Trazodone does not have any significant effect on prolactin release (Roccatagliato et al, 1979)[335]. Trazodone possesses alpha 1-adrenergic receptor antagonistic property, which may attribute to postural hypotension [19].

c) Trazodone appears to be equally effective in bipolar and unipolar depression. Its main benefit in antidepressant therapy is its short onset of action and low incidence of anticholinergic and cardiovascular effects. However, some studies have indicated the onset of action of trazodone is similar to that of amitriptyline. Some data has suggested an anxiolytic effect of trazodone which may be less than or equal to other benzodiazepines; however, sufficient data have not been provided to determine that these effects are related directly to properties of the drug or secondary to improvement in existing depression [324][326][336].

4.5] Therapeutic Uses

4.5.1] FDA Uses

4.5.1.A] Trazodone Hydrochloride

4.5.1.A.1] Major depressive disorder

FDA Labeled Indication

a) Overview

FDA Approval: Adult, yes; Pediatric, no

Efficacy: Adult, Effective

Recommendation: Adult, Class IIb

Strength of Evidence: Adult, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:

Evidence (Adult)

Extended-release trazodone significantly improved symptoms of depression vs placebo at the end of the 6-week treatment interval in a randomized, double-blind trial (N=412). A significant benefit was observed as early as the first week of therapy and persisted throughout the study [5]. When extended-release and immediate-release trazodone were compared in

a double-blind study (N=347), no significant difference in symptoms of depression were observed after 6 weeks [6].

[Trazodone](#) was associated with greater improvements in depression symptoms compared with [imipramine](#) in a year-long study (N=79) [7], in a double blind, controlled study of hospitalized adults (N=45) treated for 4 weeks [8], and in a double-blind study for up to 4-weeks (N=28) [9].

Evidence (Geriatric)

In a double-blind study of geriatric patients (N=60), [trazodone](#) was associated with similar reductions in depressive symptoms at 4-weeks vs [imipramine](#); both treatment groups had significant improvements compared to placebo, and [trazodone](#) was related with fewer side effects [10].

4.5.2] Non FDA Uses

4.5.2.A] [Trazodone](#)

4.5.2.A.1] [Electroconvulsive therapy](#)

See Drug Consult reference: Drugs for Seizure Prolongation in ECT

4.5.2.B] [Trazodone Hydrochloride](#)

4.5.2.B.1] [Dementia](#)

See Drug Consult reference: Behavioral and Psychological Symptoms of [Dementia](#)

4.5.2.B.2] [Erectile dysfunction](#)

a) Overview

FDA Approval: Adult, no; [Pediatric, no](#)

Efficacy: Adult, Ineffective

Recommendation: Adult, Class III

Strength of Evidence: Adult, Category B

See Drug Consult reference: [RECOMMENDATION AND EVIDENCE RATINGS](#)

b) Summary:

Evidence

No significant difference in efficacy for [erectile dysfunction](#) was shown with [trazodone](#) vs placebo in 3 separate randomized, double blind trials (N=154) with durations of 3 to 4 weeks [11][12][13].

4.5.2.B.3] [Insomnia](#)

a) Overview

FDA Approval: Adult, no; [Pediatric, no](#)

Efficacy: Adult, Evidence favors efficacy

Recommendation: Adult, Class IIb

Strength of Evidence: Adult, Category B

See Drug Consult reference: [RECOMMENDATION AND EVIDENCE RATINGS](#)

b) Summary:

Evidence

In a randomized, double-blind trial of non-depressed patients with insomnia (N=278), [trazodone](#) significantly reduced sleep latency compared with placebo during the first week; however, there was no significant difference at week 2. [Zolpidem](#) produced significantly shorter sleep latencies vs placebo and [trazodone](#) groups during both weeks of the study [15]. [Trazodone](#) was associated with an improvement in antidepressant associated insomnia in a double blind, placebo controlled, crossover study (N=13) [16] and improved objective but not subjective sleep parameters in a double blind, crossover study in women with SSRI associated insomnia (N=12) [14].

4.5.2.B.4] Migraine, Pediatric; Prophylaxis

See Drug Consult reference: [Migraine -- Recommendations for Treatment in Children and Adolescents](#)

4.6] Comparative Efficacy / Evaluation With Other Therapies

4.6.A] Amitriptyline

4.6.A.1] Depression

a) SUMMARY: Many comparative studies have reported that [trazodone](#) is as effective as [amitriptyline](#) in the treatment of [endogenous depression](#) [339][340][341][342].

b) In a study of 40 depressed patients (20 agitated, 20 retarded), patients received [amitriptyline](#) 50 milligrams (mg) three times a day or [trazodone](#) 50 mg three times a day after a 5- to 7-day placebo washout period [352]. The agitated, depressed patients who were treated with [amitriptyline](#) and the retarded, depressed patients who were treated with [trazodone](#) were significantly more improved than the agitated, depressed patients on [trazodone](#) and the retarded, depressed patients on [amitriptyline](#). Based on multivariate analysis of the clinical global impression, [amitriptyline](#) achieved better results in agitated depressed patients and [trazodone](#) was more effective in retarded depressed patients.

c) The efficacy of [trazodone](#) was compared with [amitriptyline](#) and placebo in the treatment of [unipolar depression](#) in 202 outpatients [339]. Patients were randomly assigned [trazodone](#) 50 milligrams (mg), [amitriptyline](#) 25 mg, or lactose placebo. Initial dose of all medications was 4 capsules daily for 7 days followed by adjustment to the maximum of eight capsules daily. Both drugs proved more effective than placebo with clinical efficacy of each agent being similar. The incidence of anticholinergic toxicity was lower in trazodone-treated patients. This study suggests that [trazodone](#) 150 to 400 mg daily is as effective as [amitriptyline](#) 75 to 200 mg in treating depression in outpatients, with [trazodone](#) producing less anticholinergic toxicity.

d) No significant difference between [trazodone](#) 150 to 300 milligrams (mg) per day and [amitriptyline](#) 75 to 150 mg/day in antidepressant effect or onset was seen in a study of 50 patients with [endogenous depression](#) [353]. [Trazodone](#) demonstrated an early superior anxiolytic effect. [Amitriptyline](#) caused dry mouth more commonly; other side effects were comparable.

4.6.A.2] Impaired cognition

a) The effects of [trazodone](#) 100 milligrams (mg), [amitriptyline](#) 50 mg, and placebo were compared in 15 healthy, geriatric patients in a double-blind, cross-over study [351]. Laboratory tests included tracking multiple stimuli to perform simultaneous tasks (DA), rapidly coordinating visual input and motor output (CTT), processing information gathered in short-term memory (VBM), and repetitively performing a task (vigilance). [Amitriptyline](#) impaired DA, CTT, and vigilance, while [trazodone](#) impaired only CTT. The authors concluded that [trazodone](#) caused less impairment of the central nervous system than did [amitriptyline](#).

4.6.A.3] Rheumatoid arthritis

a) [Amitriptyline](#) 1 milligram/kilogram (mg/kg) per day for 3 days, followed by 1.5 mg/kg/day thereafter, was reported superior to both [desipramine](#) 1 mg/kg/day for 3 days, followed by 1.5 mg/kg/day thereafter, and [trazodone](#) 1.5 mg/kg/day for 3 days, followed by 3 mg/kg/day thereafter, in the treatment of pain in both depressed and nondepressed patients with [rheumatoid arthritis](#) [354]. Although all 3 drug regimens produced significant decreases in pain relative to baseline, only [amitriptyline](#) was significantly better than placebo; [amitriptyline](#) was associated with a significant reduction in the number of painful and tender joints.

4.6.B] Chlordiazepoxide

4.6.B.1] Anxiety

a) No significant difference in improvement of anxiety in patients treated with [trazodone](#) or [chlordiazepoxide](#) has been reported [357]. A double-blind study compared [trazodone](#) 25 to 50 mg/day and [chlordiazepoxide](#) for a 4-week period using the Hamilton Anxiety Rating Scale. Eleven patients from each treatment group were very much improved. Ten [trazodone](#) and 13 [chlordiazepoxide](#) patients were much improved and 10 [trazodone](#) and 11 [chlordiazepoxide](#) patients were minimally improved or worse. Three patients were not evaluable. For both treatment groups drowsiness was the most frequent adverse effect with 22 patients experiencing the effect.

4.6.C] Clorazepate

4.6.C.1] Adjustment disorder - Cancer

a) SUMMARY: [TRAZODONE](#) may have equal or greater efficacy compared with [CLORAZEPATE](#) for the treatment of adjustment disorders in [breast-cancer](#) patients; [trazodone](#) and [clorazepate](#) had similar safety and tolerability.

b) A small, double-blind pilot study (n=23; efficacy analysis=18) found that a 28-day course of oral [TRAZODONE](#) had equal or greater benefit compared with [CLORAZEPATE](#) for [breast-cancer](#) patients with adjustment disorders (DSM-III-R) accompanied by anxiety or depressed mood and/or mixed disturbance of emotion and conduct [358]. Included were women with a 14 or greater score on the French Hospital Anxiety and Depression Scale (HADS). Enrollees were randomized to oral [trazodone](#) 50 milligrams (mg)/day (n=13) or oral [clorazepate](#) 10 mg/day (n=10), with upward titration of both drugs over 5 days. [Trazodone](#) mean daily dose was 111.5 mg, and [clorazepate](#), mean 17.5 mg. After 28 days, investigator ratings on the Clinical Global Impression (CGI) scale showed that 90.9% of the [trazodone](#) group (10 of 11) and 57.1% of the [clorazepate](#) group (4 of 7) were 'very much improved', 'improved', or 'minimally improved' (p=0.14). Improvement on the Global Severity Index was more pronounced in trazodone-treated patients (-0.68) compared with clorazepate-treated patients (-0.34) (p=0.25). Four adverse events rated as severe occurred in the [trazodone](#) and 5 severe adverse events occurred in the [clorazepate](#) group. One patient receiving [trazodone](#) withdrew due to adverse effects.

4.6.C.2] Adjustment disorder - HIV infection

a) SUMMARY: **TRAZODONE** may be more efficacious than **CLORAZEPATE** for the treatment of adjustment disorders in patients with HIV; **trazodone** appeared to have greater tolerability.

b) A small, double-blind trial (n=21) found a 28-day course of **TRAZODONE** to provide more successful treatment than **CLORAZEPATE** for HIV-positive patients with adjustment disorders (DSM-III-R) accompanied by anxiety or depressed mood and/or mixed disturbance of emotion and conduct. Included were patients with a 14 or greater score on the French Hospital Anxiety and Depression Scale (HADS). Enrollees were randomized to oral **trazodone** 50 milligrams/day (mg/day) (n=10) or oral **clorazepate** 10 mg/day (n=11), with upward titration of both drugs over 5 days. After 28 days, investigator ratings on the Clinical Global Impression (CGI) scale showed that 80% of the **trazodone** group and 64% of the **clorazepate** group were 'very much improved', 'improved', or 'minimally improved' (p=0.37). Improvements appeared to be more marked in the **trazodone** group for depressive symptoms (-0.34 versus -0.09), but slightly more pronounced in the **clorazepate** group for anxiety symptoms (-0.32 versus -0.34). At least 1 adverse event occurred in 8 clorazepate-treated patients and 6 trazodone-treated patients. After 2 weeks of treatment, doses were reduced in 1 patient treated with **trazodone** and 2 treated with **clorazepate** due to adverse effects. More adverse events and a higher number of severe adverse events were associated with **clorazepate** treatment. One patient in each group withdrew due to adverse effects and 1 in each group due to lack of efficacy [359].

4.6.D] Desipramine

4.6.D.1] Depression

a) A double-blind study of 30 patients with endogenous, endoreactive, reactive and involutive depression compared the effects of **trazodone** 200 to 400 mg/day to **desipramine**. After 3 days of therapy there were similar results for both drugs for the parameters of depression, suicide, insomnia, work interest and agitation as measured by the Hamilton Rating scale. Trazodone-treated patients had greater relief of anxiety than did **desipramine** treated patients [356].

4.6.E] Dothiepin

4.6.E.1] Depression

a) In a 6-week, double-blind study, lofepramine and dothiepin had similar efficacy in the treatment of depression in elderly patients (range 65 to 88 years); lofepramine had an earlier onset of effect and lower incidence of dry mouth, blurred vision, and drowsiness [355]. Eight subjects in the dothiepin-treated group and 6 in the lofepramine-treated group did not complete the trial, leaving 24 patients in each group. Many of the participants were receiving other medications, including phenothiazines, benzodiazepines, and chlormethiazole, throughout the trial. Dothiepin 50 mg/d or lofepramine 70 mg/d were given for 1 week, then doses were doubled for the remaining 5 weeks. As measured on the Montgomery-Asberg Depression Scale (MADRS) at weeks 1, 3, and 6, significant improvement occurred in both treatment groups. There were not significant differences between groups. Compared with dothiepin-treated patients, the lofepramine-treated patients had significantly less dry mouth and day-time drowsiness; only 1 patient in each group withdrew from the study because of adverse effects.

b) No significant differences in efficacy or type of adverse effects were seen when dothiepin was compared with **trazodone** in 196 patients with mixed anxiety/depression [360]. **Trazodone** may be preferable to dothiepin because of lesser severity of side effects. In a 6-week, double-blind, parallel group study, either **trazodone** 150 mg (n=97) or dothiepin 75 mg (n=99) were administered. Measures of efficacy included the 17-item and 21-item Hamilton Depression Rating Scales (HDRS), the Hamilton Anxiety Rating Scale

(HARS), and the investigator's judgement of global severity and improvement. Significant improvement in depression scores ($P=0.0001$) and anxiety scores ($P=0.0001$) was seen in both groups. Global severity significantly improved in both groups; at week 6, improvement was rated as very much improved for 54 patients (71%) in the [trazodone](#) group and 52 patients (69%) in the dothiepin group. Although types of adverse effects were similar for both groups, the [trazodone](#) group reported a larger proportion of mild symptoms compared with the dothiepin group; at weeks 2, 4, and 6, the [trazodone](#) group reported a lower percentage of symptoms as severe.

c) Dothiepin (75 to 150 mg/d) and [trazodone](#) (150 to 300 mg/d) were equally effective in the treatment of depression in a single-blind, 24-week study of 35 depressed patients [361]. The treatment groups were not matched for severity of depression which varied greatly among the subjects. Twenty-six subjects completed the 6-month trial. Both treatment groups showed significant reduction in Hamilton depression ratings from 4 weeks onward, and there was significant improvement in the Beck self rating scores from the first week onward. There were no significant differences between the 2 groups for either parameter. Drowsiness was the most frequent side effect in the trazodone-treated group, and anticholinergic effects were more common in the dothiepin-treated group.

4.6.F] [Doxepin](#)

4.6.F.1] Depression

a) No significant difference in safety or efficacy was seen in a comparison of [trazodone](#) (mean daily dose during weeks 1, 3, and 6 was 125 milligrams (mg), 221 mg, and 246 mg) with [doxepin](#) (mean daily dose during weeks 1, 3, and 6 was 58 mg, 105 mg, and 127 mg) in 30 outpatients with [major depressive disorder](#) in a 6-week, double-blind, parallel study [362].

b) No significant difference was reported in a double-blind study of 101 patients, on the efficacy of [trazodone](#) and [doxepin](#) in the treatment of depression [363].

4.6.G] [Fluoxetine](#)

4.6.G.1] Depression

a) [Fluoxetine](#) was as effective as [trazodone](#) in the treatment of [major depression](#) in a 6-week, double-blind, outpatient study involving 43 patients [348]. The mean final doses of oral [trazodone](#) and [fluoxetine](#) in the responding patients were 284 and 29 mg daily, respectively. In nonresponders, the corresponding doses were 327 and 33 mg, respectively. HAM-D scores were lower at weeks 1 and 2 with [fluoxetine](#) when compared to [trazodone](#) and sleep was improved to a greater degree with [trazodone](#). Adverse effects occurred to a similar degree with each agent with the exception of weight loss (more frequent with [fluoxetine](#)) and dizziness (more frequent with [trazodone](#)).

b) A six-week, double-blind trial compared [fluoxetine](#) (21 patients) with [trazodone](#) (19 patients) in the treatment of [major depression](#) [349]. Although [trazodone](#) appeared to provide significantly greater improvement in HAM-D and Clinical Global Impressions scores at 3 weeks, the differences were not statistically significant at 4, 5, and 6 weeks. The authors surmise that the early difference may have been due to: an insufficient [fluoxetine](#) dose early in the trial (mean daily doses of [fluoxetine](#) and [trazodone](#) during week 3 were 21 mg and 241 mg, respectively), which was mitigated by larger subsequent increases in [fluoxetine](#) doses compared to [trazodone](#) doses; a slower onset of antidepressant action for [fluoxetine](#), compared to [trazodone](#); or a higher incidence of [depressive illness](#) lasting longer than one year in the [fluoxetine](#) group (67%) than in the [trazodone](#) group (37%, reported incorrectly as 35%). Although the authors cite the statistically significant fluoxetine-associated weight loss seen in this trial (mean 1.98 lb/patient) as a clinically significant advantage for this agent, [trazodone](#) was also associated with weight loss in this study (mean 0.13 lb/patient), and the weight losses exhibited by the treatment groups were not significantly different.

4.6.G.2] Mania

a) In literature reports of drug-induced mania caused by fluoxetine or trazodone, fluoxetine-treated patients manifested symptoms of mania more slowly than trazodone-treated patients [350]. Mean time to onset of mania in fluoxetine-treated patients was significantly longer than trazodone-treated patients; 59 days (range = 10 to 154 days) versus 16 days (range = 4 to 70 days) respectively.

4.6.H] Imipramine

4.6.H.1] Depression

a) Trazodone is not therapeutically superior to imipramine, but its side effects are less troublesome [371] [372][373][374][375][376]. Anticholinergic side effects occurred more frequently in patients treated with imipramine than those treated with trazodone in a multi-centre trial [343].

b) A multicenter trial involving 379 patients treated with trazodone 200 to 600 milligrams (mg) per day imipramine 100 to 300 mg/day or placebo for 21 to 24 days demonstrated imipramine and trazodone to be of equal efficacy [343]. Another study involving 28 patients with endogenous depression receiving an average trazodone dose of 287 mg/day or an average imipramine dose of 140 mg/day for 28 days also demonstrated equal effectiveness between the 2 drugs [371]. The results of a double-blind study involving 45 patients suggested that trazodone 200 to 600 mg/day produced a more rapid and prolonged improvement than did imipramine 100 to 300 mg/day [372]. In a double-blind controlled study of 40 patients with endogenous depression, imipramine (maximum daily dose 300 mg) produced more improvement of Hamilton depression scale scores on days 14 and 28 than trazodone (maximum daily dose 600 mg) [374].

c) Seventy-four patients were enrolled in a nonrandomized study with placebo baseline treatment to evaluate the efficacy of imipramine, alprazolam, and trazodone in the treatment of agoraphobia [377]. Twenty-nine patients were assigned to imipramine, 28 to trazodone, and 26 to alprazolam treatment. All patients were treated with placebo for 3 weeks and then blindly switched to active treatment for clinical response and side effects. Both imipramine and alprazolam were effective in controlling the agoraphobia, however, alprazolam had a faster onset of action. Clinical responses were observed within one week with alprazolam therapy and were generally not observed in imipramine treated patients until the third or fourth week of therapy. Trazodone therapy was considered not effective in the treatment of agoraphobia.

d) In a double-blind controlled study, imipramine and placebo were compared with trazodone in the treatment of 45 hostile patients with primary depression. The mean doses received during this study were 6.26 capsules/day of 50 milligrams (mg) trazodone, 6.37 capsules/day of imipramine 25 mg or 10.67 capsules/day of placebo. Three of 17 patients in the trazodone groups experienced a 50% reduction in the Hamilton total score on or before day 7 of therapy. On day 14, 8 patients from the trazodone group achieved this level of improvement. Of the imipramine-treated patients, no one in the group showed a 50% improvement at day 7. However, by day 14, eight patients in the group had also experienced at least a 50% reduction in total Hamilton differences in the subjects tested through the structured clinical interview. Clinical global impressions showed a highly significant difference between trazodone and placebo in the proportion of improved patients at the end of 28 days of treatment. Global ward behavior indicated that trazodone was significantly (p less than 0.01) better than placebo for tense, anxious, inwardly distressed behavior and difficulty in sleeping. It was significantly (p less than 0.05) better for tired, worn out and lacking energy behavior and anxious, worried, afraid behavior and concern for bodily health. Trazodone was slightly better (p less than 0.10) for irritable, annoyed, impatient or angry behavior. Drowsiness was the most frequent side effect experienced by trazodone treated patients. Anticholinergic effects were the most common effects in the imipramine group [372].

e) Ten institutions participated in a multi-center, double-blind, placebo-controlled evaluation of either trazodone or imipramine in 263 in-patients. Inclusion criteria included primary depression of the

endogenous type, minimum score of 18 on the Hamilton Rating Scale for depression (HAM-D) and at least 7 of 21 symptoms in 3 of 5 categories of the symptom profile for depression. Initial doses were 200 mg and 100 mg daily for [trazodone](#) or [imipramine](#). At the end of 28 days, 113 patients dropped out due to lack of efficacy or side effects. Drop out rates were 37% each for [imipramine](#) and [trazodone](#) and 58% for placebo. Both drugs were statistically superior to placebo in improvement of HAM-D and clinical global interview. There was no significant difference between [trazodone](#) and [imipramine](#). Both [trazodone](#) and placebo caused statistically significantly fewer anticholinergic side effects, 19% and 14% compared WITH [imipramine](#) 52% [378].

4.6.I] Mianserin

4.6.I.1] Depression

a) SUMMARY: Several clinical trials have shown mianserin to be equally effective as [trazodone](#) in the treatment of depression [365][366][367]. In a 6-week, double-blind trial, 100 to 200 milligrams (mg) [trazodone](#) was compared with 60 to 120 mg mianserin [367]. Although there were significant dropouts in the mianserin group, both drugs were equally effective. Due to side-effects associated with mianserin, [trazodone](#) was the favored drug. Mianserin (30 to 80 mg) was compared with [trazodone](#) (150 to 400 mg) and placebo in a double-blind, cross-over study involving 16 cardiac patients [366]. Both drugs were equally effective with no significant cardiovascular effects detected. A trend toward hypotension was noted with [trazodone](#).

b) Oral mianserin 30 to 120 milligrams (mg) daily was reported as effective as oral [trazodone](#) 100 to 400 mg daily in the treatment of mild-to-moderate depression (endogenous or reactive) in one multicentre trial [368].

c) [Trazodone](#) in doses of 100 to 200 milligrams (mg) daily was reported significantly superior to mianserin (60 to 120 mg daily) and [diazepam](#) (15 to 30 mg daily) in reducing symptoms of depression. A controlled study over 3 to 6 weeks compared the antidepressant and anxiolytic effects of [trazodone](#), mianserin, and [diazepam](#) in patients with mild to moderate depression (with or without anxiety). The [trazodone](#) was also superior to [diazepam](#) in improving the patients ability to concentrate and reducing daytime tiredness. Significantly more patients developed side effects with mianserin than either [trazodone](#) or [diazepam](#) [369].

d) Clinical outcomes were equal in all 3 groups of patients in a double-blind, multicenter trial comparing [trazodone](#), mianserin, and [amitriptyline](#) in the treatment of 106 elderly depressed patients. [Trazodone](#) was associated with fewer overall side effects [365].

4.6.I.2] Erectile dysfunction

a) [Trazodone](#) was more effective than mianserin, ketanserin, or placebo in treating [erectile dysfunction](#) in a double-blind, randomized, placebo-controlled trial. One hundred patients were randomized to receive [trazodone](#) 50 milligrams (mg) three times a day, ketanserin 20 mg twice a day, mianserin 10 mg three times a day, or placebo. Patients were evaluated after 30 days. Positive responses were attained in 65.2% of trazodone-treated patients, 19.1% of ketanserin-treated patients, 31.6% of mianserin-treated patients, and 13.6% with placebo. Response to [trazodone](#) was significantly greater than placebo [370].

4.6.J] Triazolam

1) Adverse Effects

a) In a comparison of adverse effects of [triazolam](#) in doses of 0.125, 0.25, and 0.5 milligram (mg) to [trazodone](#) in doses of 50, 100, and 200 mg and placebo, [trazodone](#) did not significantly impair performance of study tasks. [Triazolam](#), in the highest dose, significantly impaired learning, recall, and performance. Subjective ratings of drug effect and sedation demonstrated comparable dose-

related increases for both drugs, indicating some equivalence on a behavioral basis. Test subjects were tested 30 minutes before and 0.5, 1, 1.5, 2, 2.5, 3, 4, 5, and 6 hours after drug administration. Testing of subjects included measures rated by subjects and/or observers, including: Profile of Mood States (POMS); Addiction Research Center Inventory (ARCI); drug effect questionnaire; end-of-day questionnaire; observer-rated questionnaire; learning, recall, and performance measures; repeated acquisition procedure; digit-enter and recall; Digit-Symbol-Substitution Test (DSST); circular lights test; balance task; and picture recall recognition. The study did not investigate the relative abuse potential of the drugs, but the authors suggested that future research in this area would be useful because of the high incidence of anxiety and sleep disorders in patients with histories of drug abuse [364].

4.6.K] Venlafaxine

4.6.K.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 [347].

4.6.L] Zolpidem

4.6.L.1] Insomnia

a) Zolpidem 10 milligrams (mg) was slightly superior to trazodone 50 mg in reducing sleep latency and increasing sleep duration in a 2-week, randomized, parallel-group, double-blind comparative study (n=278). The periods of sleep latency at the end of week 1 were 48.2 minutes and 57.7 minutes for the groups treated with zolpidem or trazodone, respectively (p less than 0.037), but did not differ significantly at the end of week 2 (64.7 minutes versus 54.5 minutes, respectively). The sleep duration was significantly higher in both groups compared to the group treated with placebo (p=0.001). Patients treated with zolpidem reported longer sleep durations at week 1 than those treated with trazodone (378.8 minutes versus 366.4 minutes, respectively) with a trend toward significance (p less than 0.060), but virtually no difference between drugs at week 2. The reduction in clinical significance in both parameters with both drugs, compared with placebo, was primarily due to improvement in the placebo-treated group over time while the level of improvement with both drugs was essentially unchanged in the second week of treatment. Because of the slightly shorter period of sleep latency, zolpidem may have some advantages over trazodone in the treatment of primary insomnia [346].

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